Diet and Supplementation Options

5-HTP (precursor of serotonin) also melatonin

https://www.healthyplace.com/depression/articles/5-htp-serotonin-connection
tryptophan —> 5-HTP —> serotonin
The effective dose of 5-HTP appears to be between 50 and 500 mg daily.[3]
5-HTP must be administered in proper balance with dopamine amino acid precursors along with proper levels of sulfur amino acids ???? https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3415362/
https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/5-hydroxytryptophan
5-Hydroxytryptophan (5-HTP) is an amino acid precursor used in the formation of serotonin. 5-HTP has been used as an oral supplement alternative to boost serotonin.[22] It has been shown in studies to improve depression, but only preliminary evidence is available suggesting that 5-HTP also may improve anxiety. L-Tryptophan, another amino acid found to improve mood, is converted to 5-HTP and then to serotonin. 5-HTP readily crosses the blood–brain barrier. **Anyone using conventional medications for depression or anxiety, particularly those agents that boost serotonin, should discuss the use of 5-HTP with his or her health care practitioner before initiating supplementation to avoid excessively elevated levels of serotonin.**
https://examine.com/supplements/5-htp/research/
5-HTP is the precursor to serotonin, the neurotransmitter sometimes touted to be responsible for happiness. **5-HTP is a simple way to increase brain serotonin levels** by bypassing the rate-limiting step, and **users reap either the rewards or the hazards of increased brain serotonin.**
https://pubmed.ncbi.nlm.nih.gov/9727088/ 5-Hydroxytryptophan: a clinically-effective serotonin precursor 1998
5-Hydroxytryptophan (5-HTP) is the intermediate metabolite of the essential amino acid L-tryptophan (LT) in the biosynthesis of serotonin. Intestinal absorption of 5-HTP does not require the presence of a transport molecule, and is not affected by the presence of other amino acids; therefore it **may be taken with meals without reducing its effectiveness**. Unlike LT, 5-HTP cannot be shunted into niacin or protein production. Therapeutic use of 5-HTP bypasses the conversion of LT into 5-HTP by the enzyme tryptophan hydroxylase, which is the rate-limiting step in the synthesis of serotonin. 5-HTP is **well absorbed from an oral dose,** with about 70 percent ending up in the bloodstream. It easily **crosses the blood-brain barrier** and effectively increases central nervous system (CNS) synthesis of serotonin. In the CNS, serotonin levels have been implicated in the **regulation of sleep, depression, anxiety, aggression, appetite, temperature, sexual behaviour, and pain sensation.** Therapeutic administration of 5-HTP has been shown to be effective in treating a wide variety of conditions, including depression, fibromyalgia, binge eating associated with obesity, chronic headaches, and insomnia.
https://pubmed.ncbi.nlm.nih.gov/35572711/ Oral Administration of 5-Hydroxytryptophan **Restores Gut Microbiota Dysbiosis** in a Mouse Model of Depression 2022
5-Hydroxytryptophan (5-HTP) has positive clinical effects on various neuropsychiatric and metabiotic disorders, especially depression. Although it increases serotonin levels in the brain and gastrointestinal tract, its pharmacology remains largely unknown. Our goal was to determine the effects of 5-HTP on the mouse gut microbiome, which has a close relationship with depression through the "microbiota-gut-brain axis." We confirmed that depressive disorder restructures the gut microbial community, and 5-HTP efficiently improves depressive symptoms in mice. Oral administration of 5-HTP significantly **restored gut microbiota dysbiosis in mice with depression-like behaviors.**
https://pubmed.ncbi.nlm.nih.gov/35967282/ *Morinda officinalis* oligosaccharides increase serotonin in the brain and ameliorate depression *via* promoting 5-hydroxytryptophan production in the gut microbiota 2022
Morinda officinalis oligosaccharides (MOO) are an oral drug approved in China for the treatment of depression in China. However, MOO is hardly absorbed so that their anti-depressant mechanism has not been elucidated. Here, we show that oral MOO acted on tryptophan → 5-hydroxytryptophan (5-HTP) → serotonin (5-HT) metabolic pathway in the gut microbiota. This study **reveals for the first time that MOO can alleviate depression *via* increasing 5-HTP in the gut microbiota.**
https://pubmed.ncbi.nlm.nih.gov/30743155/ Bifidobacterium with the role of 5-hydroxytryptophan synthesis regulation alleviates the symptom of depression and related microbiota dysbiosis 2019
Here we studied the effect of **f lactic acid bacteria (LAB) treatment** on depression. C57BL/6J mice were administered with LAB during a 5-week chronic unpredictable mild stress. Bifidobacterium longum subsp. infantis E41 and Bifidobacterium breve M2CF22M7, which **improved the expression** of Tph1 and **secretion of 5-hydroxytryptophan (5-HTP)** in RIN14B cells, **significantly reduced depressive behaviors of mice** in the forced swim test, sucrose preference test and step-down test, as well as increased the level of 5-hydroxytryptamine and brain-derived neurotrophic factor concentration in brain. These results indicate that Bifidobacterium E41 and M2CF22M7 have an antidepressant effect in mice partly in a 5-HTP dependent and microbiota-regulating manner. Nurturing the **gut microbiota** with these strains may become an emerging therapeutic way for mood disorder.
https://pubmed.ncbi.nlm.nih.gov/33375373/ 5-Hydroxytryptophan (5-HTP): Natural Occurrence, Analysis, Biosynthesis, Biotechnology, Physiology and Toxicology 2020
L-5-hydroxytryptophan (5-HTP) is both a drug and a natural component of some dietary supplements. 5-HTP is produced from tryptophan by tryptophan hydroxylase (TPH), which is present in two isoforms (TPH1 and TPH2). Decarboxylation of **5-HTP yields serotonin** (5-hydroxytryptamine, **5-HT) that is further transformed to melatonin** (*N*-acetyl-5-methoxytryptamine). 5-HTP plays a major role both in neurologic and metabolic diseases and its synthesis from tryptophan represents the limiting step in serotonin and melatonin biosynthesis.

Alpha-lipoic acid ALA (organosulfur compound) [also known as LA] (iron chelator)(see Walnuts)

-also TNF inhibitor, water and fat soluble, crosses BBB, converted to EPA and DHA in the body, also good for kidneys

- increases insulin sensitivity, lowers blood pressure, good for AMD

Sources: flaxseed, flaxseed Oil(7458mg/Tblsp), Chia seeds(2534mg/Tblsp), Walnuts(2500mg/ounce(28g)=6 walnuts), 5g/Walnut (446mg/whole Walnut)
Canola Oil(1279/Tblsp), spinach(93ng/mg), broccoli(41ng/mg), tomato(49ng/mg), green pea(17ng/mg)
Supplement Intake: 200-600mg/day (better off using Walnuts or Chia Seeds)
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7889054/pdf/nihms-1667349.pdf Sulfur-containing therapeutics in the treatment of Alzheimer's disease 2021
The anti-AD effect of lipoic acid (ALA, 10) is attributed to multitude of properties. The chemical activity of ALA is mainly due to the dithionate ring, **whose sulfur atoms** confer high electron density to ALA making it an efficient antioxidant. The long carbon chain and ring system make it more lipophilic than other natural antioxidants. **ALA could easily cross the blood–brain barrier (BBB)** and keep a uniform uptake profile throughout the central nervous system (CNS), which is beneficial against AD.
https://pubmed.ncbi.nlm.nih.gov/17982894/ Alpha-lipoic acid as a new treatment option for Alzheimer's disease--a 48 months follow-up analysis 2007
In this report, we have extended the analysis to 43 patients over an observation period of up to 48 months. **In patients with mild dementia (ADAScog < 15), the disease progressed extremely slowly** (ADAScog: +1.2 points/year, MMSE: -0.6 points/year), in p**atients with moderate dementia at approximately twice the rate.** However, the **progression appears dramatically lower than data reported for untreated patients** or patients on choline-esterase inhibitors in the second year of long-term studies. Despite the fact that this study was not double-blinded, placebo-controlled and randomized, our data suggest that treatment with alpha-lipoic acid might be a successful 'neuroprotective' therapy option for AD. However, a state-of-the-art phase II trial is needed urgently.
https://pubmed.ncbi.nlm.nih.gov/34450170/ Decrypting the potential role of α-lipoic acid in Alzheimer's disease 2021
Alpha-lipoic acid (α-LA), a **natural antioxidan**t present in food and used as a dietary supplement, has been considered a promising agent for the **prevention or treatment of neurodegenerative disorders**. Despite multiple preclinical studies indicating beneficial effects of α-LA in memory functioning, and pointing to its neuroprotective effects, to date only a few studies have examined its effects in humans. Studies performed in animal models of memory loss associated with aging and AD have shown that α-LA improves memory in a variety of behavioral paradigms. Furthermore, molecular mechanisms underlying α-LA effects have also been investigated. Accordingly, **α-LA shows antioxidant, antiapoptotic, anti-inflammatory, glioprotective, metal chelating properties** in both in vivo and in vitro studies. In addition, it has been shown that **α-LA reverses age-associated loss of neurotransmitters and their receptors**.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2756298/pdf/nihms-142024.pdf Alpha-lipoic acid as a dietary supplement: Molecular mechanisms and therapeutic potential 2009
Current trials are investigating whether these beneficali properties of LA make it an appropriate treatment not just for diabetes, but also for the prevention of vascular disease, hypertension, and **inflammation**.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6723188/pdf/biomolecules-09-00356.pdf Insights on the Use of α-Lipoic Acid for Therapeutic Purposes 2019
Non-steroidal anti-inflammatory drugs (NSAIDs) have been proposed for the therapy of neurodegenerative diseases, including AD. However, the **prolonged NSAIDs administration results in gastrointestinal toxicity** due cyclooxygenase (COX) inhibition [35,53]. **To overcome this limitation, ALA has been selected based on the intended role of oxidative stress in the development of AD**. Studies have also shown that **ALA show anti-dementia or anti-AD properties** by increasing acetylcholine (ACh) production through activation of choline acetyltransferase, which increases glucose absorption and, hence, supply more acetyl-CoA for ACh production
On the other hand, **inflammation has a key function in AD**. Similarly,Dinicola et al. [67] found that **ALA downregulated the levels of the inflammatory cytokines** IL-1B and IL-6 in SK-N-BE human neuroblastoma cells through DNA methylation-dependent modulation, paving the way for the impact of epigenetic mechanisms in AD control/prevention
A study suggests that **ALA bioavailability is greatly reduced after food intake** and it has been recommended that **ALA should be admitted at least 2 h after eating or if taken before; meal should be taken at least 30 min a**fter ALA administration. Therefore, ALA supplements are preferably taken on an **empty stomach to benefit of the acidic stomach** pH. Moreover, it also reduces ALA competition with other nutrients for absorption Since **ALA is poorly soluble, lecithin has been used** as an amphiphilic matrix to enhance its bioavailability.
ALA could be detected for up to 2 h after IV drug administration and for up to 4 h after oral administration.
ALA bioavailability is markedly increased when orally administered in the **liquid form r**ather than a solid dosage form. Moreover, it presents prolonged stability, high plasma concentrations and accelerated absorption of ALA
https://pubmed.ncbi.nlm.nih.gov/11689467/ **Alpha-lipoic acid inhibits TNF-alpha-induced** NF-kappaB activation and adhesion molecule expression in human aortic endothelial cells 2001

We investigated the role of (R)-alpha-lipoic acid (LA) vs. glutathione and ascorbic acid in tumor necrosis factor alpha (TNF-alpha) -induced adhesion molecule expression and nuclear factor kappaB (NF-kappaB) signaling in human aortic endothelial cells (HAEC). LA also strongly inhibited TNF-alpha-induced mRNA expression of monocyte chemoattractant protein-1 but did not affect expression of TNF-alpha receptor

Heavy Metal Chelator

https://pubmed.ncbi.nlm.nih.gov/32670009/ Alpha-Lipoic Acid Mediates Clearance of Iron Accumulation by Regulating Iron Metabolism in a Parkinson's Disease Model Induced by 6-OHDA 2020
The **disruption of neuronal iron homeostasis and oxidative stress are related to the pathogenesis of Parkinson's disease (PD)**. **Alpha-lipoic acid (ALA) is a naturally occurring enzyme cofactor with antioxidant and iron chelator properties** and has many known effects. **ALA has neuroprotective effects** on PD. However, its underlying mechanism remains unclear. In the present study, we established PD models induced by 6-hydroxydopamine (6-OHDA) to explore the neuroprotective ability of ALA and its underlying mechanism *in vivo* and *in vitro*. Our results showed that ALA could provide significant protection from 6-OHDA-induced cell damage *in vitro* by decreasing the levels of intracellular reactive oxygen species and iron. Therefore, **ALA may provide neuroprotective therapy for PD and other diseases related to iron metabolism disorder**.
https://pubmed.ncbi.nlm.nih.gov/7605337/ Thioctic (lipoic) acid: a therapeutic metal-chelating antioxidant? 1995
We suggest that one component of its antioxidant activity requiring study is the direct transition **metal-chelating activity** of the drug. We found that TA had a profound dose-dependent inhibitory effect upon Cu(2+)-catalysed ascorbic acid oxidation (monitored by O2 uptake and spectrophotometrically at 265 nm) and also increased the partition of Cu2+ into n-octanol from an aqueous solution suggesting that TA forms a lipophilic complex with Cu2+. **TA also inhibited Cu(2+)-**catalysed liposomal peroxidation. Furthermore, TA inhibited intracellular H2O2 production in erythrocytes challenged with ascorbate, a process thought to be mediated by loosely chelated Cu2+ within the erythrocyte. These data, taken together, suggest that prior intracellular reduction of TA to dihydrolipoic acid is not an obligatory mechanism for an **antioxidant effect of the drug, which may also operate via Cu(2+)-chelation**.
https://pubmed.ncbi.nlm.nih.gov/30939378/ Insights on alpha lipoic and dihydrolipoic acids as promising scavengers of oxidative stress and **possible chelators in** mercury toxicology 2019
Alpha lipoic acid (α-LA) and its reduced form dihydrolipoic acid (DHLA) have been historically considered as excellent anti-oxidants and oxidative stress scavengers. Upon oxidation with reactive oxygen species (ROS) and pro-oxidants, α-LA may be reconstituted from DHLA and other reduced forms. Oxidative stress is one of the fundamental causes of functional degeneration, autophagy and apoptosis leading to cytotoxicity and loss of cell survival, often due to exposure to xenobiotics, pollutants, heavy metals, and other environmental and endogenous toxicants. α-LA and DHLA can react with these molecules to strengthen the primary antioxidant defense system during cell injury. The compound **α-LA is suggested for heavy metal detoxification,** in particular for supporting the mercury (Hg) detoxifying process.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3654245/ Chelation: Harnessing and Enhancing Heavy Metal Detoxification—A Review 2013
Chelation, that is multiple coordination bonds between organic molecules and metals, is very common in the body and at the heart of enzymes with a metal cofactor such as copper or zinc. Peptides glutathione and metallothionein chelate both essential and toxic elements as they are sequestered, transported, and excreted. Enhancing natural chelation detoxification pathways, as well as use of pharmaceutical chelators against heavy metals are reviewed. **Alpha lipoic acid is a powerful antioxidant that regenerates other antioxidants (e.g., vitamins E and C, and reduced glutathione) and has metal-chelating activity. Both fat and water soluble, it is readily absorbed from the gut and crosses cellular and blood-brain membrane barriers [22, 53].**
https://pubmed.ncbi.nlm.nih.gov/26995676/ Vegetable oils rich in alpha linolenic acid increment hepatic n-3 LCPUFA, modulating the fatty acid metabolism and antioxidant response in rats 2016
Alpha-linolenic acid (C18:3 n-3, ALA) is an essential fatty acid and the metabolic precursor of long-chain polyunsaturated fatty acids (LCPUFA) from the n-3 family with relevant physiological and metabolic roles: eicosapentaenoic acid (C20:5 n-3, EPA) and docosahexaenoic acid (C22:6 n-3, DHA). **Western diet lacks of suitable intake of n-3 LCPUFA** and there are recommendations to increase the dietary supply of such nutrients.
sunflower oil (SFO, 1% ALA) as control group, canola oil (CO, 10% ALA), rosa mosqueta oil (RMO, 33% ALA), sacha inchi oil (SIO, 49% ALA) and **chia oil (ChO, 64% ALA)**

Bioavialability

https://superfoodly.com/top-10-list-of-foods-high-in-alpha-lipoic-acid-ala/
Once exposed to the atmosphere and light, it rapidly degrades. This is why we personally **don't like taking anything other than enclosed capsules**.
What is the half-life of alpha lipoic acid? In blood it's only 30 minutes, as demonstrated *in vivo* in at least one study (13). **ALA supplement once every 3 to 6 hours** would be higher preferable over a higher dose that's once or twice daily.
If you can afford it, go with R lipoic. You may have noticed some bottles touting the R version which are about 2x the price or higher. What is the difference between alpha lipoic acid and R lipoic acid? The regular is a 50/50 split of R- (the natural bioavailable form of lipoic acid) and S- (unnatural form). Humans have difficult absorbing the S version it may actually inhibit some properties of the R version being expressed.
https://pubmed.ncbi.nlm.nih.gov/18689552/ Bioavailability of alpha-linolenic acid in subjects after ingestion of three different forms of flaxseed 2008
The flaxseed components (**30 g of seed or 6 g of ALA in the oil) were baked into muffins** for delivery over a 3 month test period in healthy male and female subjects.
Conclusion: In summary, **ingestion of flax oil and milled flaxseed delivered significant levels of ALA to the plasma whereas whole flaxseed did not**. Whole seed and oil preparations induced adverse gastrointestinal effects within 4 weeks and these were severe enough to induce the withdrawal of some subjects from these two groups. No one withdrew from the group that **ingested milled flaxseed and, therefore, may represent a good form of flaxseed to avoid serious side-effects and still provide significant increases in ALA to the body.**
https://www.nature.com/articles/ejcn200941 Bioavailability of α-linolenic acid from flaxseed diets as a function of the age of the subject 2009
All subjects who received **flaxseed oil showed a significant increase in plasma ALA and eicosapentaenoic acid (EPA)** concentrations over the course of this study. Subjects who received ground flaxseed in the 18–29-year-old group showed a statistically significant increase in their plasma ALA levels, and although there was a trend in the same direction for the 45–69-year-old subjects, this did not achieve statistical significance. The diets induced no major changes in platelet aggregation, plasma total cholesterol, low-density lipoprotein or high-density lipoprotein cholesterol levels in any of the groups. Younger subjects showed a decrease in triglyceride (TG) values compared with older subjects. There were **no significant side effects** that caused compliancy issues.
Conclusion:
Subject age does not seem to be a major determining factor in influencing ALA absorption from a flaxseed-supplemented diet nor in the metabolism of ALA to EPA in the groups fed flaxseed oil. Concerns about side effects in older subjects administered a higher fiber load in a flaxseed-supplemented diet are not justified.
https://www.hsph.harvard.edu/nutritionsource/food-features/chia-seeds/ Chia Seeds
People often wonder if chia seeds should be eaten ground instead of whole. The surface of chia seeds is delicate and easily breaks apart when exposed to moisture, so they are **typically prepared with liquid foods** (as seen with the recipe ideas below). In **this way, they are absorbed and digested well in their whole form, unlike flax seeds.** If eating the seeds dry, choosing ground chia seeds may help to improve absorption.
https://walnuts.org/nutrition/nutrition-info/alpha-linolenic-acid/
Walnuts are the only tree nut that is an excellent source of alpha-linolenic acid (ALA), the plant-based omega-3 essential fatty acid. As one of the best plant food sources of omega-3s, **a one-ounce serving of walnuts provides 2.5 grams of ALA.**

Anserine (derviative of carnosine, see carnosine)

Anthocyanin (antioxidants found in red, purple, and blue fruits and vegetables. Grape, blueberry, cherry juice, bilberry) TNF inhibitor

BlueBerries(529mg), Elderberries(1993mg), Eggplants(750mg), Purple(Blue)Corn(1642mg), Oranges(200mg), Red Onion(39mg), Red Grapes(43mg), StrawBerries(69mg), Raspberries(116mg) CranBerries(91mg),
Average Intake from food: 12.5 mg/day/person in the United States
Recommended as supplement: 100mg (usually a berry extract, bilberry, grape seed, cherry)
https://www.ars.usda.gov/ARSUserFiles/80400525/Articles/JAFC54_4069-4075.pdf Concentrations of Anthocyanins in Common Foods in the United States and Estimation of Normal Consumption 2006
Anthocyanins (ACNs) are water-soluble plant pigments that have important functions in plant physiology as well as possible health effects. On the basis of the concentration data and updated food intake data from NHANES 2001-2002, the daily intake of ACNs is estimated to be 12.5 mg/day/person in the United States. Of the different aglycones, cyanidin, delphinidin, and malvidin were estimated to contribute 45, 21, and 15%, respectively, of the total ACN intake. Nonacylated contributed 77% compared to 23% from
acylated ACNs Anthocyanins (ACNs) are water-soluble plant pigments responsible for the blue, purple, and red color of many plant tissues. They occur primarily as glycosides or acylglycosides of their respective aglycone anthocyanidins (1). Aglycones are rarely found in fresh plant materials. There are about 17 anthocyanidins found in nature (1), whereas only 6 of them, cyanidin (Cy), delphinidin (Dp), petunidin (Pt), peonidin (Pn), pelargonidin (Pg), and malvidin (Mv), are ubiquitously distributed (Figure 1). Thus far, over 600 naturally occurring ACNs have been reported (2, 3), and they are known to vary in (1) the number and position of hydroxyl and methoxyl groups on the basic anthocyanidin skeleton; (2) the identity, number, and positions at which sugars are attached; and (3) the extent of sugar acylation and the identity of the acylating agent (4)
Rising Sun, MD) was used for separation. The experimental conditions
were described in our former papers (26, 27).
Table 2. Concentration of Anthocyanins Grouped by Aglycones in Common Foods in the United States
fruits
1. apple
Fuji 1.8

	Gala	3.2
	Red Delicious	17.0
2. blackberry		
	blackberry	353
	Marion blackberry	433
3. blueberry – – – – – – – – –		
	cultivated	529
	wild	705
4. cherry, sweet		177
5. chokeberry		2147
6. cranberry		133
7. currant		
	black currant	533
	red currant	14.3
8. elderberry		1993
9. gooseberry		
	group 1	15.1
	group 2	3.2
	group 3	1.0
10. grape		
	red grape	42.7
	Concord grape	192
11. nectarine		9.2
12. peach		4.7
13. plum		
	plum	12.5
	black plum	82.2
14. raspberry		
	black raspberry	845
	red raspberry	116
15. strawberry		
	strawberry	35.0
	strawberry OSC	69.2
vegetables		
1. black bean		23.1
2. eggplant		35.1
3. red cabbage		113
4. red leaf lettuce		1.5
5. red onion		38.8
6. red radish		116
7. small red bean		6.2
nuts		
1. pistachio		2.1

https://pubmed.ncbi.nlm.nih.gov/28964358/

https://www.myprotein.com/thezone/supplements/what-is-anthocyanin-health-benefits-side-effects-dosage/ Influence of fruit juice processing on anthocyanin stability 2017

Conventional thermal or novel non-thermal treatments to ensure microbial safety have both positive and negative effects on the anthocyanins. By inactivation of oxidizing enzymes, profiles and quantities of anthocyanins may be maintained, but more severe conditions may have adverse effects. To improve juice extraction and to increase yield, enzyme-assisted degradation of the cell walls is conducted. The applied enzyme preparations contain numerous side activities which also may degrade anthocyanins. **Clarification and concentration will further reduce the final anthocyanin concentrations.** Many studies have been published regarding evaluating individual fruits or single processing steps but, obviously, these results are not necessarily transferable. Accordingly, this review aims to summarize all relating studies comprehensively to the fate of anthocyanins during juice processing giving an overview of underlying mechanisms as well as the chemical and analytical background.

https://www.healthline.com/nutrition/anthocyanin#foods-list Anthocyanin-containing foods

Red, blue, and purple produce is generally the richest in anthocyanins. **Raw, ripe varieties** tend to have the highest amounts due to variability in this nutrient. To maximize your intake of anthocyanins from these foods, eat them raw and at their ripest if possible.

Anthocyanin-rich foods are generally considered safe. However, the **same cannot necessarily be said about anthocyanin supplements.**

Anthocyanin supplements may provide larger quantities of polyphenols than you'd typically get from a healthy diet (33Trusted Source).

Animal studies indicate that **high dose polyphenol supplements may damage your kidneys,** cause tumors, or unbalance your thyroid hormones (33Trusted Source).

https://pubmed.ncbi.nlm.nih.gov/31766696/ Anthocyanins Potentially Contribute to Defense against Alzheimer's Disease 2019

These compounds are primarily found in fruits and vegetables, with an average daily intake of 180 mgd^{-1} of these compounds in the developed world. **ANTs are potent antioxidants** that might regulate the free radical-mediated generation of amyloid peptides (Abeta-amyloids) in the brain, which causes Alzheimer's disease (AD).

https://pubmed.ncbi.nlm.nih.gov/35217244/ Anthocyanin as a therapeutic in Alzheimer's disease: A systematic review of preclinical evidences 2022

The aim of this systematic review is to ponder the **possible mechanism of action of anthocyanin in Alzheimer's disease (AD)**, to prompt the development of anthocyanin-based dietary supplementation or therapeutic intervention for AD and to explore the natural sources of anthocyanins. **Discussion:** Efficacy of anthocyanin in alleviating **oxidative stress**, reactive astrogliosis, cholinergic dysfunction, apoptosis, synaptotoxicity, **neuroinflammation**, tau hyperphosphorylation, dysregulated membrane potential, neuronal extracellular calcium, dysfunctional amyloidogenic pathway, and **cognitive deficits in various rodent models of AD** is manifested compositely in 12 studies.

https://www.frontiersin.org/articles/10.3389/fneur.2020.00916/full Effects of Purified Anthocyanins in People at Risk for Dementia: Study Protocol for a Phase II Randomized Controlled Trial 2020

Anthocyanins, a subclass of the flavonoids found in dark berries and fruits, are among the dietary factors that may have **potentially positive effects on the pathogenesis of AD**. Findings from cell, animal, and human studies suggest that they have **antioxidant effects** (17, 18), **improve the blood lipid profile** (19), and also have **anti-inflammatory effects** (20). Also, anthocyanins have been shown to increase flow-mediated dilatation (21–23) and to **cross the blood–brain barrier** (24). Thus, these substances have several effects relevant to protection against key mechanisms leading to cognitive decline and dementia in older people.

Interestingly, placebo-controlled studies have reported improvement of memory functioning in older people with memory problems or even dementia, **after consumption of grape juice (25), blueberry juice (26), and cherry juice (27) as the source of anthocyanins**. More recently, a randomized controlled trial has concluded that **food-based anthocyanidin consumption was associated with a reduced risk of AD** (28). However, previously published studies have major methodological limitations, including small sample sizes, short duration, and lack of biomarkers (29).

https://pubmed.ncbi.nlm.nih.gov/31847371/ Association of Strawberries and Anthocyanidin Intake with Alzheimer's Dementia Risk 2019

A total of 245 participants developed Alzheimer's dementia over the mean follow-up of 6.7 (±3.6) years. **Higher strawberry intake was associated with reduced risk of Alzheimer's dementia (HR = 0.76**, 95% CI: 0.60-0.96). In separate adjusted models, highest vs. lowest quartile intakes of **Vitamin C (HR = 0.64**, 95% CI: 0.45, 0.92), Pelargonidin (0.63, 95% CI: 0.43, 0.92), total **anthocyanidins (0.69**, 95% CI: 0.48, 0.99), and total flavonoids (0.67, 95% CI: 0.46, 0.98) were **each associated with lower Alzheimer's dementia risk**.

https://pubmed.ncbi.nlm.nih.gov/32003387/ Bilberry anthocyanins improve neuroinflammation and cognitive dysfunction in APP/PSEN1 mice via the CD33/TREM2/TYROBP signaling pathway in microglia 2020

Alzheimer's disease, characterized by neuroinflammation and beta-amyloid protein plaques, is a memory-threatening neurodegenerative disease with no effective treatment. Here, the effect of bilberry anthocyanins (BA) on cognitive functions was evaluated using APP/PSEN1 transgenic Alzheimer's disease model mice and their WT littermates. Our results revealed that **BA appreciably improves learning and memory abilities and reverses defects to cognitive functions i**n APP/PSEN1 mice. Furthermore, **BA reverses brain, liver and kidney damage caused by Alzheimer's disease**, with no significant changes in oxidative stress and lipid metabolism-related indicators.

https://pubmed.ncbi.nlm.nih.gov/22995388/ Anthocyanin-enriched bilberry and blackcurrant extracts modulate amyloid precursor protein processing and alleviate behavioral abnormalities in the APP/PS1 mouse model of Alzheimer's disease 2012

Soluble Aβ40 and Aβ42 levels were significantly decreased in bilberry-fed mice as compared to blackcurrant-fed mice. Conversely, the ratio of insoluble Aβ42/40 was significantly decreased in blackcurrant-fed mice relative to bilberry-fed mice. Both berry diets alleviated the spatial working memory deficit of aged APdE9 mice as compared to mice on the control diet.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5872786/ A Review of the Health Benefits of Cherries

Cherries are a rich source o**f polyphenols and vitamin C which have anti-oxidant and anti-inflammatory** properties.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7961347/pdf/molecules-26-01403.pdf Tart Cherry Juice and Seeds Affect Pro-Inflammatory Markers in Visceral Adipose Tissue of High-Fat Diet Obese Rats 2021
A randomized and crossover pilot study demonstrated a significant reduction in pro-inflammatory molecule CCL-2, a **reducing trend for tumor necrosis factor alpha (TNF-α)** and a significant difference, compared to placebo, in erythrocyte sedimentation rate after consumption of 100% tart cherry juice for four weeks in overweight individuals [25].

Cherry juice

https://www.arthritisdaily.net/how-much-cherry-juice-for-arthritis/ Arthritis And Gout Relief From Cherries
Current research has only reinforced what many have already known to be true – that Montmorency **tart cherries may help reduce inflammation related to arthritis and gout**. Tart cherries are one of the highest sources of phenolic compounds, which have been known to have anti-inflammatory properties – even going up against some pain medications, and notably, the highest of any other food!
https://pubmed.ncbi.nlm.nih.gov/26482148/ Consumption of anthocyanin-rich cherry juice for 12 weeks improves memory and cognition in older adults with mild-to-moderate dementia 2017
Methods: A 12-week randomised controlled trial assessed cognitive outcomes in older adults (+70 year) with mild-to-moderate dementia (n = 49) after consumption of **200 ml/day** of either a cherry juice or a control juice with negligible anthocyanin content. **Results: Improvements in verbal fluency (p = 0.014), short-term memory (p = 0.014) and long-term memory (p ≤ 0.001) were found in the cherry juice group. A significant reduction in systolic (p = 0.038) blood pressure and a trend for diastolic (p = 0.160) blood pressure reduction was evident in the intervention group.** Markers of inflammation (CRP and IL-6) were not altered.
Conclusion: Inclusion of an **anthocyanin-rich beverage may be a practical and feasible way to improve total anthocyanin consumption in older adults with mild-to-moderate dementia, with potential to improve specific cognitive outcomes.**

Apoaequorin (Prevagen)

https://pubmed.ncbi.nlm.nih.gov/35879840/ Prevagen®: Analysis of Clinical Evidence and Its Designation as a "#1 Pharmacist Recommended Brand" 2022
The authors' search of the literature identified one clinical study that evaluated the efficacy and safety of Prevagen®; however, this **study possesses significant limitations and therefore one must question the merits of such clinical evidence**. Prevagen®'s designation as a "#1 Pharmacist Recommended Brand" is based on a survey facilitated by Pharmacy Times® that is designed to identify the brand name over-the-counter products that pharmacists recommend most frequently. Because of the limited clinical data supporting Prevagen®'s efficacy, it is likely that the survey results reflect pharmacists' familiarity with this product, which may be influenced by extensive advertising techniques. As practitioners of evidence-based medicine, pharmacists should not recommend a product with limited evidence to support its use. Furthermore, pharmacists should proactively educate their patients, especially those who are most vulnerable, about the rational use of all pharmacologically active substances, including dietary supplements.
https://www.ijest.org/nootropics/does-prevagen-work-for-dementia/ Prevagen only contains one active ingredient (besides the pointless vitamin D), and that's a substance called **apoaequorin**.
https://pubmed.ncbi.nlm.nih.gov/26878676/ Effects of a Supplement Containing Apoaequorin on Verbal Learning in Older Adults in the Community 2016
The results indicated a **strong relationship between apoaequorin and improvements on a quantitative measure of cognitive function, specifically verbal learning**.
https://www.ncbi.nlm.nih.gov/books/NBK552157/ Apoaequorin
Apoaequorin is a calcium binding protein **found in luminescent jellyfish** (Aequorea victoria). A single trial of oral apoaequorin in patients with memory problems found n**o overall differences in changes in measures of verbal learning in comparison to placebo**, but slightly greater improvements were reported in a subset of patients with normal cognitive test values at baseline. These findings were questioned later because of the lack of evidence that apoaequorin is absorbed orally or can cross the blood-brain barrier. Nevertheless, apoaequorin is marketed as a dietary supplement that supports brain health and helps with aging-related memory loss.
https://pubmed.ncbi.nlm.nih.gov/26878676/ Effects of a Supplement Containing Apoaequorin on Verbal Learning in Older Adults in the Community 2016
The intervention group (apoaequorin group) showed a statistically significant improvement in verbal learning and recall on the ISL and the ISL-DR, respectively, during the 90-d study. Apoaequorin was tolerated very well in the study.
Conclusions: The results indicated a strong relationship between apoaequorin and improvements on a quantitative measure of cognitive function, specifically verbal learning. The study found that apoaequorin is a well-tolerated supplement that improved cognitive function in aging adults. The results suggest **potential utility for apoaequorin in addressing the declines in cognitive function associated with aging.**
https://www.verywellhealth.com/does-jellyfish-protein-work-for-memory-loss-2252421 What Is Jellyfish Protein (Apoaequorin)? 2022
In nature, apoaequorin produces a blue light when exposed to calcium. Today it is **produced in a lab** by a company called Quincy Bioscience.2 It is the primary ingredient in the dietary supplement Prevagen.
Alternative practitioners say jellyfish protein (apoaequorin) taken by mouth **can bind to calcium in the brain and improve the electrical signals between nerve cells**. This is believed to i**mprove memory while slowing the progressive loss of cognitive function.**
It is thought that calcium deposits in the brain can contribute to dementia and Alzheimer's disease. This is why jellyfish protein has been suggested as a possible prevention strategy and treatment.

Artemisia annua (plant + antimalarial drug source)

https://pubmed.ncbi.nlm.nih.gov/30399421/ Artemisinin B Improves Learning and Memory Impairment in AD Dementia Mice by Suppressing Neuroinflammation 2018
We previously found that artemisinin B from Artemisia annua Linn. has **strong anti-inflammatory and immunological activities**. In the present study, we assessed the anti-neuroinflammatory effects of artemisinin B in vitro and in vivo, exploring the underlying mechanisms. The results demonstrated that artemisinin B inhibited NO secretion from LPS-induced BV2 cells and significantly r**educed the expression levels of the inflammatory cytokines IL-1β, IL-6 and TNF-α.** This was accompanied by reduced gene expression levels of MyD88 and NF-κB as well as TLR4 and MyD88 protein levels. These inhibitory effects were further confirmed in AD model mice. This study also showed that **artemisinin B improved spatial memory in dementia mice** in the water maze and step-through tests, and altered the pathological features and the levels of inflammatory cytokines in the hippocampus and the cortex. These results suggested that artemisinin B might inhibit neuroinflammation and exert neuroprotective effects on cognitive functions by modulating the TLR4-MyD88-NF-κB signaling pathway. This study provides **direct evidence for the potential application of artemisinin B in the treatment of neuroinflammatory diseases.**
https://pubmed.ncbi.nlm.nih.gov/35683033/ Artemisinin Attenuates Amyloid-Induced Brain Inflammation and Memory Impairments by Modulating TLR4/NF-κB Signaling 2022
The abnormal immune response is an early change in the pathogenesis of Alzheimer's disease (AD). Microglial activation is a crucial regulator of the immune response, which contributes to progressive neuronal injury by releasing neurotoxic products. Therefore, finding effective drugs to **regulate microglial homeostasis and neuroinflammation has become a new AD treatment strategy.** Artemisinin has **potent anti-inflammatory and immune activities**. However, it is unclear whether Artemisinin contributes to the regulation of microglial activation, thereby improving AD pathology. This study found that Artemisinin significantly reduced amyloid beta-peptide 1-42 ($A\beta_{1-42}$)-induced increases in nitric oxide and reactive oxygen species and inflammatory factors in BV2 cells. In addition, Artemisinin inhibited the migration of microglia and prevented the expansion of the inflammatory cascade. The mechanical studies **showed Artemisinin inhibited neuroinflammation and exerted neuroprotective effects by regulating the Toll-like receptor 4** (TLR4)/Nuclear factor-kappa B (NF-κB) signaling pathway. Similar results were obtained in AD model mice, in which Artemisinin administration attenuated $A\beta_{1-42}$-induced neuroinflammation and neuronal injury, **reversing spatial learning and memory deficits**. The anti-inflammatory effect of Artemisinin is also accompanied by the activation of the TLR4/NF-κB signaling pathway in the animal model. Our results indicate that **Artemisinin attenuated $A\beta_{1-42}$-induced neuroinflammation and neuronal injury by stimulating the TLR4/NF-κB signaling pathway. These findings suggest that Artemisinin is a potential therapeutic agent for AD.**
https://pubmed.ncbi.nlm.nih.gov/33758353/ Artemisinin improves neurocognitive deficits associated with sepsis by activating the AMPK axis in microglia 2021
We showed that **artemisinin administration significantly improved LPS-induced cognitive impairments assessed in Morris water maze** and Y maze tests, attenuated neuronal damage and microglial activation in the hippocampus. In BV2 microglial cells treated with LPS (100 ng/mL), pre-application of artemisinin (40 μM) significantly reduced the production of proinflammatory cytokines (i.e., TNF-α, IL-6) and suppressed microglial migration. Furthermore, we revealed that artemisinin significantly suppressed the nuclear translocation of NF-κB and the expression of proinflammatory cytokines by activating the AMPKα1 pathway; knockdown of AMPKα1 markedly abolished the anti-inflammatory effects of artemisinin in BV2 microglial cells. In conclusion, **atemisinin is a potential therapeutic agent for sepsis-associated neuroinflammation and cognitive impairment,** and its effect is probably mediated by activation of the AMPKα1 signaling pathway in microglia.

Ashawagandha (nightshade herb)(Withania somnifera) (active ingredient Withaferin A?) **(TNF inhibitor)**

Supplement: 300mg twice/day
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3295277/ *Withania somnifera* reverses Alzheimer's disease pathology by enhancing low-density lipoprotein receptor-related protein in liver

A 30-d course of oral administration of a **semipurified extract of the root of *Withania somnifera*** consisting predominantly of **withanolides and withanosides reversed behavioral deficits, plaque pathology, accumulation of β-amyloid peptides (Aβ) and oligomers in the brains of middle-aged and old APP/PS1 Alzheimer's disease transgenic mice.**
https://pubmed.ncbi.nlm.nih.gov/19957250/ Withanamides in Withania somnifera fruit protect PC-12 cells from beta-amyloid responsible for Alzheimer's disease
Our earlier investigations of the Withania somnifera fruit afforded lipid peroxidation inhibitory withanamides that are more potent than the commercial antioxidants. In this study, we have tested two major withanamides A (WA) and C (WC) for their ability to protect the PC-12 cells, rat neuronal cells, from beta-amyloid induced cell damage. The **cell death caused by beta-amyloid was negated by withanamide treatment.**
https://pubmed.ncbi.nlm.nih.gov/32240781/ Neurodegenerative diseases and Withania somnifera (L.): An update
Withania somnifera (L.) Dunal also known as '**Ashwaghanda**' in Sanskrit and as 'Indian Winter Cherry' in english. is an important medicinal herb in India. It is widely used in Indian systems of medicine as an adaptogen, nerve tonic, **anti-stress, memory enhancer and against cognitive deficits, insomnia, anxiety, infectious diseases, infertility, rheumatoid arthritis and gout over thousands of years**. Its formulations are mainly used in Unani and Ayurvedic system of medicine. Research reports based largely on preclinical studies as well as few clinical trials have **highlighted the neuroprotective role of Ashwagandha against many neurodegenerative diseases including Alzheimer's, Huntington's and Parkinson's disease**. The protective effects of Ashwagandha were accomplished by restoring mitochondrial and endothelial function, mitigation of apoptosis, inflammation and oxidative stress mechanisms
https://www.biorxiv.org/content/10.1101/2020.04.27.063107v1 *Withania somnifera* showed neuroprotective effect and increase longevity in *Drosophila* Alzheimer's disease model
In this study, *Drosophila* melanogaster AD model was used to study the effect of Ashwagandha on the toxicity of beta amyloid and also the longevity effect of the compound. **We found that 20 mg/mL of Ashwagandha was shown to be effective in rescuing the "rough eye phenotype" of AD *Drosophila***. Furthermore, **Ashwagandha also promotes longevity in AD as well as wild-type *Drosophila***. The results above showed that **Ashwagandha could potentially be a potent drug to treat AD as well as maintaining the wellbeing of cells**.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8529567/ Critical review of the *Withania somnifera* (L.) Dunal: ethnobotany, pharmacological efficacy, and commercialization significance in Africa
Withania somnifera (L.) Dunal (*W. somnifera*) is a herb commonly known by its English name as **Winter Cherry**. Africa is indigenous to many medicinal plants and natural products. However, there is inadequate documentation of medicinal plants, including *W. somnifera*, in Africa. Notably, the root extract of *W. somnifera* has been d**emonstrated to significantly reduce the level of Aβ-induced reactive oxygen species in N-SH neuron-like cells (Singh and Ramassamy 2017) and reverse cognitive impairments by ameliorating dendritic, axonal, and synaptic integrity in animal models of AD** (Uddin et al. 2019). Furthermore, the *W. somnifera* root extracts have shown **promising results in the aspects of cognitive and memory improvement in several preclinical studies of AD, including a pilot study in adults with mild-cognitive degeneration** (Choudhary et al. 2017a). **The protective mechanisms of *W. somnifera* root extract against AD pathology presumably involve binding of the extract–biochemically active constituents to the active motif of Aβ, thereby preclude Aβ fibril formation.**
https://pubmed.ncbi.nlm.nih.gov/22754076/ An overview on ashwagandha: a Rasayana (rejuvenator) of Ayurveda
Withania somnifera (Ashawagandha) is very revered herb of the Indian Ayurvedic system of medicine as a Rasayana (tonic). . It has a **Cognition Promoting Effect** and was useful in children with memory deficit and in **old age people loss of memory**. It was also found useful in **neurodegenerative diseases** such as Parkinson's, Huntington's and **Alzeimer's diseases**. . It has **GABA mimetic** effect and was shown to promote formation of dendrites. It has anxiolytic effect and improves energy levels and mitochondrial health. It is an **anti-inflammatory and anti-arthritic agent** and was found useful in clinical cases of Rheumatoid and Osteoarthritis. Ashwagandha is commonly available as a churna, a **fine sieved powder that can be mixed with water, ghee (clarified butter) or honey.** The Nagori Ashwagandha is the supreme among all Ashwagandha varieties. Maximum benefit appears when fresh Ashwagandha powder is used (Singh, 1983).
In patients with Alzheimer's disease, neuritic atrophy and synaptic loss (Dickon and Vicker, 2001) are considered the major causes of cognitive impairment, as based on the results of neuropathological post-mortem studies of the brain (Dekosky & Scheff, 1990). In the brains of patients suffering from other neurodegenerative diseases such as Parkinson's disease, Huntington's disease, and Creutzfeldt- Jakob disease, the atrophy of neurites has also been observed as a significant part of the etiology. There are dozens of studies that show that Ashwagandha slows, stops, reverses or removes neuritic atrophy and synaptic loss. Therefore Ashwagandha can be used to treat Alzheimer's, Parkinson's, Huntington's and other neurodegenerative diseases at any stage of the disease, even before a person has been diagnosed and is still in the state of mild forgetfulness, etc. Glycowithanolides withaferin- A and sitoindosides VII–X isolated from the roots of Ashwagandha significantly reversed ibotenic acid induced cognitive defects in Alzheimer's disease model (Bhattacharya et al., 1995)

GABA-mimetic effect on neurodegeneration and neuroregenerative potential

Behavioral experiments have lent support to the GABA-mimetic activity of Ashwagandha root extract. GABAergic neurodegeneration due to neuroleptic-induced excitotoxicity and oxidative stress is one of the etiopathological mechanisms in the pathophysiology of tardive dyskinesia (Gunne et al., 1993)
An intriguing study demonstrated that chronic oral administration of withanoside IV attenuated the axonal, dendritic and synaptic losses and memory deficits induced by amyloid peptide Aβ(25–35) in mice (Kuboyama et al, 2006). After oral administration in mice, withanoside IV was metabolized into sominone, which induced marked recovery in neurites and synapses and also enhanced axonal and dendritic outgrowth and synaptogenesis. These effects were maintained for at least 7 days after discontinuing withanoside IV administration. **These data suggest that withanoside IV, and its metabolite, sominone, may have clinical usefulness as antidementia drugs**
https://pubmed.ncbi.nlm.nih.gov/32305638/ Ashwagandha in brain disorders: A review of recent developments. 2020
Withania somnifera (Family: Solanaceae), commonly known as Ashwagandha or **Indian ginseng** is distributed widely in India, Nepal, China and Yemen. The roots of plant consist of active phytoconstituents mainly withanolides, alkaloids and sitoindosides and are conventionally used for the **treatment of multiple brain disorders**.
Identified neuroprotective phytoconstituents of Ashwagandha are sitoindosides VII-X, withaferin A, withanosides IV, withanols, withanolide A, withanolide B, anaferine, beta-sitosterol, withanolide D with key pharmacological effects in brain disorders mainly anxiety, **Alzheimer's**, Parkinson's, Schizophrenia, Huntington's disease, dyslexia, depression, autism, addiction, amyotrophic lateral sclerosis, attention deficit hyperactivity disorder and bipolar disorders. The literature survey does not highlight any toxic effects of Ashwagandha. Further, multiple available marketed products and patents recognized its beneficial role in various brain disorders; however, very few data is available on mechanistic pathway and clinical studies of Ashwagandha for various brain disorders is scarce and not promising.
https://pubmed.ncbi.nlm.nih.gov/24147038/ Ashwagandha (Withania somnifera) reverses β-amyloid1-42 induced toxicity in human neuronal cells: implications in HIV-associated neurocognitive disorders (HAND)
Alzheimer's disease (AD) is characterized by progressive dysfunction of memory and higher cognitive functions with abnormal accumulation of extracellular amyloid plaques and intracellular neurofibrillary tangles throughout cortical and limbic brain regions. At present no curative treatment is available, and research focuses on drugs for slowing disease progression or providing prophylaxis. Withania somnifera (WS) also known as 'ashwagandha' is used widely in Ayurvedic medicine as a **nerve tonic and memory enhancer**. However, there is a paucity of data on the potential neuroprotective effects of W.somnifera against β-Amyloid (1-42)-induced neuropathogenesis. In the present study, we have tested the neuroprotective effects of methanol:Chloroform (3:1) extract of ashwagandha against β-amyloid induced toxicity and HIV-1Ba-L (clade B) infection using a human neuronal SK-N-MC cell line.
https://pubmed.ncbi.nlm.nih.gov/32240781/ Neurodegenerative diseases and Withania somnifera (L.): An update
Withania somnifera (L.) Dunal also known as 'Ashwaghanda' in Sanskrit and as '**Indian Winter Cherry' in english**. is an important medicinal herb in India. It is widely used in Indian systems of medicine as an adaptogen, nerve tonic, **anti-stress, memory enhancer and against cognitive deficits**, insomnia, anxiety, infectious diseases, infertility, rheumatoid arthritis and gout over thousands of years. Although, the exact molecular pathogenesis of neurodegeneration due to the dysregulation of pro- and anti-oxidant mechanisms remains elusive; however, numerous potent anti-oxidants have demonstrated great potential in modifying disease phenotypes (Liu et al., 2017). Withania somnifera (L.) has **shown to prevent neurotoxic and neurodegenerative conditions by modulating the anti-oxidant mechanisms** (Dar et al., 2015). Comparative studies investigating the anti-oxidant potential of different natural product formulations containing Withania somnifera (L.) have shown the highest activity compared to other formulations and standard ascorbic acid.
https://www.alzheimers.net/ashwagandha-for-alzheimers. How Can Ashwagandha Fight Alzheimer's? 2013
Studies
Researchers at Newcastle University have found that it inhibits the formation of beta-amyloid plaques. These plaques, considered toxic to brain cells, accumulate in the brains of people with neurodegenerative diseases, such as Alzheimer's. Because the studies were conducted in test tubes, however, researchers emphasize that more testing is needed.
At the **National Brain Research Center (NBRC), scientists tested the herb on mice with Alzheimer's.** After 20 days of treatment cognitive performance of the mice **improved significantly**. At the end of 30 days, their brain function had returned to normal and the amyloid plaques that had been present in the mice's brains were reduced.
Moreover, the **study showed that rather than altering brain chemistry directly, ashwagandha boosts a protein in the liver**. This protein clears amyloid from the brain.
https://pubmed.ncbi.nlm.nih.gov/25803089/ Effect of Withania somnifera (Ashwagandha) root extract on amelioration of oxidative stress and autoantibodies production in collagen-induced arthritic rats 2015
Rheumatoid arthritis is an inflammatory autoimmune disorder. Withania somnifera Dunal (Solanaceae) (WS), is a common medicinal plant used in traditional systems of medicine for the treatment of arthritis, and **is an ingredient of anti-arthritic polyherbal formulations such as Habb-e-Asgand® and Arthritin™**. In the present study, we evaluated the antioxidant and anti-arthritic activity of aqueous extract of WS root (WSAq) in collagen-induced arthritic (CIA) rats.
Results: Treatment with WSAq resulted in a dose-dependent reduction in arthritic index, autoantibodies and CRP ($p < 0.05$) with maximum effect at dose of **300 mg/kg b. wt. and the results were comparable to that of MTX-treated rats.** Similarly, oxidative stress in CIA rats was ameliorated by treatment with different doses of WSAq, as evidenced by a **decrease in lipid peroxidation** and **glutathione-S-transferase activity and an increase in the glutathione content** and **ferric-reducing ability of plasma** ($p < 0.05$).
Conclusions: The results showed that WSAq exhibited antioxidant and anti-arthritic activity and reduced inflammation in CIA rats and suggests the potential use of this plant in the treatment of arthritis.
https://pubmed.ncbi.nlm.nih.gov/29846872/ Withania somnifera as a **Potential Anxiolytic and Anti-inflammatory Candidate** Against Systemic Lipopolysaccharide-Induced Neuroinflammation. 2018
activities. In Ayurveda, Ashwagandha (Withania somnifera) is well known for its **immunomodulatory properties.** The current study is an extension of our previous report on in vitro model system and was aimed to investigate **anti-neuroinflammatory potential of water extract from the Ashwagandha leaves (ASH-WEX)** against systemic LPS-induced neuroinflammation and associated behavioral impairments using in vivo rat model system. The current study provides first ever preclinical evidence and scientific validation that ASH-WEX exhibits the anti-neuroinflammatory potential against systemic LPS-induced neuroinflammation and ameliorates associated behavioral abnormalities. **Aqueous extract from Ashwagandha leaves and its active phytochemicals may prove to be promising candidates to prevent neuroinflammation associated with various neuropathologies.**
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6979308/ Adaptogenic and Anxiolytic Effects of Ashwagandha Root Extract in Healthy Adults: A Double-blind, Randomized, Placebo-controlled Clinical

Study 2019
In this **eight-week, prospective, randomized, double-blind, placebo-controlled study, the stress-relieving effect of Ashwagandha root extract** was investigated in stressed healthy adults. Sixty male and female participants with a baseline perceived stress scale (PSS) score >20 were randomized to receive capsules of Ashwagandha extract 125 mg, Ashwagandha extract 300 mg or identical placebo twice daily for eight weeks in a 1:1:1 ratio. Stress was assessed using PSS at baseline, four weeks and eight weeks.
A significant reduction in PSS scores was observed with Ashwagandha 250 mg/day ($P < 0.05$) and 600 mg/day ($P < 0.001$). Serum cortisol levels reduced with both Ashwagandha 250 mg/day ($P < 0.05$) and Ashwagandha 600 mg/day ($P < 0.0001$). **Compared to the placebo group participants, the participants receiving Ashwagandha had significant improvement in sleep quality.**
Conclusion Ashwagandha root aqueous extract was beneficial in reducing stress and anxiety.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3573577/ A Prospective, Randomized Double-Blind, Placebo-Controlled Study of Safety and Efficacy of a High-Concentration Full-Spectrum Extract of Ashwagandha Root in Reducing Stress and Anxiety in Adults 2012
A total of 64 subjects with a history of chronic stress were enrolled into the study after performing relevant clinical examinations and laboratory tests. These included a measurement of serum cortisol, and assessing their scores on standard stress-assessment questionnaires. They were randomized to either the placebo control group or the study drug treatment group, and were asked to take one capsule twice a day for a period of 60 days. In the study drug treatment group, each capsule contained 300 mg of high-concentration full-spectrum extract from the root of the Ashwagandha plant. The findings of this study **suggest that a high-concentration full-spectrum Ashwagandha root extract safely and effectively improves an individual's resistance towards stress** and thereby improves self-assessed quality of life.
https://genefitletics.com/2022/03/17/is-ashwagandha-anti-inflammatory-or-pro-inflammatory-role-of-our-gut/ Is Ashwagandha Anti-inflammatory or Pro-inflammatory? Role of our gut. 2022
It is not brainer- by now we know that our **gut microbiome**, which is home to 40 trillion microbes, has a brain of its own. Our **gut is not only regarded as a second brain** with its ability & competence to communicate via cellular messages across the body but also interacts with the food we eat to modify how our body responds to these foods. It is these gut microbiome-food interactions, which by the way are **unique for every individual**, that determine the level of inflammation in our body & whether a particular food is going to be beneficial or toxin.
Therefore, depending upon **gut microbiome-food interaction, foods, supplements or herbs which are considered to be healthy can trigger inflammation**, cause digestive discomfort, allergy, food intolerance, sensitivities, or even have minimal or no benefits at all.
There can be multiple reasons for this.
Populations of microorganisms & their diversity.
Imbalance in the gut can make it difficult to digest or convert many ingredients into beneficial compounds. Sometimes such imbalance can lead to release of harmful compounds that can trigger body wide inflammation & trigger multiple chronic health conditions.
It is clear, there is nothing called a standard health solution, food, herb or supplement. Nature has put beneficial medicine properties in many foods but whether we get those benefits or such properties create inflammation depends upon how our gut microbiome interacts with such foods. Besides, there are a number of foods with similar beneficial properties. This is where our system biology team suggest food or herbs based on an individual's unique microbiome which can offer more benefits than others.
It would be surprising to learn that ashwagandha can have a proinflammatory impact on your body & instead of relieving stress, it can trigger various other proinflammatory impacts such as fatigue, nasal inflammation, headache, sinus, chest pain & difficulty breathing. Have you ever wondered why? **Ashwagandha is a nightshade herb & people who have high histamine intolerance would find nightshade foods & herb in their avoid list. In such conditions, ashwagandha may be poisonous for their body.** In such situations, our clinical team would pick up & recommend other herbs such as **Lemon Balm & Rhodiola instead of Ashwagandha** which would have similar stress relieving impact.
https://naturalpulse.com/blogs/natural-pulse/anti-inflammatory-effects-of-black-seed-oil-and-ashwagandha . Anti-inflammatory Effects of Black Seed Oil and Ashwagandha 2022
While **black seed acts a natural anti-inflammatory**, **ashwagandha is also no slouch when it comes to moderating the inflammatory state** of the body. Due to its active compounds known as **withaferins**, several studies suggest that ashwagandha can target multiple inflammatory mechanisms in the body to reduce overall inflammation. Recent research has uncovered the ability of withaferins from ashwagandha to impact two primary signaling markers of inflammation in humans, nuclear factor kappa B (NF-κB) and nuclear factor erythroid 2 related factor 2 (Nrf2). These signaling molecules cause a downstream release of inflammatory proteins that serve to increase inflammation and oxidative stress throughout the body. By targeting these pathways specifically, ashwagandha suppresses the overall inflammatory state.
https://pubmed.ncbi.nlm.nih.gov/34204308/ Role of **Withaferin A** and Its Derivatives in the Management of Alzheimer's Disease: Recent Trends and Future Perspectives 2021
Withaferin A (WA) is a steroidal lactone glycowithanolides, a secondary metabolite with comprehensive biological effects. **Biosynthetically, it is derived from *Withania somnifera* (Ashwagandha)** and *Acnistus breviflorus* (Gallinero) through the mevalonate and non-mevalonate pathways. Mounting evidence shows that **WA possesses inhibitory activities against developing a pathological marker of Alzheimer's diseases**. Several cellular and animal models' particulates to AD have been conducted to assess the underlying protective effect of WA. In AD, the **neuroprotective potential of WA is mediated by reduction of beta-amyloid plaque aggregation, tau protein accumulation, regulation of heat shock proteins, and inhibition of oxidative and inflammatory constituents.** Despite the various preclinical studies on WA's therapeutic potentiality, less is known regarding its definite efficacy in humans for AD. Accordingly, the present study focuses on the biosynthesis of WA, the epidemiology and pathophysiology of AD, and finally the therapeutic potential of WA for the treatment and prevention of AD, highlighting the research and augmentation of new therapeutic approaches
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6190869/ Withaferin A Suppresses Beta Amyloid in APP Expressing Cells: Studies for Tat and Cocaine Associated Neurological Dysfunctions 2018
AD is one of the prominent neurodegenerative disease, and is characterized as a progressive impairment of memory and neurocognitive functions due to abnormal accumulation of extracellular **amyloid beta (Aβ)** and intracellular neurofibrillary tangles (NFTs; Dorszewska et al., 2016). Aβ aggregation is prominent in the cortical and limbic regions of the brain (Snider et al., 1983; Kurapati et al., 2013, 2014). Alternative or abnormal cleavage of integral membrane amyloid precursor protein (APP) by β and γ secretases (Ghosh et al., 2008; Guardia-Laguarta et al., 2010) lead to abnormal Aβ processing, resulting into insoluble Aβ aggregation (Zheng et al., 2002; Kretner et al., 2016). Aβ peptides then aggregate into extracellular insoluble senile plaques (Echeverria et al., 2004; Guardia-Laguarta et al., 2010; Ahyayauch et al., 2012). This Aβ accumulation leads to decreased neuronal health and stability, increased deterioration, synaptic depression (Venkitaramani et al., 2007; Palop and Mucke, 2010; Li et al., 2017), oxidative stress (Butterfield et al., 2013;
In summary, it is **critical to design and identify compounds that specifically target and inhibit Aβ secretion and aggregatio**n, and also the interaction between Aβ and HIV-Tat 1 and drug of abuse, against their synergistic role towards neurodegenerative disorders. When combined with other strategies targeting Aβ, including immunotherapy, these approaches might allow for a reduction, if not elimination, of Aβ-related toxicity. Further *in vivo* efficacy and drug delivery mechanistic studies are necessary to **explore WA's therapeutic role in neurological disorders like HIV associated neurocognitive disorders and Alzheimer's disease.**
https://pubmed.ncbi.nlm.nih.gov/26667305/ Ashwagandha attenuates TNF-α- and LPS-induced NF-κB activation and CCL2 and CCL5 gene expression in NRK-52E cells. 2015
Results: Elderberry water-soluble extract (WSE) was pro-inflammatory, while sutherlandia WSE only partially attenuated the TNF-α-induced changes in CCL5. However, **ashwaganda WSE completely prevented TNF-α-induced increases** in CCL5, while attenuating the increase in CCL2 expression and NF-κB activation. The same pattern of ashwagandha protection was seen using LPS as the pro-inflammatory stimuli. Conclusions: Taken together, these results demonstrate the ashwaganda WSE as a valid candidate for evaluation of therapeutic potential for the treatment of chronic renal dysfunction.
https://pubmed.ncbi.nlm.nih.gov/31991752/ Super Critical Fluid Extracted Fatty Acids from Withania somnifera Seeds Repair Psoriasis-Like Skin Lesions and Attenuate Pro-Inflammatory Cytokines (TNF-α and IL-6) Release 2020
Conclusion: Here we show that the fatty acids from W. somnifera seeds have **strong anti-inflammatory properties**, along with remarkable therapeutic potential on psoriasis-like skin etiologies.
https://pubmed.ncbi.nlm.nih.gov/31958022/ Neuroprotective Effect of Ashwagandha Extract against the Neurochemical Changes Induced in Rat Model of Hypothyroidism. 2021
The present data indicate that AE could prevent thyroid dysfunction and **reduce its complications on the nervous system including oxidative stress and neuroinflammation.**
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3214041/ Protective Role of Ashwagandha Leaf Extract and Its Component Withanone on Scopolamine-Induced Changes in the Brain and Brain-Derived Cells. 2021
Scopolamine is a well-known cholinergic antagonist that causes amnesia in human and animal models. Scopolamine-induced amnesia in rodent models has been widely used to understand the molecular, biochemical, behavioral changes, and to delineate therapeutic targets of memory impairment. Conclusion Our study suggested that besides cholinergic blockade, scopolamine-induced memory loss may be associated with oxidative stress and Ashwagandha i-Extract, and **withanone may serve as potential preventive and therapeutic agents for neurodegenerative disorders** and hence warrant further molecular analyses.
Bioavailability:
https://www.japtr.org/article.asp?issn=2231-4040;year=2015;volume=6;issue=4;spage=159;epage=164;aulast=Devkar;type=3 Evaluation of the bioavailability of major withanolides of *Withania somnifera* using an *in vitro* absorption model system 2015
Based on the present studies on the absorption characteristics of the tested **withanolides it may be concluded that WN A, WNN, 1,2 DWM and WN B were highly permeable**; whereas **WS IV, and WS V showed low permeable.** Surprisingly **WF A, the highly biologically active withanolide was found to be either impermeable or metabolized on passing through the cell layer**. It is likely that absorption of WFA *in vivo* is a complex process and possibly a system employing Caco-2 cells could provide better insight in the absorption characteristics of WF A.

Bacopa monnieri Herb, (Brahmi, Water Hyssop)

Supplement: 300-400 mg per day
https://www.alzheimersorganization.org/bacopa-monnieri-and-alzheimers Researchers have found that Bacopa monnieri has several abilities **which could treat Alzheimer's**. Similar to Salvia Officinalis, **Bacopa monnieri inhibits the harmful enzyme cholinesterase**. Bacopa monnieri also **reduces the formation of amyloid fibril**s and removes the amyloid fibrils which have already accumulated. Amyloid fibrils are clumps of abnormal materials that have built up in the brain. Amyloid fibrils are believed to be one of the major causes of Alzheimer's.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5448442/ Neurocognitive Effect of Nootropic Drug Brahmi (Bacopa monnieri) in Alzheimer's Disease 2017

The main role of EBm as an antioxidant appears to be due to its effect on increasing concentration of GSH and enzymatic antioxidants like SOD, CAT, and GPx and as free radical scavenging agent as illustrated in Figure Figure3.3. Hence, its administration in indicated doses **may act as a remedy for age-associated memory and cognitive decline in AD**.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3153866/ Effects of a Standardized Bacopa monnieri Extract on Cognitive Performance, Anxiety, and Depression in the Elderly: A Randomized, Double-Blind, Placebo-Controlled Trial 2008
Controlling for baseline cognitive deficit using the Blessed Orientation–Memory–Concentration test, Bacopa participants had enhanced AVLT delayed word recall memory scores relative to placebo. Stroop results were similarly significant, with the **Bacopa group improving and the placebo group unchanged**. CESD-10 depression scores, combined state plus trait anxiety scores, and heart rate decreased over time for the Bacopa group but increased for the placebo group. No effects were found on the DAT, WAIS digit task, mood, or blood pressure. The dose was well tolerated with few adverse events (Bacopa n = 9, placebo n = 10), primarily stomach upset.
https://pubmed.ncbi.nlm.nih.gov/31622587/ Brahmi (Bacopa monnieri): An ayurvedic herb against the Alzheimer's disease 2019
The neuroprotective properties of Brahmi and its bioactive components including **reduction of ROS, neuroinflammation, aggregation inhibition of Amyloid-β and improvement of cognitive and learning behaviour.** Here on basis of earlier studies we hypothesize the inhibitory role of Brahmi against Tau-mediated toxicity. The overall studies have concluded that Brahmi can be used as a lead formulation for treatment of Alzheimer's disease and other neurological disorders.
https://pubmed.ncbi.nlm.nih.gov/30604025/ Bacopa monnieri prevents colchicine-induced dementia by anti-inflammatory action 2019
On the other hand, BM supplementation was **able to improve cognitive functions, suppress Aβ formation by reducing BACE-1 activity. Inflammatory and oxidative stress markers were attenuated i**n the brain regions of BM supplemented animals. Taken together, the findings reveal that **BM reverses colchicine-induced dementia by its anti-inflammatory and anti-oxidant action** suggesting that it may be an effective therapeutic intervention to ameliorate progression of AD.
https://pubmed.ncbi.nlm.nih.gov/35612544/ Use of Bacopa monnieri in the Treatment of Dementia Due to Alzheimer Disease: Systematic Review of Randomized Controlled Trials 2022
There was no difference between B. monnieri and the placebo or donepezil in the treatment of Alzheimer disease based on very low certainty evidence. No major safety issues were reported in the included trials. Future randomized controlled trials should aim to recruit more participants and report clinically meaningful outcomes.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7484969/ *Bacopa monnieri* (L.) *wettst*. Extract protects against glutamate toxicity and increases the longevity of *Caenorhabditis elegans 2020*
In conclusion, ***B.monnieri* prevents mitochondrial, and oxidative stress in the cultured cells**. Furthermore, it can prolong the healthy lifespan of *C.elegans*, indicating that *B.monnieri* the potential for therapeutic and preventative use in neurodegenerative disease.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3153866/ Effects of a Standardized *Bacopa monnieri* Extract on Cognitive Performance, Anxiety, and Depression in the Elderly: A Randomized, Double-Blind, Placebo-Controlled Trial 2008
The study was a randomized, double-blind, placebo-controlled clinical trial with a placebo run-in of 6 weeks and a treatment period of 12 weeks. Fifty-four (54) participants, 65 or older (mean 73.5 years), without clinical signs of dementia, were recruited and randomized to *Bacopa* or placebo. Forty-eight (48) completed the study with 24 in each group. Standardized *B. monnieri* extract 300 mg/day or a similar placebo tablet orally for 12 weeks. Controlling for baseline cognitive deficit using the Blessed Orientation–Memory–Concentration test, ***Bacopa* participants had enhanced AVLT delayed word recall memory** scores relative to placebo. Stroop results were similarly significant, with the ***Bacopa* group improving** and the placebo group unchanged. CESD-10 depression scores, combined state plus trait anxiety scores, and heart rate decreased over time for the *Bacopa* group but increased for the placebo group. This study provides further **evidence that *B. monnieri* has potential for safely enhancing cognitive performance in the aging**.
https://link.springer.com/article/10.1007/s12035-022-03066-0 Discovery of Molecular Networks of Neuroprotection Conferred by *Brahmi* Extract in $A\beta_{42}$-Induced Toxicity Model of *Drosophila melanogaster* Using a Quantitative Proteomic Approach 2022
Accumulation of $A\beta_{42}$ peptides forming plaque in various regions of the brain is a hallmark of Alzheimer's disease (AD) progression. In the present study, we aimed to understand the **neuroprotective effects of the aqueous extract of *Bacopa monnieri*** and *Centella asiatica* (both commonly known as *Brahmi*) against the $A\beta_{42}$ expressing model of the *Drosophila melanogaster.* The *Brahmi* restored proteins were part of neuronal pathways associated with cell cycle re-entry, apoptosis, and mitochondrial dynamics. The neuroprotective effect of *Brahmi* was also validated by negative geotaxis behavioral analysis suggesting its protective role against behavioral deficits exerted by $A\beta_{42}$ toxicity. We believe that these discoveries will provide a platform for developing novel therapeutics for AD management by deciphering molecular targets of neuroprotection conferred by an aqueous extract of *Bacopa monnieri* or *Centella asiatica.*
https://journals.sagepub.com/doi/full/10.1177/1177392819866412 ***Bacopa monnieri*, a Neuroprotective Lead in Alzheimer Disease**: A Review on Its Properties, Mechanisms of Action, and Preclinical and Clinical Studies 2019
https://pubmed.ncbi.nlm.nih.gov/34010562/ Evolving Role of Natural Products from Traditional Medicinal Herbs in the Treatment of Alzheimer's Disease 2019
Brahmi, or Bacopa monnieri (Bm), is a perennial creeper medicinal plant found in the damp and marshy wetlands of Southern and Eastern India, Australia, Europe, Africa, Asia, and North and South America. In the Ayurvedic system of medicine, **Bm is recommended for mental stress, memory loss,** epilepsy, insomnia, and asthma [34,36]. The bioactive phytochemicals present in this plant include saponins, bacopasides III, IV, V, bacosides A and B, bacosaponins A, B, C, D, E, and F, alkaloids, sterols, betulic acid, polyphenols, and sulfhydryl compounds, which may be responsible for the neuroprotective roles of the plant.
https://pubmed.ncbi.nlm.nih.gov/17189676/ Bacopa monniera prevents from aluminium neurotoxicity in the cerebral cortex of rat brain 2007
The potential of Bacopa monniera extract to prevent aluminium neurotoxicity was reflected at the microscopic level as well, indicative of its neuroprotective effects. These findings strongly implicate that Bacopa monniera has potential to protect brain from oxidative damage resulting from aluminium toxicity.

Sixty healthy adults between 19 and 22 years from Government Medical College, Nagpur, India. Double-blind, randomized placebo-controlled no-crossover, parallel trial was employed	Bacopa extract, 150 mg, for 15 days	Significant improvement in memory test, neuropsychological tests (digit span memory task, paired associate task, logical memory test [story recall], memory span for nonsense syllables) and computerized tests (finger tapping test, simple reaction test, choice reaction test, choice discrimination test, and digit picture substitution test (symbol digit modalities test). Blood biochemistry showed significant elevation in serum calcium levels (still within normal range).	Kumar et al[41]
Ten subjects (mean age: 61.88 ± 6.69 years) from Germany with mild cognitive impairment.	Sideritis extract, 500 mg combined with Bacopa extract, 160 and 320 mg	*Sideritis* extract combined with *Bacopa* extract indicated better performances in d2-test test only contrasted with memory test and arithmetic calculation test (CPT). Quantitative EEG assessment revealed that *Sideritis* extract combined with *Bacopa* extract at lower dose (160 mg) increased the spectral power while combined with *Bacopa* extract at higher dose (320 mg) formed attenuation of all waves except for Delta in frontal-temporal brain areas, indicating massive differences between both extracts	Dimpfel et al[79]

Table 3. Summary of clinical studies of *Bacopa* extract in cognition.

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Participants/study design/geographical region	Intervention	Clinical outcome	References
Healthy children, 6-8 years from rural India. Double-blind, randomized placebo-controlled independent-group study was employed	One teaspoonful of *Bacopa* syrup 3 times daily for 3 months. (Each teaspoonful was equivalent to 350 mg of crude Brahmi.)	Strengthened exploratory drive (as measured by maze learning), improved perceptual images of patterns, and increased perceptual organization and reasoning ability (as measured by reaction time)	Sharma et al[83]
Healthy adults, between 18 and 60 years, in Swinburne University, Australia. A double-blind, placebo-controlled independent group design in which subjects were randomly allocated to 1 of 2 treatment conditions.	Bacopa extract, 300 mg daily, for 12 weeks	Significant improvement in speed of visual information processing measured by the IT task, learning rate, and memory consolidation measured by the AVLT ($P < .05$) and state anxiety ($P < .001$) compared to placebo, with maximal effects evident after 12 weeks.	Stough et al[84]
Healthy adults, between the ages of 40 and 65 years in University of Wollongong, Australia. Double-blind, randomized placebo-controlled independent group study was employed	Bacopa extract, 300 mg if subject <90 kg and 450 mg if >90 kg, for 12 weeks	Significant effect on a task requiring the retention of new information ($P < .05$) where the group who received the Brahmi retained more word pairs over the delay than the placebo group.	Roodenrys at al[81]
Healthy adults (mean age 73.5 years) in University of Catania, Italy. Double-blind, randomized placebo-controlled clinical trial with a placebo run-in of 6 weeks	Bacopa extract, 300 mg daily, for 12 weeks	Enhanced AVLT delayed word recall memory scores relative to placebo, significant improvement in stroop results ($P < .05$) and also decreased in CESD-10 depression scores over time, as well as decreased in combined state plus trait anxiety scores and heart attack.	Calabrese et al[33]
Healthy adults, between 18 and 60 years, in Swinburne University, Australia. A double-blind, placebo-controlled independent group design was employed	Bacopa extract, 300 mg daily, for 90 days	Significant improvement in working memory ($P = .035$), spatial working memory ($P = .0510$), and significant reduction ($P = .029$) in the amount of false alarms produced during RVIP task.	Stough at al[80]
Children requiring individual educational support, 10.5 years in Center for Research in Mental Retardation (CREMERE), Mumbai, India. The study was conducted as outpatient procedure in hospital settings with close monitoring.	Bacopa extract, 225 mg daily, for 16 weeks	Significant change in the baseline value of working memory and short-term verbal memory from 5.21 ± 0.32 to 6.38 ± 0.25 ($P \leqslant .05$) and 5.33 ± 0.44 to 6.54 ± 0.35 ($P \leqslant .05$). Significant improvement ($P < .05$) was also seen in logical memory, memory related to personal life and also in visual as well as auditory memory.	Usha et al[85]
Ninety eight healthy subjects, age ⩾ 55 years in Lismore, New South Wales, Australia. Double-blind, randomized placebo-controlled design was employed	Bacopa extract, 300 mg daily, for 12 weeks	Significantly enhanced the memory acquisition, verbal learning, and delayed recall measure by Rey Auditory Verbal Learning Test (AVLT); Trial a4 ($P = .000$), Trial a5 ($P = .016$); Trial a6 ($P = .000$); Trial a7 (delayed recall, $P = .001$); Total learning ($P = .011$) as well retroactive interference ($P = .048$). Scores including MAC-Q, TMT, and CFT improved the group differences and nevertheless were not significant	[82]
Sixty healthy adults, mean age: 62.62 ± 6.46 years (37 females and 23 males) in Thailand. Double-blind, randomized placebo-controlled design was employed	Bacopa extract, 300 mg or 600 mg daily, for 12 weeks	Treated extract group displayed an enhanced working memory as well a reduction in both P300 and N100 latencies. The plasma AChE activity suppression was also seen, which suggest that it could enhance the cognitive ability and working memory and improve attention	Peth-Nui et al[86]
Seventeen healthy volunteers (13 females and 4 males), mean age 25.23 ± 5.97 in Melbourne, Australia. Double-blind, placebo-controlled cross-over study was employed	Bacopa extract, 320 mg or 640 mg daily, 1 hour and 2 hour	Bacopa consumption showed a change from baseline score indicative of positive cognitive effects at first and second hour post consumption on the Stroop tasks as well Letter Search. It produced some nootropic and adaptogenic effects. Positive mod effects and reduction in cortisol levels (physiological stress response) were associated with Bacopa consumption by participants.	Benson et al[35]

Black Seed Oil **Thymoquinone** **(protective effect from aluminum chloride)**

- note has bio-availability problems

https://www.iosrjournals.org/iosr-jpbs/papers/Vol17-issue1/Ser-1/E1701013241.pdf Study Effectiveness and Stability Formulation Nanoemulsion of Black Cumin Seed (Nigella sativa L.) Essential Oil: A Review 2022

Conclusion: **Nanoemulsions** containing black cumin seed essential oil have been shown to increase drug solubility, **increase drug bioavailability**, stability and effectiveness of drug preparations.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6317145/pdf/main.pdf Neuroprotective efficacy of thymoquinone against amyloid beta-induced neurotoxicity in human induced pluripotent stem cell-derived cholinergic neurons 2019

The obtained results showed that Aβ1–42 caused cell death and apoptosis, which was efficiently attenuated by the co-treatment of TQ. Moreover, TQ restored the decrease in the intracellular antioxidant enzyme glutathione levels and inhibited the generation of reactive oxygen species induced by Aβ1–42 . Furthermore, using the fluorescent dye FM1–43 we demonstrated that TQ was able to reduce synaptic toxicity caused by Aβ1–42. Thus, the f**indings of our study suggest that TQ holds a neuroprotective potential and could be a promising therapeutic agent to reduce the risk of developing AD** and other disorders of the central nervous system.

Since AD atrophy results from the degeneration of synapses [45], in our final experiment, the results indicated that $A\beta_{1-42}$ caused a significant increase (6 fold) in the uptake of the fluorescent dye FM1−43 and therefore induced an increase in synaptic activity.

TNF Inhibitor:

https://en.m.wikipedia.org/wiki/TNF_inhibitor . Anti-TNF agents in nature

TNF or its effects are inhibited by several natural compounds, including **curcumin**[36][37][38][39] (a compound present in turmeric), and **catechins** (in green tea). **Cannabidiol**[40] and **Echinacea purpurea** also seem to have anti-inflammatory properties through inhibition of TNF-α production, although this effect may be mediated through cannabinoid CB1 or CB2 receptor-independent effects.[41] **5-HT2A receptor agonists** have also been shown to have potent inhibitory effects on TNF-α, including Psilocybin found in many species of mushrooms.[42][43]

Thymoquinone, a compound found in the flower **Nigella sativa,** has been studied for possible TNF-α inhibition and related benefits for autoimmune disorder treatment.[44][45][46][47]

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4549173/ **Thymoquinone inhibits TNF-α-induced inflammation** and cell adhesion in rheumatoid arthritis synovial fibroblasts by ASK1 regulation 2015

Evaluation of the signaling events showed that **TQ inhibited TNF-α-induced** phospho-p38 and phospho-JNK expression, but had no inhibitory effect on NF-κB pathway, in RA-FLS ($p<0.05$; n=4). Interestingly, we observed that selective **down-regulation of TNF-α-induced** phospho-p38 and phospho-JNK activation by TQ is elicited through inhibition of apoptosis-regulated signaling kinase 1 (ASK1).

https://www.sciencedirect.com/science/article/pii/S0753332220313500?via%3Dihub **Thymoquinone** in autoimmune diseases: Therapeutic potential and molecular mechanisms 2021

. Several anti-inflammatory, biologics, and AUD-modifying drugs are found effective against them, but their repeated use are associated with various adverse effects. In this review article, we have focused on the regulation of inflammatory molecules, molecular signaling pathways, immune cells, and epigenetics by natural product thymoquinone on AUDs. Studies indicate **that thymoquinone can regulate inflammatory molecules including interferons, interleukins, tumor necrosis factor-α (TNF-α), oxidative stress, regulatory T cells, and various signaling pathways such as nuclear factor kappa beta (NF-κβ), janus kinase/signal transduction and activator of transcription (JAK-STAT), mitogen-activated protein kinase (MAPK) at the molecular level and epigenetic alteration.**

https://pubmed.ncbi.nlm.nih.gov/34303824/ Thymoquinone: A small molecule from nature with high therapeutic potential. 2021

Thymoquinone (TQ; 2-isopropyl-5-methylbenzo-1, 4-quinone), the main active constituent of Nigella sativa, has been proven to have great therapeutic properties in numerous in vivo and in vitro models. Nevertheless, this molecule is not yet in clinical trials, largely because of its **poor bioavailability and hydrophobicity.** This review examines the different activities of TQ, as well as various combination therapies, nanotechnologies and clinical trials involving TQ. The **TQ nanoparticle formulation shows better bioavailability than free TQ,** and it is time for clinical trials of these formulations to realize the potential of TQ as a therapeutic.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5898665/ The Neuroprotective Effects of Thymoquinone: A Review

Thymoquinone may be considered as a therapeutic agent for the prevention of oral supplementation of chrysin (100 mg/kg body weight) to hyperammonemic rats, which considerably restored the levels of brain ammonia, water content, and the expressions of glutamine synthetase (GS), glial fibrillary acidic protein (GFAP), **tumor necrosis factor α (TNF-α),** interleukin (IL) 1β, IL-6, p65, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2).

https://pubmed.ncbi.nlm.nih.gov/32920292/ Thymoquinone administration ameliorates Alzheimer's disease-like phenotype by promoting cell survival in the hippocampus of amyloid $beta_{1-42}$ infused rat model 2020

Thymoquinone (TQ), a biologically active ingredient of Nigella sativa, has **anti-inflammatory, anti-oxidative and neuroprotective properties**. Therefore, it could be a good candidate in the recovery of Alzheimer`s disease (AD) pathology rather than current symptomatic reliefs. **Conclusion: TQ has the capacity to recover the neuropathology by removing Aβ plaques and by restoring neuron viability.** All might have established the molecular basement of the consolidation in the memory observed by means of TQ treatment.

https://pubmed.ncbi.nlm.nih.gov/35455405/ Thymoquinone: Review of Its Potential in the Treatment of Neurological Diseases 2022

Thymoquinone **(TQ) possesses anticonvulsant, antianxiety, antidepressant, and antipsychotic properties**. It could be utilized to treat drug misuse or dependence, and those with memory and cognitive impairment. TQ protects brain cells from oxidative stress, which is especially pronounced in memory-related regions. TQ exhibits antineurotoxin characteristics, implying its role in preventing neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease. TQ's antioxidant and anti-inflammatory properties p**rotect brain cells from damage and inflammation**. Glutamate can trigger cell death by causing mitochondrial malfunction and the formation of reactive oxygen species (ROS). Reduction in ROS production can explain TQ effects in neuroinflammation. TQ can help prevent glutamate-induced apoptosis by suppressing mitochondrial malfunction. Several studies have demonstrated TQ's role in inhibiting Toll-like receptors (TLRs) and some inflammatory mediators, leading to reduced inflammation and neurotoxicity.

https://pubmed.ncbi.nlm.nih.gov/29405769/ Thymoquinone alleviates the experimentally induced Alzheimer's disease inflammation by modulation of TLRs signaling 2018

Thymoquinone (TQ), the main active constituent of Nigella sativa oil, has been reported by several previous studies for its potent anti-inflammatory effect. The aim of this study is to elucidate the effect of TQ in improving learning and memory, using a rat model of AD induced by a combination of aluminum chloride ($AlCl_3$) and d-galactose (d-Gal). TQ was administered orally at doses of **10, 20, and 40 mg/kg/day** for 14 days after AD induction. TQ improved AD rat cognitive decline, decreased Aβ formation and accumulation, **significantly decreased TNF-α** and IL-1β at all levels of doses and significantly downregulated the expression of TLRs pathway components as well as their downstream effectors NF-κB and IRF-3 mRNAs at all levels of doses ($p < 0.05$). **We concluded that TQ reduced the inflammation** induced by d-Gal/$AlCl_3$ combination. It is therefore reasonable to assign the anti-inflammatory responses to the modulation of TLRs pathway

https://pubmed.ncbi.nlm.nih.gov/29464986/ Protective effects of thymoquinone on D-galactose and aluminum chloride induced neurotoxicity in rats: biochemical, histological and behavioral changes 2018

Our results indicate tha**t TQ prevents D-gal/$AlCl_3$-induced cognitive decline by enhancing cholinergic function** and synaptic plasticity as well as attenuation of oxidative damage, neuronal apoptosis, and neuroinflammation. These results indicate that **TQ holds potential for neuroprotection and may be a promising approach for the treatment of neurodegenerative disorders.**

https://pubmed.ncbi.nlm.nih.gov/36142148/ The Role of Thymoquinone in Inflammatory Response in Chronic Diseases

However, TQ has poor bioavailability and is **hydrophobic**, prohibiting clinical trials with TQ alone. Studies have explored the combination of TQ with **biological nanomaterials to improve its bioavailability**. The TQ nanoparticle formulation shows better bioavailability than free TQ, and these formulations are ready for clinical trials to determine their potential as therapeutic agents.

https://pubmed.ncbi.nlm.nih.gov/32003249/ Enhanced oral bioavailability and hepatoprotective activity of thymoquinone in the form of phospholipidic nano-constructs 2020

The poor biopharmaceutical properties of thymoquinone (TQ) obstruct its development as a hepatoprotective agent. T**o surmount the delivery challenges of TQ, phospholipid nanoconstructs (PNCs) were constructed.**

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5785894/ Chronic diseases, inflammation, and spices: how are they linked? 2018

Thymoquinone is isolated from black cumin *Nigella sativa)*. It has been shown to possess anti-inflammatory, anti-oxidant, and chemopreventive activities [129]. A recent report has depicted that this bioactive component inhibited IL-1β-induced inflammation via downregulating NF-κB and MAPKs signaling in human osteoarthritis chondrocytes [130]. It also prevented inflammation, neoangiogenesis, and vascular remodeling in asthma in vivo [131]. Thymoquinone also inhibited TNF-α-induced inflammation and cell adhesion in RA, thus making it a promising anti-inflammatory agent [132].

Blueberries (or juice, or extract) (see Anthocyanin)

https://pubmed.ncbi.nlm.nih.gov/28221821/ Enhanced neural activation with blueberry supplementation in mild cognitive impairment 2017

Methods: In a randomized, double-blind, placebo-controlled trial we performed pre- and post-intervention **functional magnetic resonance imaging during a working memory (WM) task to assess the effect of blueberry supplementation on blood oxygen level-dependent signal in older adults with mild cognitive impairment, a risk condition for dementia**. Results: Following daily supplementation for 16 weeks, blueberry-treated participants **exhibited increased activation in the left pre-central gyrus, left middle frontal gyrus, and left inferior parietal lobe during WM**

load conditions (corrected P < 0.01). There was **no clear indication of WM enhancement** associated with blueberry supplementation. Diet records indicated no between-group difference in anthocyanin consumption external to the intervention.
https://pubmed.ncbi.nlm.nih.gov/35458181/ Blueberry Supplementation in Midlife for Dementia Risk Reduction 2022
The demonstration of these benefits in middle-aged individuals with insulin resistance and SCD suggests that ongoing blueberry supplementation **may contribute to protection against cognitive decline when implemented early in at-risk individuals**.
https://pubmed.ncbi.nlm.nih.gov/34739938/ Anthocyanin-rich blueberry extracts and anthocyanin metabolite protocatechuic acid promote autophagy-lysosomal pathway and alleviate neurons damage in in vivo and in vitro models of Alzheimer's disease 2022
Neuron damage in morphology was reduced and the expression of autophagy-related proteins in APP/PS1 mice were promoted after BBE treatment. This study elucidated the mechanism of BBE for reducing neuronal damage by promoting neuronal autophagy and proved PCA may be the main bioactive metabolite of BBE for neuroprotective effects, providing a basis for dietary intervention in AD.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2850944/ Blueberry Supplementation Improves Memory in Older Adults 2010
We investigated the effects of daily consumption of wild blueberry juice in a sample of nine older adults with early memory changes. At 12 weeks, we observed **improved paired associate learning (p = 0.009) and word list recall (p = 0.04). In addition, there were trends suggesting reduced depressive symptoms (p = 0.08) and lower glucose levels** (p = 0.10). We also compared the memory performances of the blueberry subjects with a demographically-matched sample who consumed a berry placebo beverage in a companion trial of identical design and observed comparable results for paired associate learning.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7442370/ Recent Research on the Health Benefits of Blueberries and Their Anthocyanins 2020
Among the more important healthful aspects of **blueberries are their anti-inflammatory and antioxidant actions** and their beneficial effects on vascular and glucoregulatory function. Blueberries are one of the richest sources of anthocyanins among common fruits. In a study with high-fat–fed rats, blueberry intake moderated the negative effects of the high-fat diet on inflammation and insulin signaling and also led to modification of the gut microbiota. lower Parkinson disease risk was associated with the highest quintile of anthocyanin (RR: 0.76) and berry (RR: 0.77) intake (P = 0.02) (90). In a prospective analysis of 16,000 women in the Nurse's Health Study, **greater intake of blueberries and strawberries was associated with slower rates of cognitive decline in older adults, with an estimated delay in decline of about 2.5 y.** Inasmuch as anthocyanins are protective against CVD and T2DM risks, greater anthocyanin intake may be associated with reduced risk of Alzheimer-type dementia in late life. After 12 wk of blueberry consumption, greater brain activity was detected using magnetic resonance imaging in healthy older adults during a cognitive challenge. The detection was associated with enhanced perfusion in regions mediating cognitive function (98). Similarly, during a memory test, regional blood oxygen level-dependent activity detected by MRI (99) was enhanced in the subjects taking blueberry, but not in those taking placebo. All subjects in this study had mild cognitive impairment (99).
https://pubmed.ncbi.nlm.nih.gov/18052240/ Saskatoon and wild blueberries have higher anthocyanin contents than other Manitoba berries 2007
Saskatoon berry and blueberry (high anthocyanin berries), raspberry and chokecherry (medium anthocyanin berries), strawberry (low anthocyanin berries), and seabuckthorn (negligible anthocyanin berries).

Boswellia Serrata (does not affect TNF- α) (bio availability increases with high fat meal)

https://pubmed.ncbi.nlm.nih.gov/31041173/ Effect of Boswellia Serrata Extract on Acute Inflammatory Parameters and Tumor Necrosis Factor-α in Complete Freund's Adjuvant-Induced Animal Model of Rheumatoid Arthritis 2019
BSE at dose 180 mg/kg showed statistically significant improvement in body weight and decrease in ankle diameter and arthritic index ($P < 0.05$); however, there was insignificant change in paw volume ($P = 0.056$). This improvement was comparable with Indomethacin. The **level of TNF-α did not show any statistically significant change** ($P = 0.076$). Histopathological results also exhibited a reduction in inflammatory parameters.
https://pubmed.ncbi.nlm.nih.gov/34607104/ Mechanistic role of boswellic acids in Alzheimer's disease: Emphasis on anti-inflammatory properties 2021
The resin/gum of Boswellia species belonging to the family of Burseraceae is a naturally occurring mixture of bioactive compounds, which was traditionally used as a folk medicine to treat conditions like chronic inflammation. Several research studies have also explored its' therapeutic **potential against multiple neurodegenerative diseases such as Alzheimer's disease (AD).** The main chemical constituents of this gum include boswellic acids (BAs) like 3-O-acetyl-11-keto-β boswellic acid (AKBA) that possess potent anti-inflammatory and neuroprotective properties in AD. It is also involved in inhibiting the acetylcholinesterase (AChE) activity in the cholinergic pathway and improve choline levels as well as its binding with nicotinic receptors to produce anti-inflammatory effects. Multiple shreds of evidence have demonstrated that BAs modulate key molecular targets and signalling pathways like 5-lipoxygenase/cyclooxygenase, Nrf2, NF-kB, cholinergic, amyloid-beta (Aβ), and neurofibrillary tangles formation (NFTs) that are involved in AD progression.
https://pubmed.ncbi.nlm.nih.gov/34542667/ Potential therapeutic effects of boswellic acids/Boswellia serrata extract in the prevention and therapy of type 2 diabetes and Alzheimer's disease 2021
Boswellia serrata (B. serrata) is used traditionally to treat chronic inflammatory diseases such as type 2 diabetes (T2D), insulin resistance (IR), and **Alzheimer's disease (AD)**. This review aims to highlight current research on the potential use of boswellic acids (BAs)/B. serrata extract in T2D and AD. According to most of the authors, the potential therapeutic effects of BAs/B. serrata extract in T2D and AD can be attributed to **immunomodulatory, anti-inflammatory, antioxidant activity, and elimination of the senescent cells**. BAs/B. serrata extract may act by inhibiting the IκB kinase/nuclear transcription factor-κB (IKK/NF-κB) signaling pathway and increasing the formation of selective anti-inflammatory LOX-isoform modulators. In conclusion, BAs/B. serrata extract may have positive therapeutic effects in prevention and therapy of T2D and AD.
https://www.alzdiscovery.org/uploads/cognitive_vitality_media/Boswellia.pdf Boswellia
Neuroprotective Benefit: Boswellia may reduce inflammatory and oxidative stress-mediated damage in the brain, but benefits are tempered by **low bioavailability.**
https://pubmed.ncbi.nlm.nih.gov/15643550/ Effect of food intake on the bioavailability of boswellic acids from a herbal preparation in healthy volunteers 2004
Plasma levels of both acetyl-alpha-boswellic acid **(AalphaBA) and alphaBA became only detectable when administered with treatment B, i.e., the high-fat meal.**
https://pubmed.ncbi.nlm.nih.gov/23092618/ Enhanced absorption of boswellic acids by a lecithin delivery form (Phytosome(®)) of Boswellia extract 2013
We present here the results of a murine comparative **bioavailability** study of **Casperome™, a soy lecithin formulation of standardized B. serrata gum resin extract (BE),** and its corresponding non-formulated extract. This was accompanied by remarkably higher tissue levels. Of particular relevance was the **marked increase in brain concentration** of KBA and AKBA (35-fold) as well as βBA (3-fold) following Casperome™ administration.
https://pubmed.ncbi.nlm.nih.gov/27054914/ Survey on the Quality of the Top-Selling European and American Botanical Dietary Supplements Containing Boswellic Acids 2016
Special focus was also set on the statements made with regard to the frankincense applied.**Only five products out of seventeen disclosed all relevant information for the Boswellia extract, mentioning the species, the part of plant used, and the boswellic acid content.** Whereas all products but one claimed to use Boswellia serrata, three products did not mention the resin as the part applied and 10 products did not declare the boswellic acid content. Apart from the different boswellic acid composition determined with a sensitive LC/MS method, 41 % of the products did not comply with the label declaration. Hence, **one product from Italy did not contain any of the six characteristic boswellic acids (KBA, AKBA, αBA, βBA, AαBA, AβBA)** at all and another US product contained only traces, suggesting the absence of frankincense or the use of Boswellia frereana instead of B. serrata. In another product, the ratios of the individual boswellic acids were different from B. serrata gum resin, indicating the use of another species such as Boswellia sacra or Boswellia carterii. Furthermore, two products revealed different boswellic acid contents from those declared on the label. Further, two products did not declare the use of manipulated Boswellia gum resin extract being enriched in acetyl-11-keto-boswellic acid content reaching up to 66 %.
https://fullscript.com/ingredient/boswellia
Six major α and β-boswellic acids have been identified, including:
- 3-acetyl-11-keto-β-boswellic acid (AKBA)
- 11-keto-β-boswellic acid (KBA)
- α-boswellic acid (αBA)
- β-boswellic acid (βBA)
- 3-acetyl-α-boswellic acid (AαBA)
- 3-acetyl-β-boswellic acid (AβBA) (15)

Calcium (see also probiotics note about milk)

https://pubmed.ncbi.nlm.nih.gov/18082291/ Dietary intake adequacy and cognitive function in free-living active elderly: a cross-sectional and short-term prospective study 2008
Increased calcium consumption is related to improved cognitive function; the exact effect of n-3 fatty acids intake remains to be assessed.
https://pubmed.ncbi.nlm.nih.gov/28061328/ Calcium Hypothesis of Alzheimer's disease and brain aging: A framework for integrating new evidence into a comprehensive theory of pathogenesis 2017
This article updates the **Calcium Hypothesis of Alzheimer's disease** and brain aging on the basis of emerging evidence since 1994
https://pubmed.ncbi.nlm.nih.gov/26477700/ **Restoring calcium homeostasis to treat Alzheimer's** disease: a future perspective 2015
Alzheimer's disease (AD) is a neurodegenerative disorder that primarily compromises memory formation and storage. Several hypotheses regarding the pathogenesis of AD have been proposed; however, no cure is available to date. Here we describe the **calcium hypothesis of AD, which is gaining popularity.** We present data supporting this hypothesis and focus on a recently discovered calcium-signaling pathway that is dysregulated in AD and propose targets for the development of disease-modifying therapies.
https://pubmed.ncbi.nlm.nih.gov/19337829/ Dysregulation of calcium homeostasis in Alzheimer's disease 2009

The accumulation of oligomeric species of beta-amyloid protein in the brain is considered to be a key factor that causes Alzheimer's disease (AD). However, despite many years of research, the mechanism of neurotoxicity in AD remains obscure. Recent evidence strongly supports the **theory that Ca2+ dysregulation is involved in AD.**
https://www.medicalnewstoday.com/articles/315833 **Calcium imbalance** within brain cells may trigger Alzheimer's disease
In a healthy brain, calcium ions leave a neuron's mitochondria to prevent an excessive buildup. A transporter protein – called the mitochondrial sodium-calcium exchanger – enables this process.
In Alzheimer's-affected tissue, Jadiya and team found that the sodium-calcium exchanger levels were extremely low. In fact, the protein was so low that it was difficult to detect.
The researchers hypothesized that this would cause an overproduction of ROS, which would, in turn, contribute to neurodegeneration.
https://alzheimersnewstoday.com/news/alzheimers-study-suggests-high-calcium-levels-mitochondria-cause-neuronal-death/
Using brain samples from Alzheimer's patients, researchers observed very **low levels of mitochondrial sodium/calcium exchanger,** the protein that transports calcium out of the mitochondria in neurons. That deficiency means that **calcium ions are trapped inside the mitochondria after entering this organelle, where they begin to accumulate**.
The toxic increase in calcium inside the mitochondria disrupts the normal functioning of the mechanisms that produce energy, triggering excessive levels of oxidant molecules, which damage the mitochondria and neurons. Low levels of the transporter are therefore linked to increased mitochondrial impairment and cell death, contributing to neuronal loss in Alzheimer's.

Capsaicin

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5785894/ Chronic diseases, inflammation, and spices: how are they linked? 2018
capsaicin (trans-8-methyl-*N*-vanillyl-6-nonenamide) is a principal component of the spice red pepper (*Capsicum*) [100, 101]. It is highly efficacious in ameliorating several chronic diseases such as asthma, diabetes, cancers of breast, cervical, stomach, etc. via the inhibition of STAT3, NF-κB, PGE2, IL-6, TNF-α, etc. In vitro and in vivo studies also revealed that capsaicin ameliorated chronic diseases such as AD, skin inflammation, small cell lung cancer, etc. [111–114]

Carnitine (Acetyl-L-carnitine, see also carnosine)

https://ods.od.nih.gov/factsheets/carnitine-HealthProfessional/ Carnitine
Carnitine, derived from an amino acid, is found in nearly all cells of the body. **Carnitine plays a critical role in energy production.** It transports long-chain fatty acids into the mitochondria so they can be oxidized ("burned") to produce energy. It also transports the toxic compounds generated out of this cellular organelle to prevent their accumulation. Given these key functions, carnitine is concentrated in tissues like skeletal and cardiac muscle that utilize fatty acids as a dietary fuel [1,2]. **Carnitine occurs in two forms, known as D and L, that are mirror images (isomers) of each other. Only L-carnitine is active in the body and is the form found in food [1,6].** Animal products like meat, fish, poultry, and milk are the best sources. In general, the redder the meat, the higher its carnitine content. Rather than being metabolized, excess carnitine is excreted in the urine as needed via the kidneys to maintain stable blood concentrations. Research in aged rats found supplementation with high doses of **acetyl-L-carnitine and alpha-lipoic acid (an antioxidant) to reduce mitochondrial decay** [13-15]. The animals also moved about more and **improved their performance on memory-requiring tasks**. At present there are no equivalent studies of this kind in humans. However, a meta-analysis of double-blind, placebo-controlled studies suggests that supplements of acetyl-L-carnitine **may improve mental function and reduce deterioration in older adults with mild cognitive impairment and Alzheimer's disease** [16]. In these studies, subjects took **1.5–3.0 grams/day of acetyl-L-carnitine for 3–12** months. Carnitine interacts with pivalate-conjugated antibiotics such as pivampicillin that are used in the long-term prevention of urinary-tract infections [51]. Chronic administration of these antibiotics increases the excretion of pivaloyl-carnitine, which can lead to carnitine depletion. However, while tissue carnitine levels may become low enough to limit fatty acid oxidation, no cases of illness due to deficiency have been described [1,6].
https://pubmed.ncbi.nlm.nih.gov/12598816/ Meta-analysis of double blind randomized controlled clinical trials of acetyl-L-carnitine versus placebo in the treatment of mild cognitive impairment and mild Alzheimer's disease 2003
The **efficacy of acetyl-L-carnitine** (gamma-trimethyl- beta-acetylbutyrobetaine (Alcar) in mild cognitive impairment (MCI) and mild (early) Alzheimer's disease (AD) was investigated with a meta-analysis of **double-blind, placebo-controlled prospective, parallel group comparison studies of at least 3 months duration.** The duration of the studies was 3, 6 or 12 months and the daily dose varied between studies from 1.5-3.0 g/day. **Meta-analysis showed a significant advantage for Alcar compared to placebo for the integrated summary effect [ES =0.201**, 95% confidence interval (CI)=0.107-0.295] and CGI-CH (ES =0.32, 95% CI=0.18-0.47). The beneficial effects were seen on both the clinical scales and the psychometric tests. The advantage for Alcar was seen by the time of the first assessment at 3 months and increased over time. Alcar was well tolerated in all studies.
https://pubmed.ncbi.nlm.nih.gov/12804452/ Acetyl-L-carnitine for dementia 2003
Acetyl-l-carnitine (ALC) is derived from carnitine and is described as having several properties which may be beneficial in dementia. This includes activity at cholinergic neurons, membrane stabilization and enhancing mitochondrial function. Work on the effects of **ALC has been ongoing since the 1980s yet the efficacy of ALC in cognitive decline remains unclear. Early studies suggested a beneficial effect of ALC on cognition and behaviour in aging subjects. However, later, larger studies have not supported these findings**. Some of the difficulties lie in the early and later studies differing widely in methodology and assessment tools used, and are therefore difficult to compare. ALC is not currently in routine clinical use. **Reviewer's conclusions:** There is evidence for benefit of ALC on clinical global impression, but there was no evidence using objective assessments in any other area of outcome. Given the large number of comparisons made, the statistically significant result may be due to chance. At present there is no evidence to recommend its routine use in clinical practice. Although the intention of the review was to access ALC for the treatment of all dementias, the included trials had confined themselves to participants with Alzheimer's disease. Individual patient data may add to the findings, as would trials including other types of dementia and other outcomes (e.g. mood and caregiver quality of life). **However, the evidence does not suggest that ALC is likely to prove an important therapeutic agent.** More work on the pharmacokinetics of ALC in humans is also required.

Carotenoids (bright yellow, red and orange fruits and vegetables)

lutein (yellow-orange, Ex egg yolk, spinach, yellow carrots, yellow indian corn)

zeaxanthin (yellow, occurs widely with lutein, bell peppers, kiwifruit)

lycopene (red carotenoid pigment, ex tomatoes)

astaxanthin (red carotenoid pigment, found in wild salmon, trout, and some crustaceans – made by type of algae)

Beta-Carotene (provide 50% of vitamin A needed)

Bio availability of carotenoids increases when consumed with fat or cooked whole egg

Greater bio availability is available from supplements

RDI: 5-6mg (beta-carotene) (hard to achieve with fruits and vegs allow, recommend supplement)
https://pubmed.ncbi.nlm.nih.gov/8815648/ Daily intake of carotenoids (carotenes and xanthophylls) from total diet and the carotenoid content of selected vegetables and fuit 1996
The recommended daily intake is currently either 2 mg of beta-carotene (recommended by DGE, Germany, in addition to 1.0 (0.8) mg retinol-equivalents for vitamin A requirement) or **5-6 mg of beta-carotene (recommended by NCI, USA)**. The present studies were carried out to investigate to what extent a balanced diet prepared using household or cafeteria methods contributes to achieve the desired intake. Beta-carotene and other carotenoids in the total daily diet samples were determined by RP-HPLC. In addition to **beta-carotene, in decreasing quantity lutein, alpha-carotene, antheraxanthin, lycopene, zeaxanthin, neoxanthin, beta-cryptoxanthin, alpha-cryptoxanthin and violaxanthin were estimated.** The intake of beta-carotene (carotenoids) ranged from 0.2 to 9.7 mg/d (0.7-16.5 mg/d) with mean values (median) of 1.1 mg/d for beta-carotene and 3.9 mg/d for carotenoids based on results from investigations of 39 total daily diet samples. The **recommended daily intake can only be achieved by consuming (100-200 g/d) of vegetables und fruits with a particularly high carotenoid content**. Kale (34.8), red peppers (27.4), parsley (25.7), spinach (17.3), lamb's lettuce (16.0), carrots (15.8) and tomatoes (12.7) headed the list of vegetables with more than 10 mg/100 g. In the case of fruit, papayas (3.8), grapefruits (3.6), nectarines (2.9) and apricots (2.6) were pre-eminent with more than 2 mg/ 100 g.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5437154/?report=reader Editorial: Impact of Diet on Learning, Memory and Cognition 2017
Dietary intake of nutrients was compared between MCI patients and cognitively normal subjects. Carotenoids, **vitamin C**, and vitamin B6 were identified as the dietary nutrients with the highest protective capacity against MCI, potentially due to their antioxidant properties.
https://pubmed.ncbi.nlm.nih.gov/33184623/ Dietary carotenoids related to risk of incident Alzheimer dementia (AD) and brain AD neuropathology: a community-based cohort of older adults 2021
Among 927 participants from the Rush Memory and Aging Project who were free from AD at baseline and were followed up for a mean of 7 y, we estimated HRs for AD using Cox proportional hazards models by intakes of energy-adjusted carotenoids. Brain AD neuropathology was assessed in postmortem brain autopsies among 508 deceased participants. We used linear regression to assess the association of carotenoid intake with AD-related neuropathology.
Results: Higher intake of total carotenoids was associated with substantially lower hazard of AD after controlling for age, sex, education, ApoE-ε4, participation in cognitively stimulating activities, and physical activity level. Comparing the top and bottom quintiles (median intake: 24.8 compared with 6.7 mg/d) of total carotenoids, the multivariate HR (95% CI) was **0.52** (0.33, 0.81), P-trend < 0.01.

Conclusions: Our findings support a **beneficial role of total carotenoid consumption,** in particular **lutein/zeaxanthin**, on AD incidence that may be related to the inhibition of brain β-amyloid deposition and fibril formation.

https://pubmed.ncbi.nlm.nih.gov/24247062/ Serum lycopene, lutein and zeaxanthin, and the risk of Alzheimer's disease mortality in older adults 2014

A total of 6,958 participants aged older than 50 years were included in this study. We found that **high serum levels of lycopene and lutein+zeaxanthin at baseline were associated with a lower risk of AD mortality** after adjustment for potential covariates. The reduction in the mortality risk was progressively raised by increasing serum lycopene (HR = 0.26, 95% CI 0.10-0.69) and lutein+zeaxanthin (HR = 0.43, 95% CI 0.22-0.85) levels.

https://www.onedaymd.com/2022/06/eat-these-2-types-of-carotenoids-to.html Lutein and Zeaxanthin to Lower Dementia and Alzheimer's Risk? (2022 Study)

https://n.neurology.org/content/98/21/e2150 Association of Serum Antioxidant Vitamins and Carotenoids With Incident Alzheimer Disease and All-Cause Dementia Among US Adults 2022

This study provides Class II evidence that **incident all-cause dementia was inversely associated with serum lutein+zeaxanthin and β-cryptoxanthin levels**.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5540884/ Effects of Lutein/Zeaxanthin Supplementation on the Cognitive Function of Community Dwelling Older Adults: A Randomized, Double-Masked, Placebo-Controlled Trial 2017

Double-masked, randomized, placebo-controlled trial. A total of 62 older adults were randomized into groups receiving either 12 mg L+Z or a visually identical placebo. Participants receiving the active L+Z supplement had statistically significant increases in MPOD ($p < 0.03$) and improvements in complex attention ($p < 0.02$) and cognitive flexibility domains ($p < 0.04$), relative to participants taking the placebo. A trend was also seen for the executive function domain ($p = 0.073$). In male participants only, supplementation yielded improved composite memory ($p = 0.04$). **Conclusions: Supplementation with L+Z improved cognitive function in community-dwelling, older men and women.**

Lutein, a dietary antioxidant, could help maintain brain structure by lowering chronic oxidative stress (Erdman et al., 2015). The brain is also susceptible to damage due to chronic inflammation and **L and Z are known to be potent anti-inflammatories** (Kijlstra et al., 2012).

https://awakeningfromalzheimers.com/this-eye-supplement-puts-a-stop-to-alzheimers/ This "Eye Supplement" Puts a Stop to Alzheimer's

The daily formula is: lutein 10 mg, zeaxanthin 10 mg, meso-zeaxanthin 2 mg, DHA 500 mg, EPA 150 mg, natural vitamin E (D-alpha tocopherol) 15 mg.

For the new trial,

12 patients with Alzheimer's took a supplement containing xanthophyll carotenoids.

13 other Alzheimer's patients (two mild, ten moderate, and one severe) took the same formula together with fish oils and vitamin E.

A third group of 15 adults free of dementia acted as a control. They took the carotenoids only.

Eighteen months later, not only did blood carotenoid concentrations rise in the fish oil/vitamin E group, but – apart from one patient who went downhill – **caregivers of the Alzheimer's patients reported improved sight, memory and mood.** The patients maintained cognitive abilities and quality of life far beyond those taking carotenoids alone.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8868069/ Serum Lutein and Zeaxanthin Are Inversely Associated with High-Sensitivity C-Reactive Protein in Non-Smokers: The Mikkabi Study 2022

Recent randomized controlled trials have demonstrated a protective **association between carotenoids and inflammation**; however, the basis of this association on lifestyle factors remains unclear. This study aimed to clarify the associations between carotenoids and inflammatory markers stratified by lifestyle factors, using baseline data from the Mikkabi Study. Serum carotenoid and high-sensitivity C-reactive protein (hs-CRP) levels were measured. **The inverse association between lutein and a high hs-CRP level was significant in non-smokers (OR: 0.41; 95% CI: 0.22–0.76) but not in smokers.**

https://www.cambridge.org/core/journals/public-health-nutrition/article/dietary-lutein-and-zeaxanthin-are-associated-with-working-memory-in-an-older-population/FEC8D9DC9C7C665612045FE26A41CF7C Dietary lutein and zeaxanthin are associated with working memory in an older population 2020

The purpose of the study was to examine the association between dietary lutein and zeaxanthin (L + Z) intake and immediate word recall (IWR) and delayed word recall (DWR), and to identify the major contributors to dietary L + Z intake in a recent and representative sample of the older US population. The analytic sample included 6390 respondents aged ≥50 years. L + Z intake was 2·44 ± 2·32 mg/d on average, and L + Z intake differed significantly across quartiles (P < 0·001). For example, average L + Z intake in Q1 was 0·74 ± 0·23 mg/d and in Q4 was 5·46 ± 2·88 mg/d. In covariate adjusted models, older adults in the highest quartiles of L + Z intake had significantly greater IWR and DWR scores than those in the lowest quartile. **Leafy vegetables, cruciferous vegetables, dark yellow vegetables, fish and seafood, legumes, eggs and fruit were significant and meaningful predictors of dietary L + Z intake.**

Conclusion: A high consumption of vegetables, fish and seafood, legumes, eggs and fruit is associated with a higher intake of L + Z and greater word recall among older adults.

https://hrbopenresearch.org/articles/2-8 Lutein and zeaxanthin: The possible contribution, mechanisms of action and implications of modern dietary intake for cognitive development in children.

The literature search revealed that the evidence concerning the effect of lutein and zeaxanthin on cognition in children is sparse. However, there is some **preliminary evidence indicating a positive association between lutein and zeaxanthin and cognition in childhood**.

https://academic.oup.com/ajcn/article/96/5/1161S/4577088?login=false A possible role for lutein and zeaxanthin in cognitive function in the elderly 2012

Among the carotenoids, **lutein and zeaxanthin are the only two that cross the blood-retina barrier** to form macular pigment (MP) in the eye. They also preferentially accumulate in the human brain. Lutein and zeaxanthin in macula from nonhuman primates were found to be **significantly correlated with their concentrations in matched brain tissue**. Therefore, **MP can be used as a biomarker of lutein and zeaxanthin in primate brain tissue**. This is of interest given that a **significant correlation was found between MP density and global cognitive function in healthy older adults**. In univariate analyses, **lutein was related to recall and verbal fluency**, but the strength of the associations was attenuated with adjustment for covariates. However, **lutein concentrations in the brain were significantly lower in individuals with mild cognitive impairment than in those with normal cognitive function**. Last, in a 4-mo, double-blinded, placebo-controlled trial in older women that involved lutein supplementation **(12 mg/d), alone or in combination with DHA (800 mg/d), verbal fluency scores improved significantly in the DHA, lutein, and combined-treatment groups.** Memory scores and rate of learning improved significantly in the combined-treatment group, who also showed a trend toward more efficient learning.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3967172/ Increases in Plasma Lutein through Supplementation Are Correlated with Increases in Physical Activity and Reductions in Sedentary Time in Older Adults 2014

Thirty-nine participants competed the study (Lutein = 19, Placebo = 20). **Lutein increased plasma lutein concentrations compared with placebo** Lutein increased plasma lutein, which was associated with **increased physical activity** and reduced sedentary time in older adults.

https://pubmed.ncbi.nlm.nih.gov/36093704/ Supplementation With Carotenoids, Omega-3 Fatty Acids, and Vitamin E Has a Positive Effect on the Symptoms and Progression of Alzheimer's Disease 2022

Patients with mild-moderate AD consumed daily **1 g fish oil (of which 500 mg DHA, 150 mg EPA), 22 mg carotenoids (10 mg lutein, 10 mg meso-zeaxanthin, 2 mg zeaxanthin), and 15 mg vitamin E or placebo for 12 months** in a double-blind, placebo-controlled, randomized clinical trial. Following 12 months of supplementation, the active group (n = 50) compared to the placebo group (n = 27), demonstrated **statistically significant improvements in skin carotenoid measurements, blood carotenoids, ω-3FAs, and vitamin E concentrations (p < 0.05, for all). The active group also performed better in objective measures of AD severity** (i.e., memory and mood), with a statistically significant difference reported in the clinical collateral for memory (p < 0.001).

https://pubmed.ncbi.nlm.nih.gov/34999335/ Omega-3 fatty acid, carotenoid and vitamin E supplementation improves working memory in older adults: A randomised clinical trial 2022

Cognitively healthy individuals aged ≥65 years consumed daily **1 g fish oil (of which 430 mg docosahexaenoic acid, 90 mg eicosapentaenoic acid), 22 mg carotenoids (10 mg lutein, 10 mg meso-zeaxanthin, 2 mg zeaxanthin) and 15 mg vitamin E or placebo** for 24 months in a double-blind, placebo-controlled, randomised clinical trial. Following 24-month supplementation, individuals in the active group (n = 30; aged 69.03 ± 4.41 years; 56.7% female) recorded **significantly fewer errors in working memory tasks than individuals receiving placebo**. These results support a biologically plausible rationale whereby these nutrients work synergistically, and in a dose-dependent manner, to improve working memory in cognitively healthy older adults. Increasing nutritional intake of carotenoids and ω-3FAs may prove beneficial in reducing cognitive decline and dementia risk in later life.

https://pubmed.ncbi.nlm.nih.gov/29945352/ Nutritional Intervention to Prevent Alzheimer's Disease: Potential Benefits of Xanthophyll Carotenoids and Omega-3 Fatty Acids Combined 2018

Three trial experiments were performed. In Trials 1 and 2 (performed on patients with AD over an 18-month period), 12 patients (AD status at baseline: 4 mild and 8 moderate) were supplemented with a xanthophyll carotenoid only formulation (Formulation 1; lutein:meso-zeaxanthin:zeaxanthin 10:10:2 mg/day) and 13 patients (AD status at baseline: 2 mild, 10 moderate, and 1 severe) were supplemented with a xanthophyll carotenoid and fish oil combination (Formulation 2; lutein:meso-zeaxanthin:zeaxanthin 10:10:2 mg/day plus 1 g/day of fish oil containing 430 mg docohexaenoic acid [DHA] and 90 mg eicopentaenoic acid [EPA]), respectively. In Trial 3, 15 subjects free of AD (the control group) were supplemented for 6 months with Formulation 1. Blood xanthophyll carotenoid response was measured in all trials by HPLC. Omega-3 fatty acids were profiled by direct infusion mass spectrometry.

This preliminary report suggests **positive outcomes for patients with AD who consumed a combination of xanthophyll carotenoids plus fish oil,** but further study is required to confirm this important observation.

https://pubmed.ncbi.nlm.nih.gov/25408222/ The impact of supplemental macular carotenoids in Alzheimer's disease: a randomized clinical trial 2015

A randomized, double-blind clinical trial with placebo and active arms. 31 AD patients and 31 age-similar control subjects were supplemented for six months with either Macushield (10 mg meso-zeaxanthin [MZ]; 10 mg lutein [L]; 2 mg zeaxanthin [Z]) or placebo (sunflower oil). **Supplementation with the macular carotenoids (MZ, Z, and L) benefits patients with AD**, in terms of clinically meaningful improvements in visual function and in terms of MP augmentation.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5651431/ Serum concentrations of vitamin E and carotenoids are altered in Alzheimer's disease: A case-control study 2017

Serum concentrations of retinol, two forms of **vitamin E (α- and γ-tocopherol)** and six carotenoids were quantified by high-performance liquid chromatography from patients with AD. Serum levels of **α-tocopherol and all six carotenoids were significantly lower** in patients with AD compared with cognitively intact controls ($P < .001$). **In contrast, γ-tocopherol was significantly higher in the serum of patients with AD**

https://pubmed.ncbi.nlm.nih.gov/35701477/ The combined effect of physical activity and fruit and vegetable intake on decreasing cognitive decline in older Taiwanese adults 2022

Trends in cognitive decline were observed over 16 years. The **risk of cognitive decline decreased by 63% when high physical activity and high fruit and vegetable intake were combined** (odds ratio 0.37; 95% confidence interval 0.23-0.59), indicating a potential combined effect of physical activity and fruit and vegetable intake on mitigating cognitive decline. These personal actions are safe, effective, and economical approaches to health promotion and disease prevention.

https://pubmed.ncbi.nlm.nih.gov/33575874/ Ameliorative effects of **astaxanthin** on brain tissues of alzheimer's disease-like model: cross talk between neuronal-specific microRNA-124 and related pathways 2021

Astaxanthin (ATX), a second-generation antioxidant, is a dark red carotenoid and exhibits the **highest antioxidant capacity, anti-inflammatory, neuroprotective, and antiapoptotic effects**. In this study, we investigated the therapeutic effect of different doses of ATX on the cerebral cortex and hippocampus of AD-like rats. The results indicated that ATX significantly and dose-dependently

improved the performance of AD-like rats treated with ATX during MWM and suppress the accumulation of amyloid β_{1-42} and malondialdehyde. Also, significantly inhibit acetylcholinesterase and monoamine oxidase activities and the expression of β-site amyloid precursor protein cleaving enzyme 1 (BACE 1). ATX also significantly **elevated the content of acetylcholine, serotonin,** and nuclear factor erythroid-2-related factor 2 (Nrf2) and miRNA-124 expression. The effect of ATX treatment was confirmed by histopathological observations using H&E stain and morphometric tissue analysis. From this study, we c**oncluded that ATX may be a promising therapeutic agent for AD through targeting different pathogenic pathways.**

https://pubmed.ncbi.nlm.nih.gov/30463045/ Neuroprotective role of **astaxanthin** in hippocampal insulin resistance induced by Aβ peptides in animal model of Alzheimer's disease 2019

Astaxanthin (ASX) is xanthophyll carotenoid which has previously demonstrated significant antidiabetic and **neuroprotective actions**. Our study concludes p**reventive action of Astaxanthin against hippocampal insulin resistance and Alzheimer's disease** complications, supporting potential role of hippocampal insulin resistance targeting against AD.

https://pubmed.ncbi.nlm.nih.gov/30649596/ Beta-carotene, telomerase activity and Alzheimer's disease in old age subjects 2019

Conclusion: Our data show that β-carotene may modulate telomerase activity in old age. Moreover, **lower plasma β-carotene levels, correlating with peripheral telomerase activity, are associated with AD** diagnosis independent of multiple covariates.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5437154/?report=reader Editorial: Impact of Diet on Learning, Memory and Cognition 2017

P**oor diet is a potential risk factor for the development of cognitive impairment;** conversely, dietary nutrients are protective against such impairments. Lu et al. reported a cross-sectional study which examined the impact of dietary nutrients on the development of mild cognitive impairment (MCI). Dietary intake of nutrients was compared between MCI patients and cognitively normal subjects. **Carotenoids, vitamin C, and vitamin B6 were identified as the dietary nutrients with the highest protective** capacity against MCI, potentially due to their antioxidant properties. Moreover, **adequate dietary intake of monounsaturated fatty acids and cholesterol were significantly associated with decreased risk of MCI**.

https://pubmed.ncbi.nlm.nih.gov/17122107/ Dose-ranging study of lutein supplementation in persons aged 60 years or older 2006

Conclusions: I**ncreasing doses of lutein supplements significantly increased the serum levels of lutein and zeaxanthin, and doses up to 10 mg were safely administered.** A long-term large clinical trial is necessary to investigate the safety and efficacy of lutein in reducing the risk of the development of advanced AMD.

Bio Availability

https://pubmed.ncbi.nlm.nih.gov/15277161/ Carotenoid bioavailability is higher from salads ingested with full-fat than with fat-reduced salad dressings as measured with electrochemical detection 2004

Essentially no absorption of carotenoids was observed when salads with fat-free salad dressing were consumed. **A substantially greater absorption of carotenoids was observed when salads were consumed with full-fat than with reduced-fat salad dressing.**

https://pubmed.ncbi.nlm.nih.gov/26016861/ Effects of egg consumption on carotenoid absorption from co-consumed, raw vegetables 2015

Dietary lipids are one of the most effective stimulators of carotenoid absorption, but very limited data exist on the impact of endogenous food sources of lipids to enhance carotenoid absorption. The co-consumption of whole egg with carotenoid-rich foods may increase overall carotenoid absorption via lipid-rich egg yolk. The TRL AUC(0-10h) of lutein and zeaxanthin increased 4-5-fold ($P < 0.001$), and the TRL AUC(0-10h) of carotenoid not present in eggs, including **α-carotene, β-carotene, and lycopene, increased 3-8-fold** ($P < 0.01$) for the HE meal compared with the control meal.

Conclusion: **These findings support the claim that co-consuming cooked whole eggs is an effective way to enhance carotenoid absorption from other carotenoid-rich foods such as a raw mixed-vegetable salad.**

https://pubmed.ncbi.nlm.nih.gov/10702576/ Dietary factors that affect the bioavailability of carotenoids 2000

The bioavailability of beta-carotene from vegetables in particular has been shown to be low (14% from mixed vegetables) compared with that of purified beta-carotene added to a simple matrix (e.g., salad dressing), whereas for lutein, the difference is much smaller (relative bioavailability of 67% from mixed vegetables). **Processing, such as mechanical homogenization or heat treatment, has the potential to enhance the bioavailability of carotenoids from vegetables (from 18% to a sixfold increase).** The amount of **dietary fat required to ensure carotenoid absorption seems low** (approximately 3-5 g per meal), although it depends on the physicochemical characteristics of the carotenoids ingested. Unabsorbable, fat-soluble compounds reduce carotenoid absorption, and interaction among carotenoids may also result in a reduced carotenoid bioavailability.

Bioavailability of Carotenoids from Vegetables 2000

There is a perception that carotenoids are destroyed by the heat process involved in cooking of vegetables. In fact, carotenoid loss is minimal with moderate cooking, and in many cases, **carotenoids become more bioavailable after cooking**, probably because heat processing liberates them from cell matrices. **Dietary fat is clearly required for optimal absorption of carotenoids**. **β-Carotene is more bioavailable from supplements** (typically supplied as absorption-enhancing beadlets or in oil) than from whole foods.

Carnosine-Anserine (anti-oxidate, see -zinc, copper -chelating)(neuroprotectic agent for ischemic stroke)

Anserine is a derivative of carnosine

Source: only found in animals Beef(372mg/100g), ChickenBreast(290mg/100g), Pork(276mg/100g), TurkeyBreast(240mg/100g)

Supplement: 750 mg of anserine and 250 mg of carnosine per day (

https://pubmed.ncbi.nlm.nih.gov/34203479/ Carnosine, Small but Mighty-Prospect of Use as Functional Ingredient for Functional Food Formulation 2021

Carnosine is a **dipeptide synthesized in the body from β-alanine and L-histidine**. It is **found in high concentrations in the brain,** muscle, and gastrointestinal tissues of humans and is present in all vertebrates. Carnosine has a number of **beneficial antioxidant properties**. For example, carnosine scavenges reactive oxygen species (ROS) as well as alpha-beta unsaturated aldehydes created by peroxidation of fatty acid cell membranes during oxidative stress. Carnosine can oppose glycation, and it can **chelate divalent metal ions**. Carnosine alleviates diabetic nephropathy by protecting podocyte and mesangial cells, and can **slow down aging**. Carnosine is **widely used among athletes** in the form of supplements

https://pubmed.ncbi.nlm.nih.gov/17522447/ Could carnosine or related structures suppress Alzheimer's disease? 2007

Reactive oxygen species, reactive **nitrogen species, copper and zinc ions,** glycating agents and reactive aldehydes, protein cross-linking and proteolytic dysfunction **may all contribute to Alzheimer's disease (AD). Carnosine (beta-alanyl-L-histidine) is a naturally-occurring, pluripotent, homeostatic agent.** These observations suggest that **carnosine and related structures should be explored for therapeutic potential towards AD and other neurodegenerative disorders.**

https://pubmed.ncbi.nlm.nih.gov/35630780/ Unveiling the Hidden Therapeutic Potential of Carnosine, a Molecule with a Multimodal Mechanism of Action: A Position Paper 2022

Carnosine (β-alanyl-L-histidine) is a naturally occurring endogenous dipeptide and an over-the-counter food supplement with a well-demonstrated multimodal mechanism of action that includes the detoxification of reactive oxygen and nitrogen species, the **down-regulation of the production of pro-inflammatory mediators**, the inhibition of aberrant protein formation, and the modulation of cells in the peripheral (macrophages) and brain (microglia) immune systems.

https://pubmed.ncbi.nlm.nih.gov/33926064/ Carnosine Protects Macrophages against the Toxicity of Aβ1-42 Oligomers by Decreasing Oxidative Stress 2021

Carnosine (β-alanyl-L-histidine) is a naturally occurring endogenous peptide widely distributed in excitable tissues such as the brain. This dipeptide has well-known **antioxidant, anti-inflammatory, and anti-aggregation** activities, and it may be useful for **treatment of neurodegenerative disorders such as Alzheimer's disease (AD)**. In this disease, peripheral infiltrating macrophages play a substantial role in the clearance of amyloid beta (Aβ) peptides from the brain. Correspondingly, in patients suffering from AD, defects in the capacity of peripheral macrophages to engulf Aβ have been reported.

https://pubmed.ncbi.nlm.nih.gov/21423579/ Effects of dietary supplementation of carnosine on mitochondrial dysfunction, amyloid pathology, and cognitive deficits in 3xTg-AD mice 2011

The pathogenic road map leading to Alzheimer's disease (AD) is still not completely understood; however, a large body of studies in the last few years supports the idea that beside the classic hallmarks of the disease, namely the accumulation of amyloid-β (Aβ) and neurofibrillary tangles, other factors significantly contribute to the initiation and the progression of the disease. Among them, mitochondria failure, an unbalanced neuronal redox state, and the **dyshomeostasis of endogenous metals like copper, iron, and zinc have all been reported to play an important role in exacerbating AD pathology.** Given these factors, the **endogenous peptide carnosine may be potentially beneficial in the treatment of AD because of its free-radical scavenger and metal chelating properties. Principal findings:** We found that carnosine supplementation in 3xTg-AD mice **promotes a strong reduction in the hippocampal intraneuronal accumulation of Aβ and completely rescues AD and aging-related mitochondrial dysfunctions**. No effects were found on tau pathology and we only observed a trend toward the amelioration of cognitive deficits.

Conclusions and significance: Our data indicate that carnosine can be part of a combined therapeutic approach for the treatment of AD.

https://pubmed.ncbi.nlm.nih.gov/36105613/ Effects of zinc and carnosine on aggregation kinetics of Amyloid-β40 peptide 2022

The accumulation and amyloid **formation of amyloid-β (Aβ) peptides is closely associated with the pathology of Alzheimer's disease**. The physiological environment wherein Aβ aggregation happens is crowded with a large variety of metal ions including Zn2+. In this study, we investigated the role of Zn2+ in regulating the aggregation kinetics of Aβ40 peptide. Our results show that Zn2+ can shift a typical single sigmoidal aggregation kinetics of Aβ40 to a biphasic aggregation process. Zn2+ aids in initiating the rapid self-assembly of monomers to form oligomeric intermediates, which further grow into amyloid fibrils in the first aggregation phase. The presence of Zn2+ also retards the appearance of the second aggregation phase in a concentration dependent manner. In addition, our results show that a natural dipeptide, carnosine, can greatly alleviate the effect of Zn2+ on Aβ aggregation kinetics, most likely by coordinating with the metal ion to form chelates. **These results suggest a potential in vivo protective effect of carnosine against the cytotoxicity of Aβ by suppressing Zn2+-induced rapid formation of Aβ oligomers.**

https://pubmed.ncbi.nlm.nih.gov/30036471/ Carnosine-LVFFARK-NH_2 Conjugate: A Moderate Chelator but Potent Inhibitor of Cu^{2+}-Mediated Amyloid β-Protein Aggregation 2018

Aggregation of amyloid-β (Aβ) protein stimulated by Cu^{2+} has been recognized as a crucial step in the neurodegenerative process of Alzheimer's disease. Hence, it is of significance to develop bifunctional agents capable of inhibiting Aβ aggregation as well as Cu^{2+}-mediated Aβ toxicity. Herein, a novel bifunctional nonapeptide, carnosine-LVFFARK-NH_2 (Car-LK7), was proposed by integrating native chelator carnosine (Car) and an Aβ aggregation inhibitor, Ac-LVFFARK-NH_2 (LK7). Results revealed the bifunctionality of Car-LK7, including remarkably enhanced inhibition capability on Aβ aggregation as compared to LK7 and a moderate Cu^{2+} chelating affinity (K_D = 28.2 ± 2.1 μM) in comparison to the binding affinity for $Aβ_{40}$ (K_D = 1.02 ± 0.13 μM).

https://pubmed.ncbi.nlm.nih.gov/34948299/ Ionophore Ability of Carnosine and Its Trehalose Conjugate Assists Copper Signal in Triggering Brain-Derived Neurotrophic Factor and Vascular Endothelial Growth Factor Activation In Vitro 2021

l-carnosine (β-alanyl-l-histidine) (Car hereafter) is a natural dipeptide widely distributed in mammalian tissues and **reaching high concentrations (0.7-2.0 mM) in the brain**. The molecular features of the dipeptide underlie the **antioxidant, anti-aggregating and metal chelating ability** showed in a large number of physiological effects, while the biological mechanisms involved in the protective role found against several diseases cannot be explained on the basis of the above-mentioned properties alone, requiring further research efforts. It has been reported that l-carnosine increases the secretion and expression of various neurotrophic factors and affects copper homeostasis in nervous cells inducing Cu cellular uptake in keeping with the key metal-sensing system. **Overall, our findings describe a copper tuning effect on the ability of l-carnosine and, particularly its conjugate, to activate tyrosine kinase cascade pathways.**

https://karnopedia.com/carnosine-alzheimers-disease/ Carnosine and Alzheimer's Disease

Carnosine levels are significantly lower in patients with Alzheimer's and other neurodegenerative disorders, suggesting either that carnosine deficiency contributes to the disease, or, more likely, that the disease symptoms are manifesting slower by using carnosine. In either case, the addition of carnosine could be expected to eliminate much of the cellular toxicity that contributes to these diseases, which is why animal and human studies now suggest an important role for carnosine usage in the prevention of Alzheimer's diseases.

Carnosine also works preventively on mechanisms that accompany Alzheimer's disease. Zinc and copper ions probably change the chemical structure of the normal β-amyloids and they are the reason for their toxicity. This change requires a slightly acidic environment to bind zinc ion and/or copper with a β-amyloid. These conditions (acidic medium and the increased concentration of ions of zinc and copper) are present as part of an inflammatory reaction at the place of damage. **Carnosine, as an excellent chelator of copper and zinc (and other metals), is able to remove these heavy metals from the body. This may indicate another important function of carnosine in preventing and delaying the progress of Alzheimer's disease and other degenerative brain diseases.**

https://link.springer.com/article/10.1007/s13105-021-00845-6 Swimming exercise versus L-carnosine supplementation for Alzheimer's dementia in rats: implication of circulating and hippocampal FNDC5/irisin 2022

The current study reveals that **carnosine is equivalent to exercise in reversing cognitive decline and Alzheimer's biomarkers**. In both interventions, enhancement of hippocampal FNDC5/irisin and insulin signalling may be involved in mediating these neuroprotective effects.

https://www.researchgate.net/publication/24377639_Carnosine_diabetes_and_Alzheimer's_disease/link/54035c380cf2c48563b02ca2/download Carnosine, diabetes and Alzheimer's disease

It has been argued that the presence of carnosinase therefore limits carnosine's use as a potential drug, however, it should be pointed out that ingestion of b-alanine can promote an increase in muscle carnosine levels in humans [51]. An alternative approach would be to present the carnosine in a form that carnosinase does not attack, such as **acetylcarnosine o**r the decarboxylated form, carcinine [52].

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3678096/ Safety and Efficacy Evaluation of Carnosine, An Endogenous Neuroprotective Agent for Ischemic Stroke 2013

In both permanent and transient ischemic models, carnosine treatment exhibited s**ignificant cerebroprotection against histological and functional damage**, with wide therapeutic and clinically relevant time windows.

https://www.frontiersin.org/articles/10.3389/fnagi.2015.00219/full Daily Carnosine and Anserine Supplementation Alters Verbal Episodic Memory and Resting State Network Connectivity in Healthy Elderly Adults 2015

Carnosine and anserine are strong antioxidants, previously demonstrated to reduce cognitive decline in animal studies. We aimed to investigate their cognitive and neurophysiological effects, using functional MRI, on humans. Thirty-one healthy participants (age 40–78, 10 male/21 female) were recruited to a double-blind placebo-controlled study. Participants were assigned to twice-daily doses of imidazole dipeptide formula (*n* = 14), containing **500 mg (carnosine/anserine, ratio 1/3)** or an identical placebo (*n* = 17). Functional MRI and neuropsychological assessments were carried out at baseline and after 3 months of supplementation. After 3 months of supplementation, the carnosine/anserine group had **better verbal episodic memory performance and decreased connectivity in the default mode network, the posterior cingulate cortex and the right fronto parietal network**, as compared with the placebo group. Furthermore, there was a **correlation between the extents of cognitive and neuroimaging changes**. These results suggest that **daily carnosine/anserine supplementation can impact cognitive function and that network connectivity** changes are associated with its effects.

https://alz-journals.onlinelibrary.wiley.com/doi/full/10.1016/j.jalz.2018.06.2595 EFFECT OF ANSERINE/CARNOSINE SUPPLEMENTATION ON THE PREVENTION OF ALZHEIMER'S DISEASE IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT 2018

A double-blind, placebo-controlled 12-week trial was performed, in which subjects with MCI were randomized to take orally **750 mg of anserine and 250 mg of carnosine per day** (active group) or a placebo (placebo group). Data were analyzed from 50 MCI subjects with a mean age of 72.8 years.

Oral ACS may protect against the onset of AD in Patients with Mild Cognitive Impairment, especially patients with the APOE4 allele.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7998783/ The Therapeutic Potential of Carnosine/Anserine Supplementation against Cognitive Decline: A Systematic Review with Meta-Analysis 2021

Carnosine is a natural occurring endogenous dipeptide that was proposed as an **anti-aging agent** more than 20 years ago. Carnosine can be found at low millimolar concentrations at brain level and different preclinical studies have demonstrated its **antioxidant, anti-inflammatory, and anti-aggregation activity with neuroprotective effects** in animal models of Alzheimer's disease (AD). In a study by Fonteh et al., a selective **deficit of carnosine has been related to cognitive decline in probable Alzheimer's disease** (pAD) subjects [10]. In this study, where the free amino acid and dipeptide changes in the body fluids from pAD subjects were analyzed, carnosine levels were significantly lower in pAD (328.4 ± 91.31 nmol/dl) than in plasma of healthy subjects (654.23 ± 100.61nmol/dl); this **deficit of carnosine correlated with reduced global cognitive** function measured by Mini-Mental State Examination (MMSE) and Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog).

Catechins **(Flavanol)(Polyphenolic compound) (bioactive components of tea)) note tea may be linked with alumimun (proanthocyanidins close relative)**

Sources: Fruits:apricots,cherries,peaches,blackberries,strawberries,blueberries,raspberries Nuts: pecans, pistachios, almonds, hazelnuts

https://pubmed.ncbi.nlm.nih.gov/30223480/ Effects of Tea Catechins on Alzheimer's Disease: Recent Updates and Perspectives 2018

Catechins, which are bioactive components of tea, have **antioxidative and anti-inflammatory** effects. Moreover, other **potential properties related to AD prevention and modification have been reported** in in vitro and in vivo studies. Several clinical studies have also been conducted to date. The current review summarizes recent updates and perspectives of the effects of catechins on AD based on the molecular mechanisms and related clinical studies.

https://pubmed.ncbi.nlm.nih.gov/29843466/ Beneficial Effects of Green Tea Catechins on Neurodegenerative Diseases 2018

Green tea, black tea, and oolong tea are made from the same plan**t *Camellia sinensis* (L.)** O. Kuntze. Among them, green tea has been the most extensively studied for beneficial effects on diseases including cancer, obesity, diabetes, and inflammatory and neurodegenerative diseases. **Several human observational and intervention studies have found beneficial effects of tea consumption on neurodegenerative impairment, such as cognitive dysfunction and memory loss.** These studies supported the basis of tea's preventive effects of Parkinson's disease, but few studies have revealed such effects on Alzheimer's disease. These findings suggest that GTCs have the **potential to be used in the prevention and treatment of neurodegenerative diseases** and could be useful for the development of new drugs.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6567241/ Green Tea Intake and Risks for Dementia, Alzheimer's Disease, Mild Cognitive Impairment, and Cognitive Impairment: A Systematic Review

Finally, we included three cohort studies and five cross-sectional studies. **One cohort study and three cross-sectional studies supported the positive effects of green tea intake**. **One cohort study and one cross-sectional study reported partial positive effects**. The remaining **one cohort study and one cross-sectional study showed no significant association of green tea intake**. These results seem to **support the hypothesis that green tea intake might reduce the risk for dementia, Alzheimer's disease**, mild cognitive impairment, or cognitive impairment.

https://www.newsdirectory3.com/confirmation-of-the-catechin-component-of-green-tea-the-effect-of-tau-protein-breakdown-the-main-cause-of-alzheimers-dementia-dong-a-science-2/ Confirmation of the catechin component of green tea, the effect of tau protein breakdown, the main cause of Alzheimer's dementia: 2022

A research team from the University of California, Los Angeles (UCLA) in the United States published the results of a study in the international scientific journal Nature Communications on the 16th (local time) ***that green tea catechins break down the tangled tau protein***.

https://www.sciencedirect.com/science/article/abs/pii/S0960308513001296 Catechins: Sources, extraction and encapsulation: A review 2015

Catechins are a group of polyphenolic compounds that extensively occur in the plants. **Extraction/isolation of catechins and making into stable deliverable form is a challenging task in view of their poor oxidative stability**.

Cats Claw

https://pubmed.ncbi.nlm.nih.gov/20096093/ The total antioxidant content of more than 3100 foods, beverages, spices, herbs and supplements used worldwide. 2010

Cat's claw (CC) is a tropical vine with hooked thorns that resemble the claws of a cat and is **mainly recommended for its potential role in the treatment of AD and pre-AD**. It is found mainly in the Amazon rainforest and other areas of South and Central America. This medicinal plant contains oxindole alkaloids, p**olyphenols (flavonoids, proanthocyanidins**, and tannins), glycosides, pentacyclic alkaloids, and sterols [38,39]. CC is known for its immune-modulating and anti-inflammatory effects and for its role as a free radical scavenger.Based on in vitro studies, the anti-inflammatory effect of CC is attributed to its ability to **inhibit** iNOS gene expression, nitrate formation, cell death, PGE2 production, and the activation of NF-κB and TNF-α [45].

Chaenomeles speciosa **(no mention of Alzheimers directly)**

https://pubmed.ncbi.nlm.nih.gov/24649061/ *Chaenomeles speciosa*: A review of chemistry and pharmacology 2014

Chaenomeles speciosa (Sweet) Nakai (*C. speciosa*, Rosaceae family) is an effective medicinal plant, which has long been used in China to treat various diseases, such as rheumatism, cholera, dysentery, enteritis, beriberi and vitamin C deficiency syndrome. A series of chemical constituents, including triterpenoid, phenolic and phenylpropionic acids, flavonoids, saccharides, essential oils and alkaloids, have been isolated from this plant and some have already been evaluated for their biological activities. Pharmacological investigations demonstrated that *C. speciosa* possesses anti-inflammatory, antinociceptive, antimicrobial, antioxidant, immunoregulatory, **antiparkinsonian,** hepatoprotective and antitumor properties.

Chamomile(flavoniods) (Apigenin-dietary flavone found in chamomile)(Apigenin-anti AChE)

Apigen Sources: Chamomile, parsley, onions, grapefruit, oranges, oregano, artichoke, celery,(drink chamomile tea with dried parsley)

Safety:Apigenin is abundant in some vegetables and herbs and is considered safe, but excessive amounts may cause drug interactions due to inhibition of CYP2C9, an enzyme responsible for metabolism of many drugs.
https://www.alzdiscovery.org/uploads/cognitive_vitality_media/Apigenin-Cognitive-Vitality-For-Researchers.pdf

https://pubmed.ncbi.nlm.nih.gov/29154054/ The effects of chamomile extract on sleep quality among elderly people: A clinical trial 2017

A convenient sample of sixty elderly people who aged sixty or more and lived in Kahrizak day care nursing home, Karaj, Iran, were randomly allocated to a control and a treatment group. The treatment group received chamomile extract capsules (200mg) twice a day for 28 consecutive days while the control group received wheat flour capsules (200mg) in the same manner. Conclusion: The **use of chamomile extract can significantly improve sleep quality among elderly people**. Thus, it can be used as a safe modality for promoting elderly people's sleep.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6472148/ The Therapeutic Potential of Apigenin 2019

Apigenin is present principally as glycosylated in significant amount in **vegetables (parsley, celery, onions) fruits (oranges), herbs (chamomile, thyme, oregano, basil)**, and plant-based beverages (tea, beer, and wine) [12]. The present review is focused on the health-promoting effects of apigenin, in particular through in vivo research.

https://www.psychiatryadvisor.com/home/topics/neurocognitive-disorders/alzheimers-disease-and-dementia/enhancing-amyloid-beta-clearance-may-improve-brain-function-alzheimer-disease/?itm_source=Bibblio&itm_campaign=Bibblio_related&itm_medium=Bibblio_carousel

Researchers used a high-throughput screening of 2600 small molecules to determine whether any compounds enhanced **aquaporin 4 (AQP4)** read-through.

In vivo analyses showed Aβ decreased steadily following apigenin and sulphaquinoxaline treatment compared with vehicle-treated mice. In APP/PS1; AQP4X mice, the medications lost their effect, indicating the necessity of AQP4 read-through for medication efficacy. These study **findings confirm previous evidence that AQP4 is essential for Aβ clearance.** These findings also suggest that **apigenin and sulphaquinoxaline may enhance AQP4 read-through, thereby increasing Aβ clearance**

https://www.sciencedaily.com/releases/2022/08/220824120827.htm New approach to clearing toxic waste from brain 2022

Thinking that **increasing the amount of long aquaporin 4 might increase waste clearance**, Sapkota screened 2,560 compounds for the ability to increase readthrough of the aquaporin 4 gene. He found two**: apigenin, a dietary flavone found in chamomile, parsley, onions and other edible plants**; and sulphaquinoxaline, a veterinary antibiotic used in the meat and poultry industries. Sulphaquinoxaline is not safe for use in people. **Apigenin is available as a dietary supplement**, but it's not known how much gets into the brain, and Cirrito cautions against consuming large amounts of apigenin in an attempt to stave off Alzheimer's.

https://academic.oup.com/brain/article-abstract/145/9/2982/6671408?redirectedFrom=fulltext *Aqp4* stop codon readthrough facilitates amyloid-β clearance from the brain 2022

Aquaporin 4 sequence and validate a subset on endogenous astrocyte Aquaporin 4. Finally, we demonstrate these compounds enhance brain amyloid-β clearance *in vivo*, which depends on AQP4X.

https://pubmed.ncbi.nlm.nih.gov/23966081/ Neuroprotective, anti-amyloidogenic and neurotrophic effects of apigenin in an Alzheimer's disease mouse model 2013

In the present study, we examined the effects of apigenin on cognitive function in APP/PS1 double transgenic AD mice and explored its mechanism(s) of action. Three-month oral treatment with apigenin rescued learning deficits and relieved memory retention in APP/PS1 mice. Apigenin also showed effects affecting APP processing and **preventing Aβ burden** due to the down-regulation of BACE1 and β-CTF levels, the relief of Aβ deposition, and the **decrease of insoluble Aβ levels**. Moreover, apigenin exhibited **superoxide anion scavenging effects and improved antioxidative enzyme activity of superoxide dismutase and glutathione peroxidase**. In addition, apigenin **restored neurotrophic ERK/CREB/BDNF pathway** in the cerebral cortex. In conclusion, apigenin may ameliorate AD-associated learning and memory impairment through relieving Aβ burden, suppressing amyloidogenic process, inhibiting oxidative stress, and restoring ERK/CREB/BDNF pathway. Therefore, **apigenin appears to represent an alternative medication for the prevention and/or therapy of AD**.

https://www.sciencedirect.com/science/article/abs/pii/S0891584917302678 OP-25 - Anti-Inflammatory and Neuroprotective Effect of Apigenin: Studies in the GFAP-IL6 Mouse Model of Chronic Neuroinflammation 2017

Results: Histological staining showed that **apigenin decreased the number of activated microglia of GFAP-IL6 mice in the cerebellum and in the hippocampus by ~30% and ~25%**. Apigenin also **improved spatial reference working memory** in the GFAP-IL6 mice. Conclusion: Apigenin is a **potent anti-inflammatory and neuroprotective drug** and can be potentially used for neurodegenerative diseases such as AD.

https://www.nature.com/articles/srep31450 Neuroprotective effects of apigenin against inflammation, neuronal excitability and apoptosis in an induced pluripotent stem cell model of Alzheimer's disease 2016

The plant polyphenol apigenin has been shown to have **anti-inflammatory and neuroprotective properties** in a number of cell and animal models; however a comprehensive assessment has not been performed in a human model of AD. Here we have used a human induced pluripotent stem cell (iPSC) model of familial and sporadic AD, in addition to healthy controls, to assess the neuroprotective activity of apigenin. We identified that apigenin has **potent anti-inflammatory properties with the ability to protect neurites and cell viability by promoting a global down-regulation of cytokine and nitric oxide (NO) release in inflammatory cells**. In addition, we show that **apigenin is able to protect iPSC-derived AD neurons via multiple means by reducing the frequency of spontaneous Ca^{2+} signals and significantly reducing caspase-3/7 mediated apoptosis**. These data demonstrate the **broad neuroprotective action of apigenin against AD pathogenesis in a human disease model.**

https://pubmed.ncbi.nlm.nih.gov/21297270/ The flavonoid apigenin protects brain neurovascular coupling against amyloid-β_{25-35}-induced toxicity in mice 2011

Apigenin, one of the most common flavonoids, has **demonstrated anti-inflammatory, anticarcinogenic, and free radical-scavenging activities**. Recent studies revealed its protective effects against amyloid-β (Aβ)-induced neurotoxicity, but the mechanism was unclear. In the present study, we aimed to explore the anti-amnesic and protective effects of apigenin against $A\beta_{25-35}$-induced toxicity and the underlying mechanisms in the cerebral cortex in mice. The learning and memory impairments, changes in morphology of major components of neurovascular unit, ultrastructural changes and oxidative stress of cerebral cortex, cerebrovascular dysfunction, and neuronal changes were detected after oral administration of apigenin continuously for 8 days. Our results demonstrate that **oral administration of apigenin for $A\beta_{25-35}$-induced amnesic mice conferred robust neurovascular coupling protection, involving improvement of the learning and memory capabilities, maintenance of neurovascular unit integrity, modulation of microvascular function, reduction of neurovascular oxidative damage, increase of regional cerebral blood flow, improvement of cholinergic system involving the inhibition of AChE activity and elevation of ACh level, and modification of BNDF, TrkB, and phospho-CREB levels.**

https://www.salubrainous.com/apigenin-for-alzheimers/ Apigenin for Alzheimer's: Research & Possible Benefits

Acetylcholine is a neurotransmitter that is involved in our memory function.

Acetylcholinesterase is an enzyme that breaks down acetylcholine.

Conventional anti-Alzheimer's drugs inhibit the action of acetylcholinesterase.

Similarly, apigenin was also found to inhibit acetylcholinesterase activity. All these effects of apigenin combined can lead to improvements in memory. A study published in Food and chemical toxicology, 2014 examined the anti-diabetic, anti-Alzheimer and anti-inflammatory activities of two carbon glycosylated **derivatives of apigenin- vitexin and isovitexin**. [10] Apigenin acts at molecular levels thereby aiding metabolic processes and improving glucose and fat metabolism in the body. [11] It can serve as a therapeutic agent for metabolic syndrome. Wang et al. have demonstrated that **apigenin reduces oxidative stress in the pancreas and can thus serve as a novel therapeutic agent for diabetes**. [13] Apigenin acts on the hippocampus (memory centre of the brain) and **prevents such oxidative damage caused by high-calorie diets**. [14] (Biomedicine & Pharmacotherapy, 2017) Amini and colleagues have been looking into this phenomenon in great detail. Their research has revealed that brain cells, when incubated or treated with apigenin have i**ncreased resistance to insulin amyloid toxicity**, a lower concentration of insulin fibrils and reduced cell death. [15]

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3281105/ Acute Exposure of Apigenin Induces Hepatotoxicity in Swiss Mice 2012

damaged histoarchitecture in the liver of 100 or 200 mg/kg Apigenin treated animals were found

https://draxe.com/nutrition/apigenin/ Apigenin: Top 9 Benefits of the Most Widely Distributed Plant Flavonoid

Chamomile

https://pubmed.ncbi.nlm.nih.gov/30000867/ Chamomile 2021

Two different plant species with similar effects are known as chamomile: German chamomile (*Matricaria recutita*) and Roman chamomile (*Chamaemelum nobile*). Both contain similar ingredients, including sesquiterpenes (e.g., bisabolol, farnesene), sesquiterpenelactones (e.g., chamazulene, matricin), **flavonoids (e.g., apigenin, luteolin**), and volatile oils. Chamomile is used orally as a sedative and for gastrointestinal conditions; it is used topically for wound healing. Chamomile is **"generally recognized as safe" (GRAS)** for use in food by the U.S. Food and Drug Administration as a spice, seasoning, or flavoring agent.

https://pubmed.ncbi.nlm.nih.gov/29154054/ The effects of chamomile extract on sleep quality among elderly people: A clinical trial 2017

The treatment group received **chamomile extract capsules (200mg) twice a day** for 28 consecutive days **Conclusion:** The use of chamomile extract can significantly improve sleep quality among elderly people. Thus, it can be used as a safe modality for promoting elderly people's sleep.

Chlorella (also heavy metal detox)

https://pubmed.ncbi.nlm.nih.gov/19699777/ Preventive effects of Chlorella on cognitive decline in age-dependent dementia model mice 2009

Oxidative stress is one of the major causes of age-dependent memory loss and cognitive decline. Cytotoxic aldehydes are derived from lipid peroxides and their accumulation may be responsible for age-dependent neurodegeneration, including Alzheimer's disease. Since Chlorella, a kind of alga, exhibits various anti-oxidative effects, we investigated whether Chlorella has the potential to prevent age-dependent cognitive impairment. The diet with **Chlorella tended to reduce oxidative stress and significantly prevented the decline of cognitive ability,** as shown by both methods. Moreover, consumption of Chlorella decreased the number of activated astrocytes in the DAL101 brain. These findings suggest that the prolonged consumption of Chlorella has the potential to prevent the progression of cognitive impairment.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6523211/ The Long-Term Algae Extract (*Chlorella and Fucus sp*) and Aminosulphurate Supplementation Modulate SOD-1 Activity and **Decrease Heavy Metals (Hg^{++}, Sn) Levels in Patients with Long-Term Dental Titanium Implants** and Amalgam Fillings Restorations 2019

https://pubmed.ncbi.nlm.nih.gov/34469852/ Impact of heavy metals in the microalga Chlorella sorokiniana and assessment of its **potential use in cadmium bioremediation** 2021

The chlorophyte microalga Chlorella sorokiniana was tested for the bioremediation of heavy metals pollution. It was cultured with different concentrations of Cu^{2+}, Cd^{2+}, As (III) and As (V), showing a significant inhibition on its growth at concentrations of 500 µM Cu^{2+}, 250 µM Cd^{2+}, 750 µM AsO_3^{3-} and 5 mM AsO_4^{3-} or higher.

Choline(Vitamin B4) (eggs, lecithin , Acetylcholine, phosphatidycholine, phospholipids, Phosphatidylserine (PS) is a phospholipid)

Sources: **Salmon 1 filet: 242 mg** (44% DV), **Eggs 1 large egg: 147 mg** (27% DV)

RDI: 550mg/day

https://pubmed.ncbi.nlm.nih.gov/28052883/ Association of dietary cholesterol and egg intakes with the risk of incident dementia or Alzheimer disease: the Kuopio Ischaemic Heart Disease Risk Factor Study 2017

Conclusions: Neither **cholesterol nor egg intake is associated with an increased risk of incident dementia or A**D in Eastern Finnish men. **Instead, moderate egg intake may have a beneficial association** with certain areas of cognitive performance.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5188439/ Eggs and Health Special Issue 2016

This special issue addresses the history of the recommendations for eggs [1], the components of eggs providing beneficial effects against disease [2,3,4,5,6], the relationship between egg intake and healthy eating index [7]; the **protective effects of eggs against inflammation [8] and oxidative stress** [9]. Finally, the controversies surrounding egg intake and risk for diabetes are presented in a review of epidemiological data [10] and in a clinical study [11].

There is evidence that **ovotransferrin and its peptides possess antiviral activity, as well as antioxidant and anti-inflammatory properties** [4].

The anti-inflammatory properties of eggs have been demonstrated in numerous studies [8]. Among the egg components with anti-inflammatory properties are: **phospholipids, the carotenoids, lutein and zeaxanthin** and egg proteins. The mechanisms of action of these anti-inflammatory components is discussed in detail [8].

https://banksnutrition.com/2019/11/07/alzheimers-and-eggs/ Alzheimers and Eggs 2019

One of only two drugs approved to treat the disease, **Aricept, attempts to delay the progression of the disease by propping up acetylcholine levels**. It does so by inhibiting the enzyme cholinesterase which eventually breaks unused acetylcholine down.

An important question should be, why is too little acetylcholine present in the first place? It seems that a growing deficiency of one of the primary ingredients, **choline,** is often the problem. The predominant source of choline in the western diet had always been eggs. The same eggs that became “evil” in the 1960’s as the cause of heart disease was an idea now known to have been based on some highly biased research. Two eggs, the breakfast of many up until that time, provided about 300 mgs of choline. This is in contrast to other high choline sources such as chicken and meat which supply about 150 mgs.

The recommended daily intake of choline is 450-550 mgs/day so dropping out the important source of 300 mgs of it is problematic. More problematic was that the rationale for avoiding those “dangerous eggs” has proven to be in error

Dr. Steven Nissen, chairman of cardiovascular medicine at the Cleveland Clinic, told CNN announcing the major cardiology professional associations new stance on dietary cholesterol: “The idea we need to limit saturated fat and cholesterol shifted Americans from a well-balanced diet to high-sugar diets, which made people eat more and get fatter.” What he did not comment on, perhaps because it was out of his research area, was that this same cholesterol phobia may have contributed a piece to the growing epidemic of Alzheimer’s disease over that 60-year period.

Back to our original discussion, **eggs have appeared to always play a role in our brain health given their potent choline content**. A key component of the Bredesen Protocol for Alzheimer’s disease is that it removes the added sugars and highly processed carbohydrates from the diet that so many “enjoy”. If there is a trade-off it may be that one could get 2 things in exchange, their eggs back and a healthier, better functioning brain

https://pubmed.ncbi.nlm.nih.gov/31560162/ Lifelong choline supplementation ameliorates Alzheimer's disease pathology and associated cognitive deficits by attenuating microglia activation

Choline is a B-like vitamin nutrient found in common foods that is important in various cell functions. 2019

serves as a methyl donor and as a precursor for production of cell membranes. **Choline is also the precursor for acetylcholine, a neurotransmitter** which activates the alpha7 nicotinic acetylcholine receptor (α7nAchR), and also acts as an agonist for the Sigma-1 R (σ1R). These receptors regulate CNS immune response, and their dysregulation contributes to AD pathogenesis. Here, we tested whether dietary choline supplementation throughout life reduces AD-like pathology and rescues memory deficits in the APP/PS1 mouse model of AD

Lifelong choline supplementation significantly reduced amyloid-β plaque load and improved spatial memory in APP/PS1 mice. Mechanistically, these changes were linked to a decrease of the amyloidogenic processing of APP, reductions in disease-associated microglial activation, and a downregulation of the α7nAch and σ1 receptors. Our results demonstrate that lifelong choline supplementation produces profound benefits and suggest that simply modifying diet throughout life may reduce AD pathology.

https://vanduyncenter.com/choline-may-be-able-to-treat-and-prevent-alzheimers-disease/ Choline may be able to Treat and Prevent Alzheimer’s Disease

Choline, a necessary nutrient that is commonly found in many foods has been shown to prevent and treat Alzheimer’s disease in mice and even pass on the benefits to later generations. This new study was published January 8, 2019 in the NATURE journal Molecular Psychiatry by researchers at the Biodesign Institute at the University of Arizona. They discovered that the nutrient **choline may be a simple and safe treatment for Alzheimer’s** and may be able to help stop the devastating effects of severe memory loss.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4787279/ Alzheimer's Disease: Targeting the Cholinergic System 2016

Acetylcholine (ACh) has a crucial role in the peripheral and central nervous systems. The enzyme **choline acetyltransferase (ChAT) is responsible for synthesizing ACh from acetyl-CoA and choline in the cytoplasm** and the vesicular acetylcholine transporter (VAChT) uptakes the neurotransmitter into synaptic vesicles. Following depolarization, ACh undergoes exocytosis reaching the synaptic cleft, where it can bind its receptors, including muscarinic and nicotinic receptors. ACh present at the synaptic cleft is promptly hydrolyzed by the enzyme acetylcholinesterase (AChE), forming acetate and choline, which is recycled into the presynaptic nerve terminal by the high-affinity choline transporter (CHT1). **Cholinergic neurons located in the basal forebrain, including the neurons that form the nucleus basalis of Meynert, are severely lost in Alzheimer’s disease (AD)**. AD is the most ordinary cause of dementia affecting 25 million people worldwide. The hallmarks of the disease are the **accumulation of neurofibrillary tangles and amyloid plaques**. However, there is no real correlation between levels of cortical plaques and AD-related cognitive impairment. Nevertheless, synaptic loss is the principal correlate of disease progression and loss of cholinergic neurons contributes to memory and attention deficits. Thus, **drugs that act on the cholinergic system represent a promising option to treat AD patients**.

Cholinergic neurotransmission has been implicated in a number of disease states. Because ACh has an important role in cognitive processes, the cholinergic system is pointed as an important factor in many forms of dementia, including AD [179, 180]. Deficits in the cholinergic transmission can potentially influence all aspects of cognition and behavior, including cortical and hippocampal processing information [181]. Disruption of cholinergic inputs to the cortex can impair attention and the use of instructive cues needed for decision-making related to ongoing behavior [182]. Moreover, it has been shown that blocking CA3 cholinergic receptors impairs the encoding of information and memory [183]. In addition to cognitive alterations, psychiatric symptoms are frequently observed in AD patients, including apathy and depression [184]. It has been postulated that the loss of cholinergic neurons and the consequent impairment in dopaminergic transmission could be the main factors underling AD-related psychiatric symptoms [184, 185].

https://pubmed.ncbi.nlm.nih.gov/7161627/ Alzheimer's disease. Correlation of cortical choline acetyltransferase activity with the severity of dementia and histological abnormalities 1982

We have **examined the choline acetyltransferase [CAT] activity in autopsy samples** of frontal and temporal lobe cortex from 47 patients (31 with Alzheimer's disease, 4 with dementia due to cerebrovascular disease and 12 undemented controls) and compared it with the severity of dementia during life and with the numbers of argyrophilic plaques and neurofibrillary tangles in the corresponding areas of cortex in the contralateral cerebral hemisphere. **CAT activity was significantly reduced, most severely in the temporal lobe, in patients with Alzheimer's disease** but not in patients with a cerebrovascular cause for their dementia, and CAT activity showed no significant reduction with age in the undemented control patients. In the patients with Alzheimer's disease the reduction in **CAT activity was significantly correlated with the severity of dementia and with the numbers of neurofibrillary tangles**, but not argyrophilic plaques, present in the corresponding contralateral cortex

https://pubmed.ncbi.nlm.nih.gov/9130295/ Acetylcholine, aging, and Alzheimer's disease 1997

A substantial body of literature has suggested that the memory and learning deficits associated with Alzheimer's disease and aging are attributable to **degeneration of the cholinergic magnocellular neurons** of the nucleus basalis of Meynert (nbM). Subsequently, lesion-induced damage to the cholinergic projections from the nbM to the neocortex has been utilized extensively as an animal model of dementia

https://draxe.com/nutrition/what-is-choline/ What Is Choline? Benefits, Sources & Signs of Choline Deficiency 2018

Choline is a macronutrient that’s important for liver function, normal brain development, nerve function, muscle movement, supporting energy levels and maintaining a healthy metabolism. **Choline is present in the form of phosphatidycholine**, a compound that makes up the structural component of fat, and thus can be found in different types of foods that naturally contain certain fats. Choline plays a part in several important processes within the body that are carried out hundreds of times, every single day.

Choline is a water soluble nutrient that is related to other vitamins, such as folate and those in the B vitamin complex family. Just like B vitamins, choline plays a similar role in terms of supporting energy and brain function, as well as keeping the metabolism active.

What is choline most beneficial for? Choline helps in the process of methylation, which is used to create DNA, for nerve signaling, and for detoxification. It's also i**mportant for the functioning of a key neurotransmitter called acetylcholine,** which similarly helps nerves to communicate and muscles to move, acts as an anti-aging neurotransmitter, and performs other basic processes.

Choline is not actually considered a mineral or a vitamin, but is known to be an essential micronutrient needed for many functions of the body, especially for brain function. So while at this time there isn't an official Daily Value Recommendation for Choline established by the USDA, it's important to avoid a choline deficiency to help support various systems throughout the body, including the nervous, endocrine, digestive and reproductive systems. Our bodies are able to make a small amount of choline on their own, but the rest we must obtain from food sources.

What is choline found in? Choline can be found naturally in foods including **eggs, liver, beef, salmon, cauliflower, Brussel sprouts and breast milk**. In fact, eggs are sometimes called "brain food" because they are known for supplying high amounts of choline.

Choline was actually only added to the Nation Academy of Science's (NAS) required nutrients list in 1998, making it one of the most recent additions of all nutrients.

Some experts recommend getting even higher levels of choline in order to boost brain function and to retain memory. Some reports have shown that a percentage of the choline found in food sources isn't actually absorbed by the body, and that this may be one reason why **certain people can experience a choline deficiency, especially those with liver damage since choline is processed partially in the liver.**

If you choose to take choline supplements, it's best to purchase one that is made from whole food sources and is of very high quality. There are several choices available for different types of choline supplements, some which will be more readily absorbed and used by the body, while others don't fully have the same effects.

This has to do with how your **body converts choline into the molecule acetylcholine,** which is responsible for many of choline's health benefits. **Different types of choline also differ in their ability to cross the blood-brain barrier** once ingested.

Some experts have pointed to the fact that the types of choline that is best used by the body are **CDP choline, also called Citicoline, or Alpha GPC choline.** These are potent types of choline that produce the most benefits in the body, according to some sources, because they closely mimic the way that choline is found naturally in food sources. (2) A choline deficiency may also play a part in age-related cognitive decline, including memory loss and Alzheimer's disease. This is because choline helps with neurotransmitter maintenance and, as someone ages, nerve signaling can decrease and signs of dementia can be experienced. (3)

Eating a varied diet is the best way to ensure you acquire enough choline. Choline is especially present in animal products, so vegetarians and vegans are more prone to experiencing a deficiency in choline.

It's also important to point out that folate plays a part in the body's ability to create and use choline — as the two nutrients have a strong relationship and rely on one another to do their jobs. Researchers used to believe that we could make enough choline on our own but are finding out otherwise in recent years, hence the addition of choline to the list of required nutrients. According to recent research, the amount of folate you consume may dictate how much choline your body makes and needs from food sources, so someone who obtains more folate from things like leafy green vegetables and certain grains will need less choline from food

The following 12 foods provide high levels of choline naturally, in addition to many other nutrients. All percentages below are based on the **recommended amount of 550 milligrams daily.**

1. Beef Liver 3 ounces: 283 mg (51% DV)
2. **Salmon 1 filet: 242 mg** (44% DV)
3. Chickpeas 1 cup uncooked: 198 mg (36% DV)
4. Split Peas 1 cup uncooked: 188 mg (34% DV)
5. Navy Beans 1 cup raw: 181 mg (32% DV)
6. **Eggs 1 large egg: 147 mg** (27% DV)
7. Grass-Fed Beef 3 ounces: 78 mg (14% DV)
8. Turkey 3 ounces: 57 mg (10% DV)
9. Chicken Breast 3 ounces: 50 mg (9% DV)
10. Cauliflower 1 cup raw: 47 mg (8% DV)
11. Goat Milk 1 cup: 39 mg (7% DV)
12. Brussel Sprouts 1 cup raw: 17 mg (3% DV)

Choline & Soy Lecithin

It's also worth noting that choline can be found in soy products, especially soy lecithin. **Choline is a key component of lecithin (phosphatidylcholine)**, which is a fat-like substance found in our cells. Soy lecithin is a controversial substance that is used in food products as an emulsifier and sold as supplements.

Soy lecithin is added to many processed, packaged foods because it helps to bind foods and acts like an emulsifier, preserving the texture of foods and making them more shelf-stable. Although soy lecithin is considered safe by the FDA, at times it can result in negative reactions including nausea, bloating, constipation, rashes on the skin, abdominal pain and other digestive problems. I have some other issues with **soy lecithin in general, including that it contains isoflavones that have estrogenic effects on the body and that the majority of soy on the market today is genetically modified.** There's really no way to detect the source of soy lecithin, so we should assume that it's extracted from GM soy, unless it's labeled as organic. (5

Health Benefits of Choline

1. Forms DNA and Cell Structures

Choline helps the body to absorb fat, and fats are then used to create cell membranes and structures. Without enough choline in the body, our cells cannot properly withhold their structure and signal messages to other parts of the body. (7) What is choline's role in gene expression and DNA? Choline is needed to create DNA that is responsible for building out entire body structure. Choline and folate are known to be key nutrients involved in the methyl group processes, which the body uses to form genetic material that helps build every system within the body.

2. Supports Central Nervous System

One of the main benefits of choline is that it is used by the body in a variety of ways that are crucial for nerve functioning, including aiding in nerve signaling and maintaining the membranes of brain cells.

Choline also helps form tissue within the nervous system that plays a part in brain development and growth. It's believed that choline can improve signaling capacity of nerves, support their structural integrity, and protect vital neuronal membranes. (8)

Choline acts like a precursor to certain important neurotransmitters, including acetylcholine, which is used in healthy nerve and muscle function. Neurotransmitters are chemical symptoms of communication used throughout the body constantly to relay information from system to system.

The neurotransmitter acetylcholine specifically plays a part in memory and learning, so a choline deficiency can result in poor concentration, poor memory, mood changes and other cognitive impairments, especially as someone ages. Acetylcholine is formed when an acetate molecule combines with a choline molecule, so without enough choline present in the body, this molecule cannot be properly produced and brain function can suffer. (9)

3. Maintains Healthy Liver Function

Choline is needed to properly transport fat from the liver to cells throughout the body. A benefit of choline is cleansing the liver because choline is partially responsible for keeping the liver clear from fat build-up that can accumulate and cause harm. Choline plays a part in transporting both cholesterol and triglycerides, two forms of important fats, from the liver to other parts of the body where they are needed. In people who have **low levels of choline present within their body, some studies have found that they are more at risk for experiencing liver damage** and even liver failure. (10)

Choline also helps form LDL cholesterol within the liver, and even though LDL is considered the "bad" kind of cholesterol, a certain level is still needed for healthy functioning — without enough, the body will suffer by storing fat in the liver.

4. Helps Protect Memory and Loss of Brain Function

Another one of the benefits of choline is its ability to keep your mind mentally sharp as you age. Because it's a component of cell membranes and neurotransmitters that are used in nerve signaling, choline also plays a role in preserving memory and preventing dementia, memory loss and other signs of cognitive decline as someone becomes older. As we age, our brain becomes less elastic. **Choline does an important job of maintaining brain elasticity by working to maintain levels of acetylcholine**, which naturally declines into old age.

Some studies point to the fact that low levels of acetylcholine may lead to cognitive decline, including Alzheimer's disease and senile dementia. (11) Patients who develop Alzheimer's at times show very low levels of acetylcholine, and some medications used to treat Alzheimer's actually mimic choline's effect of increasing this neurotransmitter's effects.

https://www.sunflowerlecithin.org/ Now Sunflower Liquid Lecithin

NOW FoodsNon-GMO Lecithin Softgels contain **15% Phosphatidyl Choline** NOW Foods Lecithin's Phosphatidyl comprises a major portion of our brain and nervous system. NOW Foods Lecithin is also a source of essential fatty acids, Choline and Inositol. NOW Foods Lecithin aids in emulsifying fats, enabling them to be dispersed in water.

https://pubmed.ncbi.nlm.nih.gov/30000831/ Lecithin 2022

Lecithin is a mixture of choline, choline esters, fatty acids, glycerol, glycolipids, triglycerides, phosphoric acid, and phospholipids, such as phosphatidylcholine that are normal components of human milk.

https://pubmed.ncbi.nlm.nih.gov/6754453/ Effects of consumption of choline and lecithin on neurological and cardiovascular systems 1982

This report concerns possible **adverse health effects and benefits that might result from consumption of large amounts of choline, lecithin, or phosphatidylcholine.** Indications from preliminary investigations that administration of choline or lecithin might alleviate some neurological disturbances, prevent hypercholesteremia and atherosclerosis, and restore memory and cognition have resulted in much research and public interest. Symptoms of tardive dyskinesia and Alzheimer's disease have been ameliorated in some patients and varied responses have been observed in the treatment of Gilles de la Tourette's disease, Friedreich's ataxia, levodopa-induced dyskinesia, mania, Huntington's disease, and myasthenic syndrome. Further clinical trials, especially in conjunction with cholinergic drugs, are considered worthwhile but will require sufficient amounts of pure phosphatidylcholine. The public has access to large amounts of commercial lecithin. Because

high intakes of lecithin or choline produce acute gastrointestinal distress, sweating, salivation, and anorexia, it is improbable that individuals will incur lasting health hazards from self-administration of either compound. Development of depression or supersensitivity of dopamine receptors and disturbance of the cholinergic-dopaminergic-serotinergic balance is a concern with prolonged, repeated intakes of large amounts of lecithin

https://pubmed.ncbi.nlm.nih.gov/7816350/ Lecithin and choline in human health and disease 1994

Choline is involved in methyl group metabolism and lipid transport and is a component of a number of important biological compounds including the membrane phospholipids lecithin, sphingomyelin, and plasmalogen; the neurotransmitter acetylcholine; and platelet activating factor. Although a required nutrient for several animal species, choline is not currently designated as essential for humans. However, recent clinical studies show it to be **essential for normal liver function.** Additionally, a large body of evidence from the fields of molecular and cell biology shows that certain phospholipids play a critical role in generating second messengers for cell membrane signal transduction. This process involves a cascade of reactions that translate an external cell stimulus such as a hormone or growth factor into a change in cell transport, metabolism, growth, function, or gene expression. **Disruptions in phospholipid metabolism can interfere with this process and may underlie certain disease states such as cancer and Alzheimer's disease.** These recent findings may be appropriate in the consideration of choline as an essential nutrient for humans.

https://pubmed.ncbi.nlm.nih.gov/11034695/ Lecithin for dementia and cognitive impairment 2000

Alzheimer's disease sufferers have been found to have a lack of the enzyme responsible for converting choline into acetylcholine within the brain. Lecithin is a major dietary source of choline, so extra consumption may reduce the progression of dementia.

Main results: Twelve randomized trials have been identified involving patients with Alzheimer's disease (265 patients), Parkinsonian dementia (21 patients) and subjective memory problems (90 patients). No trials reported any clear clinical benefit of lecithin for Alzheimer's disease or Parkinsonian dementia. Few trials contributed data to meta-analyses. The only statistically significant result was in favour of placebo for adverse events, based on one trial, which appears likely to be a spurious result. A **dramatic result in favour of lecithin was obtained in a trial of subjects with subjective memory problems**.

Reviewer's conclusions: **Evidence from randomized trials does not support the use of lecithin in the treatment of patients with dementia.** A moderate effect cannot be ruled out, but results from the small trials to date do not indicate priority for a large randomized trial.

https://pubmed.ncbi.nlm.nih.gov/3897460/ A double-blind, placebo controlled trial of high-dose lecithin in Alzheimer's disease 1985

The first long-term double-blind placebo controlled trial of high dose lecithin in senile dementia of the Alzheimer type is reported. Fifty one subjects were given **20-25 g/day of purified soya lecithin (containing 90% phosphatidyl plus lysophosphatidyl choline)** for six months and followed up for at least a further six months. Plasma choline levels were monitored throughout the treatment period. There were **no differences between the placebo group and the lecithin group** but there was an improvement in a subgroup of relatively poor compliers. These were older and had intermediate levels of plasma choline. It is suggested that the **effects of lecithin are complex but that there may be a "therapeutic window" for the effects of lecithin in the condition and that this may be more evident in older patients**.

https://pubmed.ncbi.nlm.nih.gov/7049290/ Fluctuations of free choline levels in plasma of Alzheimer patients receiving lecithin: preliminary observations 1982

Plasmas of 12 patients currently taking part in a double-blind trial of lecithin in senile or presenile dementia of Alzheimer type were analysed for plasma choline levels at fixed intervals during lecithin treatment. The v**alues were not maintained at a constant level and showed a decline after one or two months of treatment, often followed by a subsequent rise.** Possible explanations for this observation are given, and its significance to the treatment of dementia discussed.

https://pubmed.ncbi.nlm.nih.gov/25784704/ **Intestinal microbiota composition modulates choline bioavailability** from diet and accumulation of the proatherogenic metabolite trimethylamine-N-oxide 2015

Choline is a water-soluble nutrient essential for human life. **Gut microbial metabolism of choline results in the production of trimethylamine (TMA),** which upon absorption by the host is **converted in the liver to trimethylamine-N-oxide (TMAO).** Recent studies revealed that TMAO exacerbates atherosclerosis in mice and positively correlates with the severity of this disease in humans. However, which microbes contribute to TMA production in the human gut, the extent to which host factors (e.g., genotype) and diet affect TMA production and colonization of these microbes, and the effects TMA-producing microbes have on the bioavailability of dietary choline remain largely unknown. We screened a collection of 79 sequenced human intestinal isolates encompassing the major phyla found in the **human gut and identified nine strains capable of producing TMA from choline in vitro.**

Remarkably, low levels of colonization by TMA-producing bacteria significantly reduced choline levels available to the host. This effect was more pronounced as the abundance of TMA-producing bacteria increased. Our findings provide a framework for designing strategies aimed at changing the representation or activity of TMA-producing bacteria in the human gut and suggest that the **TMA-producing status of the gut microbiota should be considered when making recommendations about choline intake requirements for humans.**

https://pubmed.ncbi.nlm.nih.gov/6684463/ Bioavailability of methyl-14C CDP-choline by oral route 1983

In this work, the bioavailability of the 14C-methyl-labelled cytidine diphosphate choline (CDP-Choline, citicoline, Somazina), has been studied by oral route, leading to the result that it is slowly and completely absorbed, with a very low urinary and fecal elimination, thus producing maintained blood levels. The bioavailability related to oral route compared with intravenous route is practically the same.

https://pubmed.ncbi.nlm.nih.gov/28317731/ Encapsulation of sesamol in phosphatidyl choline micelles: Enhanced bioavailability and anti-inflammatory activity 2017

Sesamol, the phenolic degradation product of sesamolin, although recognised for its anti-inflammatory effects, has low bioavailability. In this manuscript, we attempted to improve its bioavailability by encapsulation in mixed phosphatidylcholine micelles. Sesamol could be solubilised and entrapped in phosphatidylcholine mixed micelles (PCS) with 96.8% efficiency (particle size 3.0±0.06nm).

https://www.mdpi.com/2072-6643/12/8/2340/htm The Relationship between **Choline Bioavailability from Diet, Intestinal Microbiota Composition**, and Its Modulation of Human Diseases 2020

The **ingestion of food containing choline or other trimethylamine-containing compounds is followed by the synthesis of TMA in the gut by microorganisms** including both Gram-positive and Gram-negative bacteria (Figure 2). Therefore, the magnitude of the production of TMA is influenced by the composition of the microbiota of the individual. It is important to note that only a minor fraction of the microorganisms present in the intestine (less than 1%) harbor the genes required for TMA production [40]. However, even very low concentrations of these microorganisms seem to be sufficient for TMA production, which **illustrates the importance of the gut microbiota in this context** [41]. Indeed, the presence of increased TMA and TMAO levels has been associated with higher activity of bacterial members of the phylum Firmicutes and Proteobacteria, which are known producers of this metabolite [40,41]. Moreover, TMA and TMAO levels have been linked to an elevated Firmicutes/Bacteroidetes ratio with higher levels of Firmicutes and lower levels of Bacteroidetes [42,43] due to the inability of Bacteroidetes to produce TMA [44,45].

Microorganisms involved in the metabolism of dietary choline and other trimethylamine-containing compounds. Following ingestion of foods containing choline/lecithin, or L- carnitine, certain intestinal microorganisms metabolize these compounds to trimethylamine (TMA) by different metabolic pathways. TMA can then be absorbed and transformed into trimethylamine N-oxide (TMAO) in the liver, or it can be reduced by methanogenic archaea in the gut to produce methane and ammonium. Once TMA is formed, it will be subsequently oxidized into TMAO in the liver through the enzyme FMO3 [53]. It is worth noting that some bacteria from the phylum Proteobacteria may

also be able to metabolize the TMAO ingested via the diet into TMA via TMAO reductase using metabolic retroconversion [54]. Finally, it has recently been found that intestinal archaea such as some members of the order Methanomassiliicoccales are able to reduce TMAO to methane [55]. Therefore, a current area of research relies on the **use of such microorganisms as potential probiotics, in order to reduce the circulating levels of TMAO, which have been associated with an increased cardiovascular disease risk.**

Diet Impact on Microbiota-Choline Metabolism

It has been demonstrated that the composition and diversity of gut microbiota can be influenced by the diet, since it is, in turn [56], an important source of variability in serum TMAO levels. In this regard, long-term individual dietary habits have been proven to influence microbiota enterotypes [57,58]. Indeed, Wu et al. [58] observed that a **Western diet consumption—typically represented by a high consumption of animal proteins, saturated fats, and low fiber—was associated with the Bacteroides enterotype,** whereas a **carbohydrate-based diet mainly consumed by agrarian societies, was linked to a Prevotella enterotype. Western diets are characterized by animal products such as liver, pork meat, and eggs, which contain large amounts of choline [59] and are known not only to increase blood and urine TMAO levels [41] but even have an effect on the gut microbiota**. In fact, Manor and colleagues [60] observed a positive correlation between intestinal microbial clades such as Neisseriaceae or Desulfovibrio and TMAO levels, which were also elevated in symptomatic coronary vascular disease (CVD) patients and those consuming an animal-based diet. Another study from Cho et al. [42] reported that men with elevated levels of TMAO in the body after consuming dietary eggs tended to have a higher abundance of Firmicutes; meanwhile, individuals with lower levels of TMAO exhibited a higher abundance of Bacteroidetes.

Similar differences in microbiota and TMAO levels have been reported between vegetarian and omnivorous diets, which were also accompanied by a lesser ability to produce TMA in vegetarians [61]. These observations reinforce the potential of modulating dietary habits to reduce the risk associated with high TMAO levels.

Nevertheless, **due to the importance of choline as an essential nutrient, choline-deficient diets may also induce gut microbiota alterations and health problems** [62,63,64,65]. Indeed, a human trial in which the choline intake was controlled demonstrated that the gut microbiota composition changed with dietary choline levels and specific alterations in Gammaproteobacteria, and Erysipelotrichi members were associated with changes in liver fat during choline depletion [66]. These results confirm the impact of diet on both gut microbiota and TMAO levels [61,66]. In addition, it has been reported that FMO3 expression is closely related to the composition of intestinal flora [53,67]. The changes observed after choline-dietary interventions, together with the putative host´s genes, could be used for predicting and modulating the risk of developing diseases related to this nutrient (overviewed in Figure 3).

Host Genotype Impact on Microbiota Choline Metabolism

The concentration of TMA/TMAO in plasma has been linked to the composition of intestinal microbiota and differences among microbiota enterotypes [57] have been proposed [68]. Nevertheless, it may be considered that the high inter-individual variability in the composition of the intestinal microbiota results in a large variability in its enzymatic capabilities [69]. Furthermore, this inter-individual variability is linked to different factors including the host's genetics.

Over a period of decades, different studies have tried to understand how a host's genetic background may influence the overall microbiome. The proportion of phenotypic variation in a trait that is attributable to genetic variation among individuals is known as heritability [70]. Among the gut microbiota, a few bacteria and archaea have arisen as heritable and have been associated with host genes. In line with this, twin studies have observed a higher similarity in the gut microbiota composition between monozygotic than dizygotic twins, which is attributable to shared genes. These studies also identified heritable bacteria including Christensenellaceae (later associated with a low body mass index), the methanogenic Archaea Methanobrevibacter smithii, and the genus Blautia [71,72]. Moreover, microbiome genome-wide association studies have also identified associations between human genes and the gut microbiome such as the lactase gene LCT and the abundance of Bifidobacterium [73,74] or the vitamin D receptor gene and microbial diversity [75].

One example is given by prebiotics, defined as non-digestible food components selectively degraded by bacteria in the gut [162] that act to promote the growth of health-benefiting microbes. Non-digestible carbohydrates are the most commonly prescribed prebiotics, with a plethora of clinical data supporting their role in promoting microbial diversity [163]. **Notably, prebiotic supplementation with soluble dietary fiber not only boosted the abundance of beneficial bacteria, but also significantly diminished TMA and TMAO metabolism** (by 40.6% and 62.6%,

respectively) in mice fed a red meat rich diet. Moreover, this was accompanied by a marked reduction in weight, decrease in energy metabolism, and improved lipid and cholesterol markers [164]. Similarly, in humans, the consumption of an **arabinoxylan-oligosaccharide-enriched prebiotic** extract as part as an intervention trial in overweight adults was shown to increase the prevalence of Prevotella normally associated with non-Western diets low in processed foods [165]. Notably, the Prevotella abundance was also associated with an increase in short chain fatty acids and a **rise in plasma phosphatidylcholine, indicative of a reduced availability of choline for TMA biosynthesis** and a potential protective role in promoting metabolic health [165]. Likewise, long-term adherence to a diet enriched with dietary fiber was associated with a reduction in the TMAO concentration, accompanied by changes in the gut microbiota and improved metabolic health in obese children [166

Polyphenols are phytochemicals produced as secondary metabolites in plants and constitute another class of chemical compounds of dietary origin with extra health benefits, **known for their potent gut microbiota modulating properties**. Notably, **dietary supplementation with resveratrol (a stilbenoid polyphenol) increased the abundance of Lactobacillus, reduced the levels of TMAO and attenuated the atherosclerosis phenotype of ApoE**-/- mice fed a high-choline diet [167]. **Flavonoids present in oolong tea extracts and citrus peel were reported to have similar Lactobacillus-boosting effects,** accompanied by a reduction in the carnitine-induced increase in TMAO plasma levels in mice [168]. A recent double-blind randomized trial evaluating the TMAO-reducing efficacy of Taurisolo, a polyphenolic-rich pomace extract, found that it induced a significant reduction in TMAO relative to the placebo (63.6% vs. 0.54%) four weeks post-intervention [169]. However, additional mechanistic and human intervention studies are needed to further elucidate the relationship between polyphenols, microbiota-dependent TMAO levels, and human disease. **Another strategy for targeting TMAO is the use of probiotics** (i.e., the ingestion of living microbes in adequate amounts that exert beneficial effects on human health) [170], with studies reporting promising microbiota re-modeling and TMAO-reducing effects in animal models. **Eight weeks of dietary supplementation with Lactobacillus paracasei F19 protected rats from oxidative stress-induced liver damage by restoring the intestinal barrier and microbiota diversity** [171], while gut colonization **with M. smithii bacterial species** was associated with a reduction in the TMAO concentration and attenuation of atherosclerosis in ApoE-/- mice [172]. **Enterobacter aerogenes i**s another bacterial strain that has been shown to effectively reduce plasma TMAO and cecal TMAO levels by shifting the ratio of commensals and pathobionts in mice on a high-choline diet [173]. While the results are promising, it is important to apply caution when extrapolating findings from animal models into a clinical setting as the microbiome of rodents and humans are very different [174] and inter-personal differences in the microbiota composition resulting from the habitual diet and genetic make-up need to be considered, as previously explained.

https://pubmed.ncbi.nlm.nih.gov/25933483/ Phosphatidylserine and the human brain 2015
Conclusion: **Phosphatidylserine is required for healthy nerve cell membranes and myelin.** Aging of the human brain is associated with biochemical alterations and structural deterioration that impair neurotransmission. Exogenous PS (300-800 mg/d) is absorbed efficiently in humans, crosses the blood-brain barrier, and safely slows, halts, or reverses biochemical alterations and structural deterioration in nerve cells. It supports human cognitive functions, including the formation of short-term memory, the consolidation of long-term memory, the ability to create new memories, the ability to retrieve memories, the ability to learn and recall information, the ability to focus attention and concentrate, the ability to reason and solve problems, language skills, and the ability to communicate. It also supports locomotor functions, especially rapid reactions and reflexes.

https://pubmed.ncbi.nlm.nih.gov/22017963/ The effects of IQPLUS Focus on cognitive function, mood and endocrine response before and following acute exercise 2011
Phosphatidylserine (PS) is a phospholipid found in cell membranes of most animals and plants. PS
has been shown to reduce stress and increase performance in runners, cyclists and golfers. The purpose of this study was to investigate the effects of a PS containing formulation on cognitive function, mood and endocrine response before and after intense resistance exercise.
Conclusion: **PS supplementation significantly increased cognitive function prior to exercise**. Improved cognitive function could benefit athletes and non-athletes alike. PS did not appear to affect mood or endocrine response prior to or following resistance exercise.

Cinnamon Cinnamaldehyde (CA)

Note Ceylon vs Cassia(toxic if regularly consumed) Cinnamon

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5785894/ Chronic diseases, inflammation, and spices: how are they linked? 2018
Cinnamaldehyde (CM) is the active component of the spice cinnamon (*Cinnamomum zeylanicum*). This component is widely known for its anti-inflammatory, anti-microbial, anti-oxidant, anti-tumor, cholesterol lowering and immunomodulatory properties [57]. CM exerted its anti-inflammatory effect in gastric inflammation by inhibiting NF-κB activation [118]. Cinnamon can also reduce allergic encephalomyelitis in vivo via regulatory T cells [119]. Cinnamon bark has a prominent action in reducing inflammation in arthritis model in vivo via inhibiting cytokines such as IL-2, IL-4, and interferon γ (IFNγ), hence may be regarded as a potent anti-rheumatic agent [120]. Moreover, cinnamon is also effective for the treatment of neurodegenerative diseases such as AD [121, 122]
https://pubmed.ncbi.nlm.nih.gov/29258915/ Cinnamon, a promising prospect towards Alzheimer's disease 2018
Various cinnamon species and their biologically active ingredients have renewed the interest towards the treatment of patients with mild-to-moderate AD through the inhibition of tau protein aggregation and prevention of the formation and accumulation of amyloid-β peptides into the neurotoxic oligomeric inclusions, both of which are considered to be the AD trademarks. In this review, we **presented comprehensive data on the interactions of a number of cinnamon polyphenols (PPs) with oxidative stress and pro-inflammatory signaling pathways in the brain.** In addition, we discussed the potential association between AD and diabetes mellitus (DM), vis-à-vis the effluence of cinnamon PPs. Cinnamon and in particular, cinnamaldehyde seem to be effective and safe approaches for treatment and prevention of AD onset and/or progression.
https://pubmed.ncbi.nlm.nih.gov/21305046/ Orally administrated cinnamon extract reduces β-amyloid oligomerization and corrects cognitive impairment in Alzheimer's disease animal models 2011
An increasing body of evidence indicates that accumulation of soluble oligomeric assemblies of β-amyloid polypeptide (Aβ) play a key role in Alzheimer's disease (AD) pathology. Specifically, 56 kDa oligomeric species were shown to be correlated with impaired cognitive function in AD model mice. Several reports have documented the inhibition of Aβ plaque formation by compounds from natural sources. Yet, evidence for the ability of common edible elements to modulate Aβ oligomerization remains an unmet challenge. Here we identify a **natural substance, based on cinnamon extract (CEppt), which markedly inhibits the formation of toxic Aβ oligomers and prevents the toxicity of Aβ on neuronal PC12 cells. When administered to an AD fly model, CEppt rectified their reduced longevity, fully recovered their locomotion defects and totally abolished tetrameric species of Aβ in their brain. Furthermore, oral administration of CEppt to an aggressive AD transgenic mice model led to marked decrease in 56 kDa Aβ oligomers, reduction of plaques and improvement in cognitive behavior.**
https://pubmed.ncbi.nlm.nih.gov/36254234/ The Therapeutic Roles of Cinnamaldehyde against Cardiovascular Diseases 2022
Cinnamaldehyde (CA) is a bioactive phytochemical isolated from the stem bark of Chinese herbal medicine Cinnamon and has been suggested to possess curative roles against the development of CVDs. The CA-related cardiovascular protective mechanisms could be attributed to the **inhibition of inflammation and oxidative stress,** improvement of lipid and glucose metabolism, regulation of cell proliferation and apoptosis, suppression of cardiac fibrosis, and platelet aggregation and promotion of vasodilation and angiogenesis. Furthermore, CA is likely to inhibit CVD progression via affecting other possible processes including autophagy and ER stress regulation, **gut microbiota** and immune homeostasis, ion metabolism, ncRNA expression, and TRPA1 activation.
https://pubmed.ncbi.nlm.nih.gov/36402912/ Identification of potential targets of cinnamon for treatment against Alzheimer's disease-related GABAergic synaptic dysfunction using network pharmacology 2022
Cinnamon aqueous extract's active substance base remains unclear and its mechanisms, mainly the **therapeutic target of anti-Alzheimer's disease (AD)**-related GABAergic synaptic dysfunction, remain unclear. Here, **30 chemical components were identified in the aqueous extract of cinnamon** using LC/MS; secondly, we explored the brain-targeting components of the aqueous extract of cinnamon, and **17 components had a good absorption due to the blood-brain barrier (BBB) limitation**; thirdly, further clustering analysis of active ingredient targets by network pharmacology showed that the **GABA pathway with GABRG2 as the core target was significantly enriched;** then, we used prominent protein-protein interactions (PPI), relying on a protein-metabolite network, and identified the GABRA1, GABRB2 and GABRA5 as the closest targets to GABRG2; finally, the affinity between the target and its cognate active compound was predicted by molecular docking. In general, we screened five components, methyl cinnamate, propyl cinnamate, (+)-procyanidin B2, procyanidin B1, and myristicin as the brain synapse-targeting active substances of cinnamon using a systematic strategy, and identified GABRA1, GABRB2, GABRA5 and GABRG2 as core therapeutic targets of cinnamon against Alzheimer's disease-related GABAergic synaptic dysfunction. Exploring the mechanism of cinnamon' activities through multi-components and multiple targets strategies promise to reduce the threat of single- target and symptom-based drug discovery failure.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4488098/ Cinnamon from the selection of traditional applications to its novel **effects on the inhibition of angiogenesis in cancer cells and prevention of Alzheimer's disease**, and a series of functions such as antioxidant, anticholesterol, antidiabetes, antibacterial, antifungal, nematicidal, acaracidal, and repellent activities 2015
The major portion of the essential oil is made up of cinnamaldehyde or cinnamic aldehyde.6 Cinnamaldehyde is responsible for the flavor and aroma of cinnamon.9 A study found that cinnamaldehyde is the major volatile component of cinnamon sticks, with 83.6% of essential oils extracted from cinnamon stick powder.2 The essential oils from *Cinnamon cassia* also contain 80–90% cinnamaldehyde with little or no eugenol, which is different from *C. zeylanicum* bark, which contains 60–80% cinnamaldehyde and approximately 2% eugenol, however, essential oils from its leaves were found to be rich in eugenol (70–75%).2 The study showed that the crude extracts of cinnamon stick also contained high levels of nonvolatile compounds (mainly condensed tannins), which consist of **23.2% proanthocyanidins and 3.6% catechins in addition to cinnamaldehyde (64.1%)**.2
https://pubmed.ncbi.nlm.nih.gov/19433898/ Cinnamon extract inhibits tau aggregation associated with Alzheimer's disease in vitro 2009
An aqueous extract of Ceylon cinnamon (C. zeylanicum) is found to **inhibit tau aggregation and filament formation, hallmarks of Alzheimer's disease (AD).** The extract can also promote complete disassembly of recombinant tau filaments and cause substantial alteration of the morphology of paired-helical filaments isolated from AD brain. Cinnamon extract (CE) was not deleterious to the normal cellular function of tau, namely the assembly of free tubulin into microtubules. An **A-linked proanthocyanidin trimer molecule was purified from the extract and shown to contain a significant proportion of the inhibitory activity.** Treatment with polyvinylpyrolidone effectively depleted all proanthocyanidins from the extract solution and removed the majority, but not all, of the inhibitory activity. The **remainder inhibitory activity could be attributed to cinnamaldehyde**. This work shows that compounds endogenous to cinnamon may be beneficial to AD themselves or may guide the discovery of other potential therapeutics if their mechanisms of action can be discerned.
https://pubmed.ncbi.nlm.nih.gov/23531502/ Interaction of cinnamaldehyde and epicatechin with tau: implications of beneficial effects in modulating Alzheimer's disease pathogenesis 2013

Abnormal modifications in tau such as hyperphosphorylation, oxidation, and glycation interfere with its interaction with microtubules leading to its dissociation and self-aggregation into neurofibrillary tangles, a hallmark of Alzheimer's disease (AD). **Previously we reported that an aqueous extract of cinnamon has the ability to inhibit tau aggregation** in vitro and can even induce dissociation of tangles isolated from AD brain. In the present study, we carried out **investigations with cinnamaldehyde (CA) and epicatechin (EC), two components of active cinnamon extract**. We found that **CA and the oxidized form of EC (ECox) inhibited tau aggregation** in vitro and the activity was due to their interaction with the two cysteine residues in tau. Mass spectrometry of a synthetic peptide, SKCGS, representing the actual tau sequence, identified the thiol as reacting with CA and ECox. Use of a cysteine double mutant of tau showed the necessity of cysteine for aggregation inhibition by CA. The interaction of CA with tau cysteines was reversible and the presence of CA did not impair the biological function of tau in tubulin assembly in vitro. Further, these compounds protected tau from oxidation caused by the reactive oxygen species, H2O2, and prevented subsequent formation of high molecular weight species that are considered to stimulate tangle formation. Finally, we observed that EC can sequester highly reactive and toxic byproducts of oxidation such as acrolein. Our results suggest that small molecules that form a reversible interaction with cysteines have the potential to protect tau from abnormal modifications.

Clove (*Syzygium aromaticum*)(phenolic compounds such as eugenol, gallic acid)

-clove powder available on amazon
supplement: 1-2.5g powder
https://pubmed.ncbi.nlm.nih.gov/25182278/ Clove (Syzygium aromaticum): a precious spice. 2014
Clove (Syzygium aromaticum) is one of the most valuable spices that has been used for centuries as food preservative and for many medicinal purposes. Clove is native of Indonesia but nowadays is cultured in several parts of the world including Brazil in the state of Bahia. This plant represents one of the **richest source of phenolic compounds such as eugenol, eugenol acetate and gallic acid** and posses great potential for pharmaceutical, cosmetic, food and agricultural applications. This review includes the main studies reporting the biological activities of clove and eugenol. The **antioxidant** and antimicrobial activity of clove is higher than many fruits, vegetables and other spices and **should deserve special attention**.
https://pubmed.ncbi.nlm.nih.gov/34770801/ Clove Essential Oil (Syzygium aromaticum L. Myrtaceae): Extraction, Chemical Composition, Food Applications, and Essential Bioactivity for Human Health 2021
Eugenol is the major compound, accounting for at least 50%. The remaining 10-40% consists of eugenyl acetate, β-caryophyllene, and α-humulene.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3819475/ Clove (*Syzygium aromaticum*): a precious spice 2014
Clove represents one of the major vegetal sources of phenolic compounds as flavonoids, hidroxibenzoic acids, hidroxicinamic acids and hidroxiphenyl propens. **Eugenol is the main bioactive compound of clove, which is found in concentrations ranging from 9 381.70 to 14 650.00 mg per 100 g of fresh plant material**[6].
With regard to the phenolic acids, **gallic acid is the compound found in higher concentration (783.50 mg/100 g fresh weight)**. However, other gallic acid derivates as hidrolizable tannins are present in higher concentrations (2 375.8 mg/100 g)[1]. Other phenolic acids found in clove are the caffeic, ferulic, elagic and salicylic acids. Flavonoids as kaempferol, quercetin and its derivates (glycosilated) are also found in clove in lower concentrations. 100 richest dietary sources of polyphenols[8]. Results indicate that the spice plants are the kind of food with higher polyphenol content followed by fruits, seeds and vegetables. Among spices, **clove showed the higher content of polyphenols and antioxidant compounds**.
https://pubmed.ncbi.nlm.nih.gov/34856360/ Exercise and Syzygium aromaticum reverse memory deficits, apoptosis and mitochondrial dysfunction of the hippocampus in Alzheimer's disease 2022
81 rats were randomly assigned to 9 groups: Healthy (H), sham (sh), Healthy-exercise (HE), Healthy-clove (HC), Healthy-exercise-clove (HEC), Alzheimer's (A), Alzheimer's-exercise (AE), Alzheimer's-clove (AC), and Alzheimer's-exercise-clove (AEC). Alzheimer's induction was induced by the injection of 1-42 amyloid into the CA1 region of the hippocampus. The exercise training protocol was performed for 3 weeks, every day for 30 min in swimming training, and clove oil supplementation (0.1 mg/kg) was gavaged daily for 3 weeks in the supplement rat. **Following endurance training and consumption of clove oil, spatial memory (P = 0.001), apoptosis (P = 0.001) and mRNAs and protein levels of PRDX6 (P = 0.001) and GCN5L1 (P = 0.017), were recovered in AE, AC and AEC groups, as compared with A group.**
https://pubmed.ncbi.nlm.nih.gov/29959974/ Neuroprotection by **ethanolic extract of Syzygium aromaticum** in Alzheimer's disease like pathology via maintaining oxidative balance through SIRT1 pathway 2018
Anti-oxidative capacity of Syzygium aromaticum was performed in $A\beta_{25-35}$ induced neurotoxicity in neuronal cells. Superoxide dismutase, Catalase and Glutathione enzyme activity were determined by the treatment of Syzygium aromaticum. These findings show a **holistic approach towards the neurodegenerative disease management by Syzygium aromaticum which could lead to the formulation of new drug for AD**. This Ayurvedic product can give a healthy aging with no side effects and also be cost effectives. It may meet unmet medical needs of current relevance.
https://www.thespruceeats.com/what-are-cloves-995621 Cooking With Cloves
Whole or ground cloves are used to **flavor sauces, soups and rice dishes**, notably a number of traditional Indian dishes, and it's one of the components of garam masala. Whole cloves are either removed before serving or picked out of the dish. Even when cooked, whole cloves have a very hard, woody texture that would be unpleasant to bite into.

Cloves also feature in any number of desserts, especially ground cloves, and particularly around the holidays. Think **eggnog or pumpkin pie spice. Cloves are often paired with cinnamon or nutmeg, but in general, it's a good idea to use cloves sparingly.**

Coenzyme Q10 (TNF inhibitor)

https://pubmed.ncbi.nlm.nih.gov/10847562/ Serum levels of coenzyme Q10 in patients with Alzheimer's disease 2000
Coenzyme Q10 levels and coenzyme Q10/cholesterol ratio of AD or VD patients were not correlated with age, age at onset, duration of the disease or scores of the MiniMental State Examination. These results suggest that these values are **not related with the risk for AD or VD**.
https://pubmed.ncbi.nlm.nih.gov/10847558/ Serum levels of coenzyme Q10 in patients with Parkinson's disease 2000
The normality of serum coenzyme Q10 and coenzyme Q10/cholesterol ratio suggest that these values are **not related with the risk for PD.**
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2931577/ Increasing evidence suggests that Alzheimer's disease (AD) is associated with oxidative damage that is caused in part by mitochondrial dysfunction. Here we investigated the feasibility of modifying Alzheimer pathology with the mitochondrial antioxidant coenzyme Q (CoQ). 2008
CoQ supplementation **significantly suppressed brain levels of protein carbonyls, which are markers of oxidative damage**. The **failure of CoQ supplementation to increase CoQ levels in brain homogenates or mitochondria was unexpected**, but consistent with many other reports, which varied in dose and duration of CoQ supplementation, strain of rodent, and fractionation of brain tissue for analysis. Our results indicate that CoQ supplementation achieves antioxidant effects in vitro and in the brains of wild type mice.
https://pubmed.ncbi.nlm.nih.gov/30285386/ Coenzyme Q10 2022
researchers hypothesize that **statin drugs may deplete the body of CoQ10**. As muscle pain and cramping are such a common adverse effect of statins, they believe this depletion of CoQ10 is the culprit.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3267988/pdf/nihms315512.pdf CoQ10 2012
treatment resulted in decreased plaque area and number in hippocampus and in overlying cortex immunostained with an Aβ42-specific antibody. Brain Aβ42 levels were also decreased by CoQ10 supplementation. Levels of amyloid-β protein precursor (AβPP) β-carboxyterminal fragments were decreased. Importantly, **CoQ10-treated mice showed improved cognitive performance** during Morris water maze testing. Our results show decreased pathology and improved behavior in transgenic AD mice treated with the naturally occurring antioxidant compound CoQ10. CoQ10 is well tolerated in humans and may be promising for therapeutic trials in AD.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5807419/pdf/fphys-09-00044.pdf Coenzyme Q10 Supplementation in Aging and Disease 2018
Here, we review the current knowledge of CoQ10 biosynthesis and primary CoQ10 deficiency syndrome, and have collected published results from clinical trials based on CoQ10 supplementation. There is **evidence that supplementation positively affects mitochondrial deficiency syndrome and the symptoms of aging based mainly on improvements in bioenergetics**. Cardiovascular disease and inflammation are alleviated by the antioxidant effect of CoQ10.
https://pubmed.ncbi.nlm.nih.gov/18806307/ Effects of Coenzyme Q10 on TNF-alpha secretion in human and murine monocytic cell lines 2007
Here we studied the influence of CoQ10 (Kaneka Q10) on secretion of the pro-inflammatory cytokine tumor necrosis factor-alpha (TNF-alpha) by using the human and murine monocytic cell lines THP-1 and RAW264.7 expressing human apolipoprotein E3 (apoE3) or pro-inflammatory apoE4. When THP-1 cells were pre-incubated with 10 microM CoQ10, **the LPS-induced TNF-alpha release was significantly decreased** to 72 +/- 32%. In conclusion, CoQ10 has moderate anti-inflammatory effects in two monocytic cell lines which could be mediated by its antioxidant
https://pubmed.ncbi.nlm.nih.gov/20354351/ **Coenzyme Q10 decreases TNF-alpha** and IL-2 secretion by human peripheral blood mononuclear cells 2010
The production of the proinflammatory cytokines IL-1beta, IL-6 and IFNgamma and that of the anti-inflammatory cytokines IL-1ra and IL-10 by PBMC was not affected by CoQ10, whereas **TNFalpha secretion was significantly decreased** when the cells were incubated with 0.6 and 1.25 muM of CoQ10. On the other hand, increasing doses of CoQ10 caused mild, but statistically significant inhibition of IL-2 secretion.

Coffee

https://pubmed.ncbi.nlm.nih.gov/20182054/ Caffeine as a protective factor in dementia and Alzheimer's disease 2010
The findings of the previous studies are somewhat inconsistent, but most studies (3 out of 5) support **coffee's favorable effects against cognitive decline**, dementia or AD. In addition, two studies had combined coffee and tea drinking and indicated some positive effects on cognitive functioning.
https://pubmed.ncbi.nlm.nih.gov/30322179/#:~:text=Meta-analysis%20of%20five%20studies%20that%20focused%20on%20Alzheimer%27s,1.01%20%2895%25%20confidence%20interval%200.95%E2%81%BB1.07%3B%20p%20%3D%200.80%29.
Coffee Consumption and Risk of Dementia and Alzheimer's Disease: A Dose-Response Meta-Analysis of Prospective Studies. 2018
These studies included 7486 dementia cases diagnosed among 328,885 individuals during an average follow-up of 4.9¯25 years. Meta-analysis of all eight studies indicated **no statistically significant association between coffee consumption and the risk of dementia** and no deviations from a linear trend (p = 0.08). The relative risk of dementia per 1 cup/day increment of coffee consumption was 1.01 (95% confidence interval (CI) 0.98¯1.05; p = 0.37).
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7915779/ Potential of Caffeine in Alzheimer's Disease—A Review of Experimental Studies 2021
In conclusion, the reports of studies on experimental AD models generally supported the notion that **caffeine may exert some beneficial effects in AD**
https://pubmed.ncbi.nlm.nih.gov/26944757/ Habitual coffee consumption and risk of cognitive decline/dementia: A systematic review and meta-analysis of prospective cohort studies 2015
The combined RR indicated that **high coffee consumption was not associated with the different measures of cognitive decline or dementia** (summary RR, 0.97; 95% CI, 0.84-1.11). Subgroup analyses suggested a significant inverse association between highest coffee consumption and the risk for Alzheimer disease (summary RR, 0.73; 95% CI, 0.55-0.97). The dose-response analysis, including eight studies, did not show an association between the increment of coffee intake and cognitive decline or dementia risk (an increment of 1 cup/d of coffee consumed; summary RR, 1.00; 95% CI, 0.98-1.02).

Convolvulus pluricaulis [Shankhpushpi](CP), a *Medhya Rasayana* (nootropic) herb {Ayurvedic and Traditional Chinese formulae indicated for neurological conditions} -see Shankhpushpi

Curcumin (400 mg of curcumin = two teaspoons of turmeric powder) note bioavialablity problem, add black pepper,piperine or other option)

-note Curcumin is also an iron chelator, and a TNF inhibitor, protects against alum
500-2000mg/day
https://pubmed.ncbi.nlm.nih.gov/19966973/ The effect of curcumin (turmeric) on Alzheimer's disease: An overview 2008
A growing body of evidence indicates that oxidative stress, free radicals, beta amyloid, cerebral deregulation caused by bio-metal toxicity and **abnormal inflammatory reactions contribute to the key event in Alzheimer's disease pathology**. Due to various effects of curcumin, such as decreased Beta-amyloid plaques, delayed degradation of neurons, metal-chelation, **anti-inflammatory, antioxidant** and decreased microglia formation, the **overall memory in patients with AD has improved**. This paper reviews the various mechanisms of actions of curcumin in AD and pathology.
https://pubmed.ncbi.nlm.nih.gov/11606625/ The curry spice **curcumin reduces oxidative damage and amyloid pathology** in an Alzheimer transgenic mouse 2001
One alternative NSAID is curcumin, derived from the curry spice turmeric. Curcumin has an extensive history as a food additive and herbal medicine in India and is also a potent polyphenolic antioxidant. To evaluate whether it could affect Alzheimer-like pathology in the APPSw mice, we tested a low (160 ppm) and a high dose of dietary curcumin (5000 ppm) on inflammation, oxidative damage, and plaque pathology. **Low and high doses of curcumin significantly lowered oxidized proteins and interleukin-1beta, a proinflammatory cytokine elevated in the brains of these mice.** With low-dose but not high-dose curcumin treatment, the astrocytic marker GFAP was reduced, and insoluble beta-amyloid (Abeta), soluble Abeta, and plaque burden were significantly decreased by 43-50%. However, levels of amyloid precursor (APP) in the membrane fraction were not reduced. Microgliosis was also suppressed in neuronal layers but not adjacent to plaques. In view of its efficacy and apparent low toxicity, this Indian spice component shows promise for the prevention of Alzheimer's disease.
https://pubmed.ncbi.nlm.nih.gov/29332042/ Protective Effects of Indian Spice Curcumin Against Amyloid-β in Alzheimer's Disease 2018
roducts derived from plants are known to have protective effects, including **anti-inflammatory, antioxidant,** anti-arthritis, pro-healing, and **boosting memory cognitive functions**. In the last decade, several groups have designed and synthesized curcumin and its derivatives and extensively tested using cell and mouse models of AD. Recent research on Aβ and curcumin has revealed that **curcumin prevents Aβ aggregation and crosses the blood-brain barrier**, reach brain cells, and protect neurons from various toxic insults of aging and Aβ in humans. Recent research has also reported that curcumin ameliorates cognitive decline and improves synaptic functions in mouse models of AD.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3580400/pdf/alzrt146.pdf Oral curcumin for Alzheimer's disease: tolerability and efficacy in a 24-week randomized, double blind, placebo-controlled study 2012
Curcumin was generally well-tolerated although three subjects on curcumin withdrew due to gastrointestinal symptoms. We were **unable to demonstrate clinical or biochemical evidence of efficacy of Curcumin C3 Complex® in AD in this 24-week placebo-controlled trial** although preliminary data suggest limited bioavailability of this compound.
https://alzheimer.neurology.ucla.edu/Curcumin.html Curcumin - Mary S. Easton UCLA Alzheimer Translation Center
India has a low incidence and prevalance of Alzheimer's, which may be related to genetics or a particular intake of specific foods. Some people attribute the low incidence of Alzheimer's to a high intake of turmeric in Asia. As turmeric contains an average of 5-10% curcumin, the daily intake of curcumin is approximated in India is thought be about 125 mg. In summary **curcumin is easily absorbed but not necessarily very bioavailable to the brain (such as dissolved in cooking oils or formulated). It is stable in fatty tissues such as the brain, but not in blood.**
Fasting improves free curcumin absorption (eg. minimum of 3 hours after a meal). You make take it with a small drink (4-6 ounces; eg. **cherry juice with a higher pH making it more soluble**. Wait an hour before eating a meal. HOWEVER, ancectodal evidence suggests that some people may have sleep disturbances if taken before bedtime. Since it takes 10 days to build up levels of curcumin in tissues, it may be important to titer up or down at 10 day intervals.
https://curcuminhealth.info/curcumins-bioavailability/ Curcumin's Bioavailability
As beneficial as Curcumin is, inexpensive supplements contain only somewhere between 2-5% (if you're lucky) of the desired compound. Curcumin's bioavailability or lack thereof is supported by the findings of the study *Bioavailability of Curcumin: Problems and Promises,* published in 2007 in Molecular Pharmaceutics. The four scientists conducting the study, Drs. Anand, Kunnumakkara, Newman, and Aggarwal, found low levels of Curcumin in plasma and tissue levels, even after high doses of Curcumin were administered. Their observations led to the **conclusions that Curcumin's bioavailability was hindered by poor absorption,** rapid metabolism, and rapid systemic elimination.
https://www.healthline.com/nutrition/turmeric-and-black-pepper#active-ingredients Piperine (Black Pepper) Enhances the Absorption of Curcumin
One study showed that adding **20 mg of piperine to 2 grams of curcumin increased its absorption significantly**
Amazon: Turmeric Curcumin with Piperine 1500mg(actually 300mg), take twice per day, $0.14/count (20X) (Note Piperine could increase bioavailability of other drugs too.....)
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8572027/ Anti-Inflammatory Effects of Curcumin in the Inflammatory Diseases: Status, Limitations and Countermeasures 2021
The physiological and pathological mechanisms of **inflammatory bowel disease, psoriasis, atherosclerosis, COVID-19** and other research focus diseases are not clear yet, and they are c**onsidered to be related to inflammation**. The anti-inflammatory effect of curcumin can effectively improve the symptoms of these diseases and is expected to be a candidate drug for the treatment of related diseases. This paper mainly reviews the **anti-inflammatory** effect of curcumin. In conclusion, curcumin has good anti-inflammatory properties, and curcumin regulates NF-κB, MAPK, AP-1, JAK/ STAT and other signaling pathways, and inhibiting the production of inflammatory mediators. Curcumin in the treatment of **IBD, arthritis, psoriasis, depression** and atherosclerosis and other diseases, can reduce inflammatory response, effectively improve symptoms, play a role in the treatment of diseases.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9372765/pdf/25789430-2022-micropub.biology.000617.pdf Curcumin, but not its degradation products, in combination with silibinin is primarily responsible for the inhibition of colon cancer cell proliferation 2022
In the present study we showed that the curcumin degradation products in combination with silibinin did not inhibit cell growth compared to the curcumin plus silibinin combination. Our result supports our previous study that **curcumin and silibinin in combination inhibit cell growth significantly** (Montgomery et al. 2016). Among the curcumin degraded products, either singly or in combination with silibinin, none of them showed significant inhibition of cell growth compared to control.
We have published data showing that a combination of curcumin and silymarin (CS), elicited synergistically enhanced anticancer activity in vitro (Montgomery et al. 2016). In the present study, we showed it is curcumin but not the curcumin degradation products that elicit the combination anticancer effects with silibinin. Our future studies will be focused on the mechanism by which curcumin plus silibinin causes the anticancer effects using in vitro and in vivo systems
https://en.m.wikipedia.org/wiki/TNF_inhibitor . Anti-TNF agents in nature
TNF or its effects are inhibited by several natural compounds, including **curcumin**[36][37][38][39] (a compound present in turmeric), and **catechins** (in green tea). **Cannabidiol**[40] and **Echinacea purpurea** also seem to have anti-inflammatory properties through inhibition of TNF-α production, although this effect may be mediated through cannabinoid CB1 or CB2 receptor-independent effects.[41] **5-HT2A receptor agonists** have also been shown to have potent inhibitory effects on TNF-α, including Psilocybin found in many species of mushrooms.[42][43]
Thymoquinone, a compound found in the flower **Nigella sativa,** has been studied for possible TNF-α inhibition and related benefits for autoimmune disorder treatment.[44][45][46][47]
https://pubmed.ncbi.nlm.nih.gov/34209461/ Metal-Curcumin Complexes in Therapeutics: An Approach to Enhance Pharmacological Effects of Curcumin 2021
It is well established that **curcumin strongly chelates several metal ions, including boron, cobalt, copper, gallium, gadolinium, gold, lanthanum, manganese, nickel, iron, palladium, platinum, ruthenium, silver, vanadium, and zinc**. In this review, the pharmacological, chemopreventive, and therapeutic activities of metal-curcumin complexes are discussed. Metal-curcumin

complexes increase the solubility, cellular uptake, and bioavailability and improve the antioxidant, anti-inflammatory, antimicrobial, and antiviral effects of curcumin. **Metal-curcumin complexes have also demonstrated efficacy against various chronic diseases, including cancer, arthritis, osteoporosis, and neurological disorders such as Alzheimer's disease.**

https://pubmed.ncbi.nlm.nih.gov/31264110/ Curcumin Acts as Post-protective Effects on Rat Hippocampal Synaptosomes in a Neuronal Model of Aluminum-Induced Toxicity. 2019

Furthermore, curcumin post-treatment significantly improved oxidative damage and morphological alterations, and suppressed cytochrome c and caspase 3 activities. Taken together, our data showed that **curcumin had more therapeutic effects than protective effects in AlCl3-induced neurotoxicity.**

https://pubmed.ncbi.nlm.nih.gov/34070220/ Curcumin Attenuated Neurotoxicity in Sporadic Animal Model of Alzheimer's Disease. 2021

We also showed that CUR post-treatment significantly improved the behavioral, oxidative stress and inflammation in AlCl3-exposed rats. Taken together, our data presented CUR as a nutraceutical potential through its **protective effects** that are more interesting than recovery ones in sporadic model of AD.

https://pubmed.ncbi.nlm.nih.gov/36342584/ Therapeutic and Preventive Effects of **Piperine and its Combination with Curcumin as a Bioenhancer Against Aluminum**-Induced Damage in the Astrocyte Cells. 2022

Recently, studies conducted with astrocyte cells have drawn attention to neurodegeneration pathologies caused by aluminum exposure. In particular, investigating the potential of herbal therapeutic agents to prevent this effect of aluminum has gained importance. The purpose of this study was to investigate the therapeutic and preventive effects of piperine, curcumin, and the combination of these compounds on reactive primary astrocyte cells. . In conclusion, the **results of the study showed that the use of different concentrations of piperine, curcumin, and their combination had significantly higher % cell viability on aluminum-induced damage in astrocyte cells compared to the damaged control group**. In addition, a decrease in the number of apoptotic and necrotic cells was observed in the same groups, which indicated that piperine increased curcumin activity. The decrease in the amount of IL-6 and TGF-β cytokines also supported that piperine increased the effectiveness of curcumin. Considering all these results, it can be said that in terms of aluminum damage in astrocyte cells, the bioavailability-enhancing property of piperine on curcumin was shown for the first time in the literature. In line with these results, it is inevitable to carry out further studies.

https://pubmed.ncbi.nlm.nih.gov/23425071/ **Curcumin: an orally bioavailable blocker of TNF** and other pro-inflammatory biomarkers 2013

TNFs are major mediators of inflammation and inflammation-related diseases, hence, the United States Food and Drug Administration (FDA) has approved the use of blockers of the cytokine, TNF-α, for the treatment of osteoarthritis, inflammatory bowel disease, psoriasis and ankylosis. In the current report, we describe an alternative, curcumin (diferuloylmethane), a component of turmeric **(Curcuma longa) that is very inexpensive, orally bioavailable and highly safe in humans, yet can block TNF-α action** and production in in vitro models, in animal models and in humans. In addition, we provide evidence for curcumin's activities against all of the diseases for which TNF blockers are currently being used.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7139886/ Curcumin in Health and Diseases: Alzheimer's Disease and Curcumin Analogues, Derivatives, and Hybrids 2020

Nowadays, several medications, among them c**urcumin, are used in the treatment of AD**. Curcumin, which is the principal component of *Curcuma longa*, has shown favorable effects forsignificantly preventing or treating AD. Azzi et al. [49] replaced the β-diketone moiety of curcumin by a carbonyl group and substituted one of the two aromatic rings with an ortho-carborane. Thus, they synthesized and evaluated a new class **of boronated monocarbonyl analogues of curcumin (BMAC)** for amyloid-β disaggregation activity.

AB50 presented two hydroxyl moieties and showed better efficiency. The presence of a second –OH group enhanced the binding. The findings from the HEWL fibril aggregation support the concept that the presence of at least one aromatic group is essential for the inhibitory efficiency of these derivatives. Finally, the presence of **boron atoms in the carborane cage support the boron neutron capture therapy (BNCT)** as a radiative boost to enhance fibril disaggregation (Figure 3 and Table 1).

https://pubmed.ncbi.nlm.nih.gov/34010562/ Evolving Role of Natural Products from Traditional Medicinal Herbs in the Treatment of Alzheimer's Disease 2019

Turmeric is a flowering plant of the ginger family Zingiberaceae and is native to the Indian subcontinent and Southeast Asia. The bright yellow–orange color that this rhizome plant displays is mainly due to the polyphenolic compounds called curcuminoids. Turmeric is **anti-inflammatory, antiseptic, and antibacterial** and has long been used to treat a wide variety of conditions including liver detoxification, to prevent infection and inflammation, to balance cholesterol levels, to treat allergies, to stimulate digestion, and to boost immunity [80]. The active constituents of turmeric are turmerone oil and water-soluble curcuminoids. Curcuminoids include curcumin, demethoxycurcumin (DMC), bisdemethoxycurcumin (BDMC), and cyclocurcumin [81]. Curcumin is the principal **curcuminoid whose anti-inflammatory property is associated with reduced risk of AD** [82]. In vitro studies revealed **curcumin's ability to block lipid peroxidation and neutralize reactive oxygen species, which was several times more potent than vitamin E [145].**

BIOAVIALABILITY OF CURCUMIN

https://pubmed.ncbi.nlm.nih.gov/17999464/ Bioavailability of curcumin: problems and promises 2007

Curcumin, a polyphenolic compound derived from dietary spice turmeric, possesses diverse pharmacologic effects including a**nti-inflammatory, antioxidant,** antiproliferative and antiangiogenic activities. Phase I clinical trials have shown that curcumin i**s safe even at high doses (12 g/day)** in humans but exhibit poor bioavailability. To improve the bioavailability of curcumin, numerous approaches have been undertaken. These approaches involve, first, the use of adjuvant like **piperine** that interferes with glucuronidation; second, the use of **liposomal curcumin**; third, **curcumin nanoparticles**; fourth, the use of curcumin **phospholipid complex**; and fifth, the use of **structural analogues** of curcumin (e.g., EF-24).

https://pubmed.ncbi.nlm.nih.gov/19491009/ **Nanoparticle** encapsulation improves oral bioavailability of curcumin by at least **9-fold** when compared to curcumin administered with **piperine** as absorption enhancer 2009

The in vivo pharmacokinetics revealed that curcumin entrapped **nanoparticles demonstrate at least 9-fold increase in oral bioavailability when compared to curcumin administered with piperine** as absorption enhancer.

https://pubmed.ncbi.nlm.nih.gov/9619120/ Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers 1998

Concomitant administration of piperine 20 mg/kg increased the serum concentration of curcumin for a **short period of 1-2 h post drug**. On the other hand in humans after a dose of 2 g curcumin alone, serum levels were either undetectable or very low. Concomitant administration of **piperine 20 mg** produced much higher concentrations from 0.25 to 1 h post drug ($P < 0.01$ at 0.25 and 0.5 h; $P < 0.001$ at 1 h), the **increase in bioavailability was 2000%**.

https://pubmed.ncbi.nlm.nih.gov/32929825/ Piperine: A review of its biological effects 2021

Piper nigrum, belonging to the family Piperaceae is one of the most widely used spices all over the world. It has a distinct sharp flavor attributed to the presence of the phytochemical, piperine. Apart from its use as a spice, P. nigrum is frequently used for medicinal, preservation, and perfumery purposes. **Black pepper contains 2-7.4% of piperine**, varying in content is associated with the pepper plant. Piperine displays numerous pharmacological effects such as **antiproliferative, antitumor, antiangiogenesis, antioxidant, antidiabetic, anti-obesity, cardioprotective, antimicrobial, antiaging, and immunomodulatory effects i**n various in vitro and in vivo experimental trials. Furthermore, piperine has also been documented for its hepatoprotective, anti-allergic, **anti-inflammatory, and neuroprotective properties.**

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2688199/ Anti-inflammatory and antiarthritic effects of piperine in human interleukin 1β-stimulated fibroblast-like synoviocytes and in rat arthritis models 2009

These results suggest that piperine has **anti-inflammatory**, antinociceptive, and **antiarthritic** effects in an arthritis animal model.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6424351/ The Holy Grail of Curcumin and its Efficacy in Various Diseases: Is Bioavailability Truly a Big Concern? 2017

Despite **thousands of *in vivo* studies demonstrating the therapeutic efficacy of curcumin, even at very low doses**, **limited systemic bioavailability has hindered its development** as a potential therapeutic agent. The low bioavailability of curcumin is primarily caused by three factors: low aqueous solubility, poor absorption, and extensive metabolic conversion of the molecule. *I*nterestingly, piperine, a major component of black and long peppers, has been shown to inhibit enzymatic conjugation of curcumin allowing greater levels of unconjugated curcumin to be absorbed into portal blood circulation[14] and increased curcumin tissue retention time,[28] as illustrated in Figure 1. Therefore, **piperine** has been investigated as a potential systemic transporter of curcumin. While this **co-delivery strategy with piperine is promising**, there are concerns for potential adverse/negative interactions of such preparations with various pharmaceutical drugs, limiting the usefulness of such curcumin preparations in various disease conditions. The use of curcumin formulations using **nanoparticles is currently one of the most popular strategies** in improving the bioavailability of curcumin. Unlike free curcumin, **nanocurcumin is readily dispersed in aqueous media**. Another type of nanoformulation, **solid lipid nanoparticle (SLN) loaded with curcumin, has also shown significant potential in delivering improved curcumin concentrations to organs such as the brain**. Moreover, nanoparticle curcumin has been widely tested in preclinical models for non-cancer diseases including **Alzheimer**, hepatitis, cerebral ischemia, asthma, and heart failure.

Another common curcumin formulation aimed at increasing higher absorption and bioavailability involves **liposomal c**oating of the active molecule. Liposomes are spherical bilayer vesicles that shield hydrophobic compounds (such as curcumin), and interact with aqueous environments to improve aqueous solubility.

E**TO (TURMERIC OIL COATED CURCUMIN) curcumin** has been shown to have **7 to 10-fold higher bioavailability** and shown to be retained longer in systemic circulation, compared with standard curcumin. ETO-curcumin consumption improved diseases including arthritis, depression, and **Alzheimer** disease. ETO-curcumin appears to be the one of most reliable sources of curcumin currently available in the market.

https://superfoodly.com/best-turmeric-curcumin-supplement/ Which Curcumin Supplement Has The Best Absorption?

For curcumin bioavailability, **Theracurmin and Longvida, and NovaSOL** are the clear winners. The enhanced absorption with piperine (i.e. BioPerine) is trivial compared to what **phospholipids** or **nano-particle** size (i.e. Theracurmin) can accomplish. Presumably this is why Longvida, NovaSOL, and Theracurmin don't even include piperine… that was a first generation supplement.

Longvida: Composition: 20% curcumin, 80% phospholipids (65X more bioavailable than curcumin) (7X longer in body) (passes blood brain barrier)
-Longvida Optimised Curcumin 500 mg (1 – 2 capsules per day, 7hr half life) almost $1 per capsule (Note UCLA says 4- 8 capsules)

Theracurmin: Composition: 10% curcumin, 90% other curcuminoids (desmethoxycurcumin and bis-desmethoxycurcumin)

NovaSOL: Composition: "Micellar matrix" which is curcumin "preferably between 7 nm and 10 nm" combined with emulsifier(s). (114X to 185x greater bioavailability)
-uses Polysorbate 80, used as emulsifier in foods
-Sisu Full Spectrum Curcumin, 60 Liquid Softgels - Water Soluble Antioxidant with NovaSOL 40mg - $0.74/count

http://blog.arthritis.org/living-with-arthritis/anti-inflammatory-tumeric-curcumin/ Stick with Supplements

Experts say to stick with curcumin supplements, preferably the high-quality extracts used in clinical trials, which contain up to 95 percent curcumin. **Look for brands using black pepper (piperine), phospholipids (Meriva, BCM-95) antioxidants (CircuWin) or nanoparticles (Theracumin) for better bioavailability.** Curcumin is hard for your body to absorb; only about 2 to 3 percent may end up in your bloodstream. To increase absorption even more, take **curcumin with a meal where you consume some fat**. Philip Barr, MD, head of Duke Integrative Medicine at Duke University in Durham, North Carolina recommends 500 mg of high-quality curcumin twice a day for both OA and RA. He suggests medical-grade products by Thorne or Pure Encapsulations.

Epigallocatechin gallate (EGCG) [grape seed extract and green and black teas] [iron chelator]

– also TNF inhibitor

https://pubmed.ncbi.nlm.nih.gov/34012254/ Epigallocatechin-3-Gallate Provides Protection Against Alzheimer's Disease-Induced Learning and Memory Impairments in Rats 2021

Recent evidence has highlighted the anti-inflammatory properties of the constituent of Green Tea Polyphenols (GTP), epigallocatechin-3-gallate **(EGCG) which has been suggested to exert a neuroprotective effect on Alzheimer's disease (AD).** The current study aimed to elucidate the effect of EGCG on memory function in rats with AD. **Conclusion:** The current study demonstrates that EGCG may diminish the hyperphosphorylation of the Tau protein, downregulate BACE1 and Aβ1-42 expression to **improve the antioxidant system and learning and memory function of rats with AD.**

https://pubmed.ncbi.nlm.nih.gov/28520620/ (-)-Epigallocatechin-3-gallate ameliorates memory impairment and rescues the abnormal synaptic protein levels in the frontal cortex and hippocampus in a mouse model of Alzheimer's disease 2017

(-)-Epigallocatechin-3-gallate (EGCG) is the **most abundant polyphenolic extract in green tea** and it has attracted increasing attention for its multiple bioactive effects. However, the mechanisms by which EGCG exerts its neuroprotective actions in Alzheimer's disease (AD) are presently lacking. The results showed that long-term oral consumption of **EGCG at a relatively high dose (15 mg/kg) improved memory function in SAMP8 mice in the Y-maze and Morris water maze.** The levels of Aβ1-42 and BACE-1 in FC and Hip were significantly reduced by EGCG treatment. EGCG treatment also prevented the hyperphosphorylation of tau and reversed the decreased synaptic protein marker synaptophysin and postsynaptic density protein 95 in FC and Hip of SAMP8 mice. The present study suggests that long-term oral consumption of **EGCG ameliorates impairments in spatial learning and memory and rescues the reduction in synaptic proteins observed in an AD mouse model. Thus, EGCG may represent a novel candidate agent for the treatment of neurodegenerative diseases.**

https://www.alzforum.org/therapeutics/epigallocatechin-gallate-egcg Epigallocatechin Gallate (EGCG)

In 2012, a Phase 2 trial began at the Parc de Salut Mar Hospital in Barcelona. It assessed the effect of 12 months of treatment with EGCG on various cognitive outcomes and plasma Aβ biomarkers in 84 people with Down's syndrome, age 14 to 29, to assess whether **EGCG slows the development of AD-like symptoms and biomarkers in Down's**. Secondary outcomes include further cognitive and brain imaging tests, among others. **Participants who received ECGC and cognitive training did significantly better on tests of memory, executive function, and attention** than those who did cognitive training only.

In January 2014, a Phase 3 trial ramped up at Ludwig Maximilians Universität and Technische Universität, both in Munich, to evaluate EGCG in multiple-system atrophy. MSA is a rapidly progressing Parkinsonian disease that responds poorly to dopaminergic therapy and for which there is no effective therapy. In this trial, 92 patients with clinically possible or probable MSA took high-dose EGCG (**1.2 g per day, equivalent to 50 cups of green tea)** for one year and were compared with patients on placebo on the Unified MSA Rating Scale (UMSARS-ME) and other clinical and neuroimaging outcomes (Levin et al., 2016). According to results presented at the April 2020 AAT-AD/PD conference, the **treatment had no effect on the primary readout, and led to liver damage in some participants.**

https://pubmed.ncbi.nlm.nih.gov/17135765/ **Epigallocatechin-3-gallate inhibits secretion of TNF-alpha**, IL-6 and IL-8 through the attenuation of ERK and NF-kappaB in HMC-1 cells

Conclusion: EGCG inhibited the production of TNF-alpha, IL-6 and IL-8 through the inhibition of the intracellular Ca(2+) level, and of ERK1/2 and NF-kappaB activation. These results indicate that EGCG may be helpful in regulating mast-cell-mediated allergic inflammatory response.

Epinephrine (Adrenaline)

https://pubmed.ncbi.nlm.nih.gov/11322936/ The anti-inflammatory interactions of epinephrine with human neutrophils in vitro are achieved by cyclic AMP-mediated accelerated resequestration of cytosolic calcium 2001

We conclude that epinephrine **down-regulates the pro-inflammatory activities** of neutrophils by cAMP-mediated enhancement of the clearance of cytosolic Ca(2+).

https://pubmed.ncbi.nlm.nih.gov/11999137/ Non-steroidal anti-inflammatory drugs inhibit epinephrine- and cAMP-mediated lipolysis in isolated rat adipocytes 2002

In conclusion, **aspirin, naproxen, nimesulide and piroxicam** reduce the release of fatty acids from adipose tissue to the liver **by inhibiting the epinephrine-stimulated lipolysis**, and this, in part, explains the protective action of these NSAIDs against hepatic signs of acute ethanol intoxication.

https://pubmed.ncbi.nlm.nih.gov/24365491/ Pseudoephedrine/ephedrine shows potent anti-inflammatory activity against TNF-α-mediated acute liver failure induced by lipopolysaccharide/D-galactosamine 2014

These results suggest that pseudoephedrine and ephedrine have a **potent anti-inflammatory** activity against D-GalN/LPS-induced acute liver failure in rats, and this comprehensive anti-inflammatory effect may result from the inhibition of TNF-α production.

https://pubmed.ncbi.nlm.nih.gov/29462033/ Low-Dose Epinephrine Plus Tranexamic Acid Reduces Early Postoperative Blood Loss and Inflammatory Response: A Randomized Controlled Trial 2018

The combined administration of low-dose epinephrine and tranexamic acid demonstrated an increased effect in **reducing perioperative blood loss and the inflammatory response** compared with tranexamic acid alone, with no apparent increased incidence of thromboembolic and other complications.

https://pubmed.ncbi.nlm.nih.gov/12180725/ Infusion of epinephrine decreases serum levels of cortisol and 17-hydroxyprogesterone in patients with rheumatoid arthritis 2002

Serum **cortisol and 17OHP (cortisol precursor) were lower in patients with RA** compared to controls despite similar ACTH levels. S**imulation of an adrenomedullary stress response by epinephrine infusion decreased serum cortisol** and 17OHP in patients but not in controls. Such a response may play an **unfavorable role during a typical stress reaction** in patients with RA that may lead to a more proinflammatory situation.

https://pubmed.ncbi.nlm.nih.gov/10700598/ Low plasma epinephrine in elderly female subjects of dementia of Alzheimer type 2000

Statistical analysis showed that the **plasma level of epinephrine during a fasting state in DAT subjects was significantly lower** than that of ND subjects; however, in VD subjects the level of epinephrine was not different from that of ND subjects. Other values did not differ significantly among the groups.

https://neuro.psychiatryonline.org/doi/full/10.1176/jnp.16.3.261 The Role of Norepinephrine in the Behavioral and Psychological Symptoms of Dementia 2004

This review examines the role of **norepinephrine (NE)** on BPSD(dementia), including depression, aggression, agitation and psychosis. A number of lines of e**vidence suggest that NE dysfunction leading to BPSD may result from increased NE activity** and/or hypersensitive adrenoreceptors compensating for loss of NE neurons with progression of Alzheimer's disease (AD).

https://pubmed.ncbi.nlm.nih.gov/3239955/ Evidence for retrograde degeneration of epinephrine neurons in Alzheimer's disease 1988

These findings provide evidence for the hypothesis that **retrograde degeneration is a mechanism** of neuronal degeneration in AD and suggest that trophic factors may play a role in this process.

https://www.nature.com/articles/1395237.pdf Cerebrospinal Fluid Epinephrine in Alzheimer's Disease and Normal Aging 1998

Resting CSF(cerebrospinal fluid) EPI(**epinephrine) was higher in AD** than in older or young subjects, and increased with dementia severity in AD subjects.

Fasting (fasting-mimicking diet (FMD)) (related to Nicotinamide Riboside) (feed brain with ketones)

- see Caprylic Acid (C8) under Coconut oil for generating Ketones

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7352172/ Effects on Longevity

Calorie restriction (CR) is considered the most effective approach to extend lifespan in eukaryotes since the first report of lifespan extension in wild-type yeast cells via regulation of Sir2 and NAD+ [114]. CR life-prolonging effects may partly be mediated via increased sirtuin function, while the requirement of NAD+ for their activity suggests a possible connection between aging and metabolism. However, the nutritional approach for increasing Sir2 activity and longevity has been accomplished by engineered gene overexpression in yeast [115], while NA failed to extend lifespan, and NAM shortened it [116,117]. On the other hand, as with CR, **NR can increase NAD+ levels** and Sir2 function, while exogenous NR promotes Sir2-dependent repression of recombination, improves gene silencing, and extends lifespan without calorie restriction [11]. Moreover, the mechanism of action of NR is completely dependent on increased net NAD+ synthesis through the Nrk1 and the Urh1/Pnp1/4 pathways. The latter is Nrk1 independent and represents a newly discovered NR salvage pathway [11]. Furthermore, a study in **mouse models documented that a one-day fast increases NAD+ in the liver [118] whereas CR elevates NAD+** and reduces NAM in the brain [119]. This implies that the increased levels of NAD+ appear to mediate several beneficial effects of CR, supporting the life-prolonging effects of NR supplementation. These effects are mediated via improvement of metabolism and decrease in chronic inflammation, a hallmark of aging [35]. Preclinical studies have reported that NR reduces macrophage infiltration in damaged muscles [38,112] and attenuates plasma TNF-α in models of fatty liver disease [44]. Nevertheless, a recent clinical study confirmed NR availability in muscular tissue in aged human subjects [120] and its anti-inflammatory effects. Namely, a 21-day supplementation of NR decreased numerous circulating inflammatory cytokines [120], implying additional mechanisms through which NR can potentially modulate the aging process and thereby exhibit life-prolonging effects. While the exact mechanisms through which NR exerts these effects remain unclear, the apparent health benefits described indicate positive effects of NR on longevity.

https://www.discovermagazine.com/health/the-growing-science-behind-a-fasting-treatment-for-alzheimers The Growing Science Behind a Fasting Treatment for Alzheimer's

Typically touted as a weight loss method, **fasting has been shown in animal studies to help improve the symptoms of Alzheimer's disease and slow cognitive decline in mice**. Research on the link between diet and brain health is now moving to humans, with some researchers hoping that fasting could one day be used to treat and prevent a debilitating disease

https://pubmed.ncbi.nlm.nih.gov/29307281/#:~:text=Alzheimer%27s%20disease%20reduced%20bone%20mineral%20density%20in%20the,fasting%20decreased%20food%20intake%20without%20changing%20energy%20expenditure.

Intermittent fasting protects against the deterioration of cognitive function, energy metabolism and dyslipidemia in Alzheimer's disease-induced estrogen deficient rats 2018

Intermittent fasting may be an effective intervention to protect against age-related metabolic disturbances, although it is still controversial. Here, we investigated the effect of intermittent fasting on the deterioration of the metabolism and cognitive functions in rats with estrogen deficiency and its mechanism was also explored. Ovariectomized rats were infused with β-amyloid (25-35; Alzheimer's disease) or β-amyloid (35-25, Non-Alzheimer's disease; normal cognitive function) into the hippocampus. Each group was randomly divided into two sub-groups: one with intermittent fasting and the other fed ad libitum: Alzheimer's disease-ad libitum, Alzheimer's disease-intermittent fasting, Non-Alzheimer's disease-ad libitum, and Non-Alzheimer's disease-intermittent fasting. Rats in the intermittent fasting groups had a restriction of food consumption to a 3-h period every day. Each group included 10 rats and all rats fed a high-fat diet for four weeks. Interestingly, Alzheimer's disease increased tail skin temperature more than Non-Alzheimer's disease and intermittent fasting prevented the increase. Alzheimer's disease reduced bone mineral density in the spine and femur compared to the Non-Alzheimer's disease, whereas bone mineral density in the hip and leg was reduced by intermittent fasting. Fat mass only in the abdomen was decreased by intermittent fasting. Intermittent fasting decreased food intake without changing energy expenditure. Alzheimer's disease increased glucose oxidation, whereas intermittent fasting elevated fat oxidation as a fuel source. Alzheimer's disease and intermittent fasting deteriorated insulin resistance in the fasting state but intermittent fasting decreased serum glucose levels after oral glucose challenge by increasing insulin secretion. Alzheimer's disease deteriorated short and spatial memory function compared to the Non-Alzheimer's disease, **whereas intermittent fasting prevented memory loss in comparison to ad libitum.** Unexpectedly, **cortisol levels were increased by Alzheimer's disease but decreased by intermittent fasting. Intermittent fasting improved dyslipidemia and liver damage index compared to ad libitum.** Alzheimer's disease lowered low-density lipoprotein cholesterol and serum triglyceride levels compared to Non-Alzheimer's disease. In conclusion, Alzheimer's disease impaired not only cognitive function but also disturbed energy, glucose, lipid, and bone metabolism in ovariectomized rats. Intermittent fasting protected against the deterioration of these metabolic parameters, **but it exacerbated bone mineral density loss** and insulin resistance at fasting in Alzheimer's disease-induced estrogen-deficient rats. Impact statement Intermittent fasting was evaluated for its effects on cognitive function and metabolic disturbances in a rat model of menopause and Alzheimer's disease. Intermittent fasting decreased skin temperature and fat mass, and improved glucose tolerance with decreasing food intake. Intermittent fasting also prevented memory loss: short-term and special memory loss. Therefore, intermittent fasting may prevent some of the metabolic pathologies associated with menopause and protect against age-related memory decline.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6836141/ Fasting as a Therapy in Neurological Disease

Fasting improves cognition, stalls age-related cognitive decline, usually slows neurodegeneration, reduces brain damage and enhances functional recovery after stroke, and mitigates the pathological and clinical features of epilepsy and multiple sclerosis in animal models. Primarily due to a lack of research, the evidence supporting fasting as a treatment in human neurological disorders, including neurodegeneration, stroke, epilepsy, and multiple sclerosis, is indirect or non-existent. Given the strength of the animal evidence, many exciting discoveries may lie ahead, awaiting future investigations into the viability of fasting as a therapy in neurological disease.

Following **12–36 hours of fasting, the human body enters a physiological state of ketosis** characterized by **low blood glucose levels, exhausted liver glycogen stores, and the hepatic production of fat-derived ketone bodies, or ketones,** which serve as a **major energy source for the brain** [26]. The liver is the primary site of ketogenesis, but brain astrocytes also generate ketones [27,28]. Within several days of initiating a fast, **ketones become the brain's preferred fuel source, providing up to 70% of its energy requirements** [29]. **Ketones** constitute a more efficient source of energy per unit oxygen in muscles [30,31], and possibly in the brain [32], **enhancing neuron bioenergetics and cognitive performance**; for example, it has been shown that rodents subjected to **a ketone ester for five days exhibit improved spatial learning and memory** [33].

Neurodegenerative disorders, such as Huntington's disease (HD), Parkinson's disease (PD), and Alzheimer's disease (AD), afflict different neurons (striatal spiny neurons in HD, widespread dopaminergic and cholinergic neurons in PD, and cortical cholinergic neurons in AD); however, all three disorders exhibit impaired neuron bioenergetics, glucose metabolism, and neurotrophic factor signaling [3,124]. In all three, there is a reduced expression of the master mitochondria regulator PGC1α, along with an associated decline in mitochondria biogenesis and function [36,124]. Moreover, the respiratory chain is impaired in PD and AD, especially PD, which demonstrates a marked deficit at complex I [125]. Furthermore, both PD and AD show impairments in neuron glucose metabolism and insulin signaling [126,127], **especially AD, which is characterized by brain insulin deficiency as well as resistance, thus leading to AD being described as a form of brain-specific, "type 3" diabetes** [128].

To date, fasting has not been explored as a therapy in people with HD, PD, and AD. However, indirect evidence has been provided by studies of **ketogenic diets** in these disorders [139]. Ketogenic diets are **high-fat, adequate-protein, low-carbohydrate diets** that **force the body to burn fats rather than carbohydrates** as the primary energy source, thus **mimicking a fasted metabolic state by generating ketones** and inducing many of the metabolic mechanisms induced by fasting. In **PD, a small case series showed improved motor symptoms after four weeks of a ketogenic diet** [140], and a subsequent randomized controlled study involving 47 people with mild-to-severe PD showed improvements in many of the most disabling, least levodopa-responsive PD nonmotor symptoms after eight weeks of a ketogenic diet [141]. Regarding the effects of a ketogenic diet in AD, a single case series involving 15 people with mild-to-moderate **AD reported mild improvements in cognition after 12 weeks of such a diet** [142]; these findings may be partly explained by the fact that **although brain glucose uptake is markedly impaired in AD, ketone utilization is not** [143].

https://www.frontiersin.org/articles/10.3389/fnmol.2017.00395/full Intermittent Fasting Protects against Alzheimer's Disease Possible through Restoring Aquaporin-4 Polarity 2017

The impairment of amyloid-β (Aβ) clearance in the brain plays a causative role in Alzheimer's disease (AD). Polarity distribution of **aquaporin-4 (AQP4) is important to remove Aβ from brain.** AQP4 polarity can be influenced by the ratio of two AQP4 isoforms M1 and M23 (AQP4-M1/M23), however, it is unknown whether the ratio of AQP4-M1/M23 changes in AD. Histone deacetylase 3 has been reported to be significantly increased in AD brain. Moreover, evidence indicated that microRNA-130a (miR-130a) possibly mediates the regulation of histone deacetylase 3 on AQP4-M1/M23 ratio by repressing the transcriptional activity of AQP4-M1 in AD. **This study aimed to investigate whether intermittent fasting (IF),** increasing the level of an endogenous histone deacetylases inhibitor β-hydroxybutyrate, restores AQP4 polarity via miR-130a mediated reduction of AQP4-M1/M23 ratio in protection against AD. The results showed that **IF ameliorated cognitive dysfunction, prevented brain from Aβ deposition, and restored the AQP4 polarity in a mouse model of AD** (APP/PS1 double-transgenic mice)

In conclusion, IF exhibits beneficial effects against AD. The mechanism may be associated with recovery of AQP4 polarity, resulting from the reduction of AQP4-M1/M23 ratio. Furthermore, β-hydroxybutyrate may partly mediate the effect of IF on the reduction of AQP4-M1/M23 ratio in AD, in which miR-130a and histone deacetylase 3 may be implicated.

https://studyfinds.org/intermittent-fasting-alzheimers/ Could intermittent fasting be secret to preventing Alzheimer's disease? 2022

Diets that mimic fasting appear to the reduce the signs of Alzheimer's disease, according to a groundbreaking new study using mice.

Researchers from USC Leonard Davis School of Gerontology say time-restricted eating lowered levels of two key hallmarks of the disease — amyloid beta and hyperphosphorylated tau protein. These substances build up and tangle in the brain, causing disruptions in cognitive function that lead to dementia.

The mice on this fasting diet — which were genetically-engineered to develop Alzheimer's — also had **less brain inflammation and performed better on cognitive tests** than other mice fed a normal diet. The **fasting-mimicking diet (FMD)** researchers examined was **high in unsaturated fats and low in overall calories, protein, and carbohydrates.** The diet mimics the impact of sticking to a water-only fast while still providing dieters with their necessary nutrients. **Previous studies have found that fasting diets display a connection to several health benefits, including stem cell regeneration, lessening the side-effects of chemotherapy, and lowering the risk for developing cancer, diabetes, heart disease, and other age-related diseases.**

In both experiments, results reveal that mice participating in FMD cycles displayed noticeable drops in amyloid beta. This substance forms sticky plaques in the brain. Tau proteins, which form tangles in the brain, also decreased among fasting mice. The FMD group also had lower levels of brain inflammation and fewer active microglia. These immune cells seek out and destroy viruses and damaged cells throughout the brain. The dieting mice even had lower levels of oxidative stress, which the researchers say plays a role in the onset of Alzheimer's. Oxidative stress, which develops due to an imbalance between the production and accumulation of oxygen reactive species (ROS), damages neurons and leads to more amyloid building up in the brain. Specifically, Longo says the free radical "superoxide" plays a key role in causing damage within Alzheimer's mouse models

Fatty Acids

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4424767/ The impact of specific fatty acids on inflammation may be central to how dietary fats affect health.

Three key fatty acid–inflammation interactions are briefly described. First, the evidence suggests that **saturated fatty acids induce inflammation in part by mimicking the actions of LPS.** Second, the often-repeated claim that **dietary linoleic acid promotes inflammation** was not supported in a recent systematic review of the evidence. Third, an explanation is offered for why omega-3 (n–3) polyunsaturated fatty acids are so much less anti-inflammatory in humans than in mice. The article closes with a cautionary tale from the genomic literature that illustrates why extrapolating the results from inflammation studies in mice to humans is problematic.

Excess **chronic inflammation** is an important etiologic factor in a wide range of common chronic diseases, including cardiovascular disease (4), diabetes (4), **Alzheimer and other neurologic diseases** (5), and cancer (6). However, there is no consensus regarding which inflammatory biomarker is best. Clearly, **not all fats under all circumstances promote postprandial inflammation**. There are insufficient data to predict when and how specific fat sources will affect inflammatory status in people. One possible explanation for the discrepancies in the literature is the variability in the types of microbes in the gastrointestinal tract of individuals being studied in these postprandial fat challenge studies. Whether dietary fats substantially affect inflammatory status of people by altering their **gut microflora remains untested**, but with the rapid advances in the field, answers should be forthcoming. **Linoleic acid (LA;** 18:2n−6, octadecadienoic acid) is an n–6 PUFA and an essential nutrient (38). LA comprises ≥50% of the most widely consumed vegetable oils in Western societies. For many decades it has been known that **LA helps reduce blood cholesterol concentrations and that substituting LA for SFAs lowers the risk of heart disease** (39). Therefore, current recommendations from numerous expert bodies, including the Institute of Medicine and the American Heart Association, are that people should consume between 5% and 10% of total energy as LA for a heart-healthy diet (40

However, a few members of the lipid research community have expressed **concerned that LA-rich diets are unhealthy and promote inflammation** (41, 42). The theoretical basis for this concern over LA's proinflammatory actions involve a number of putative interrelated metabolic processes, including the following: 1) dietary LA promoting tissue arachidonic acid (AA; 20:4n−6, eicosatetraenoic acid) accumulation, 2) enhanced synthesis of proinflammatory eicosanoids derived from AA, 3) **reduced conversion of α-linolenic acid (ALA; 18:3n−3, octadecatrienoic acid) into EPA (eicosapentaenoic acid; 20:5n−3) and/or DHA, and 4) diminished synthesis of anti-inflammatory eicosanoids from EPA and DHA**. The experimental evidence supporting each step of this paradigm originated primarily from rodent and cell culture studies. More recently, and in contrast with the multistep process described above, it was suggested that **various oxidized forms of LA are**

directly responsible for stimulating inflammation
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6448040/ Diet-Derived Fatty Acids, Brain Inflammation, and Mental Health
Neuroinflammation stands out as a hallmark feature of brain disorders that may be linked to peripheral metabolic dyshomeostasis caused by an unhealthy diet. **Dietary fatty acids are of particular interest**, as they may play a dual role, both as a component of high-calorie obesogenic diets and as signaling molecules involved in **inflammatory responses**. Long-term longitudinal studies have **linked a low intake of PUFAs and a high intake of cholesterol and SFAs to increased risk of impaired cognitive function and development of dementia, including Alzheimer's disease**
https://pubmed.ncbi.nlm.nih.gov/19828712/ A saturated fatty acid-rich diet induces an obesity-linked proinflammatory gene expression profile in adipose tissue of subjects at risk of metabolic syndrome
Consumption of the **SFA diet resulted in increased expression of genes involved in inflammation** processes in adipose tissue, without changes in morphology or insulin sensitivity. The **MUFA diet led to a more antiinflammatory gene expression profile**
https://pubmed.ncbi.nlm.nih.gov/9392577/ Dietary fat intake and the risk of incident dementia in the Rotterdam Study
We investigated the association between fat intake and incident dementia among participants, age 55 years or older, from the population-based prospective Rotterdam Study. Food intake of 5,386 nondemented participants was assessed at baseline with a semiquantitative food-frequency questionnaire. At baseline and after an average of 2.1 years of follow-up, we screened for dementia with a three-step protocol that included a clinical examination. The risk of dementia at follow-up (RR [95% CI]) was assessed with logistic regression. After adjustment for age, sex, education, and energy intake, high intakes of **the following nutrients were associated with an increased risk of dementia: total fat (RR = 2.4 [1.1-5.2]), saturated fat (RR = 1.9 [0.9-4.0]), and cholesterol (RR = 1.7 [0.9-3.2]**). Dementia with a vascular component was most strongly related to total fat and saturated fat. **Fish consumption, an important source of n-3 polyunsaturated fatty acids, was inversely related to incident dementia (RR = 0.4 [0.2-0.91), and in particular to Alzheimer's disease (RR = 0.3 [0.1-0.9]).** This study suggests that a high saturated fat and cholesterol intake increases the risk of dementia, whereas fish consumption may decrease this risk
https://pubmed.ncbi.nlm.nih.gov/12580703/ Dietary fats and the risk of incident Alzheimer disease
We performed clinical evaluations on a stratified random sample of 815 community residents aged 65 years and older who were unaffected by Alzheimer disease at baseline and who completed a food-frequency questionnaire a mean of 2.3 years before clinical evaluation. After a mean follow-up of 3.9 years, 131 persons developed Alzheimer disease. **Intakes of saturated fat and trans-unsaturated fat were positively associated with risk of Alzheimer disease**, whereas **intakes of omega-6 polyunsaturated fat and monounsaturated fat were inversely associated.** Persons in the **upper fifth of saturated-fat intake had 2.2 times the risk of incident Alzheimer disease.** Risk also increased with consumption of trans-unsaturated fats, beginning with the second fifth of intake (relative risk, 2.4 compared with the lowest fifth; 95% confidence interval, 1.1-5.3). We observed **linear inverse associations between Alzheimer disease and vegetable fat (**P =.002), and, after further adjustment for other types of fat, marginally significant associations with intake of omega-6 polyunsaturated fat (P =.10 for trend) and monounsaturated fat (P =.10 for trend). Intakes of total fat, animal fat, and dietary cholesterol were not associated with Alzheimer disease.
Conclusion: **High intake of unsaturated, unhydrogenated fats may be protective against Alzheimer disease, whereas intake of saturated or trans-unsaturated (hydrogenated) fats may increase risk**.
https://pubmed.ncbi.nlm.nih.gov/24916582/ Saturated and trans fats and dementia: a systematic review
Saturated fat intake was positively associated with AD risk in 3 of 4 studies, whereas the fourth suggested an inverse relationship. Saturated fat intake was also positively associated with total dementia in 1 of 2 studies, with MCI in 1 of 4 studies, and with cognitive decline in 2 of 4 studies. Relationships between trans fat intake and dementia were examined in 3 reports with mixed results. Several, although not all, prospective studies i**ndicate relationships between saturated and trans fat intake and risk of cognitive disorder**s.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5437154/?report=reader Editorial: Impact of Diet on Learning, Memory and Cognition
Moreover, **adequate dietary intake of monounsaturated fatty acids and cholesterol were significantly associated with decreased risk of MCI**.
https://pubmed.ncbi.nlm.nih.gov/9322553/ Dietary intake and cognitive function in a group of elderly people
. A **diet with less fat, saturated fat,** and cholesterol, and more carbohydrate, fiber, vitamins (especially folate, vitamins C and E, and beta-carotenes), and minerals (iron and zinc) may be advisable not only to improve the general health of the elderly but also to improve cognitive function.
https://pubmed.ncbi.nlm.nih.gov/12947454/ Influence of nutrition on cognitive function in a group of elderly, independently living people
Subjects with an adequate cognitive capacity (MMSE>/=28) showed a greater intake of total foods, fish, and alcoholic drinks, but took less foods from the 'various' group (chocolates, cakes, etc). These subjects had a **more adequate intake of fatty acids** and cholesterol, and a greater intake of vitamins implicated in correct brain function (thiamine, folic acid, vitamin C).
https://pubmed.ncbi.nlm.nih.gov/11965506/ Nutritional status of healthy elderly persons living in Dordogne, France, and relation with mortality and cognitive or functional decline
Conclusion: In apparently healthy elderly people a **BMI ranging between 23 and 27 is associated with lower risks of functional and cognitive declines** in the subsequent 5 y.
https://pubmed.ncbi.nlm.nih.gov/21539488/ Diet and Alzheimer's disease risk factors or prevention: the current evidence
Elevated saturated fatty acids could have negative effects on age-related cognitive decline and mild cognitive impairment (MCI).
Furthermore, at present, epidemiological evidence suggests a possible association between **fish consumption, monounsaturated fatty acids and polyunsaturated fatty acids (PUFA; in particular, n-3 PUFA) and a reduced risk of cognitive decline and dementia**. **cognitive function and an increased risk of vascular dementia (VaD) were found to be associated with a lower consumption of milk or dairy products.** However, the consumption of **whole-fat dairy products may be associated with cognitive decline in the elderly**.
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Neuroinflammation stands out as a hallmark feature of brain disorders that may be linked to peripheral metabolic dyshomeostasis caused by an unhealthy diet. **Dietary fatty acids are of particular interest,** as they may play a dual role, both as a component of high-calorie obesogenic diets and as signaling molecules involved in **inflammatory** responses. **Long-term longitudinal studies have linked a low intake of PUFAs and a high intake of cholesterol and SFAs to increased risk of impaired cognitive function and development of dementia, including Alzheimer's disease**
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Conclusion: **High intake of unsaturated, unhydrogenated fats may be protective against Alzheimer disease**, whereas intake of saturated or trans-unsaturated (hydrogenated) fats may increase risk.
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. A diet with **less fat, saturated fat, and cholesterol,** and **more carbohydrate, fiber, vitamins (especially folate, vitamins C and E, and beta-carotenes), and minerals (iron and zinc) may be advisable not only to improve the general health of the elderly but also to improve cognitive function.**
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Conclusion: In apparently healthy elderly people a **BMI ranging between 23 and 27 is associated with lower risks of functional and cognitive declines** in the subsequent 5 y.
https://pubmed.ncbi.nlm.nih.gov/30351155/ [Nutrition strategies that improve cognitive function
Cognitive capacity can be influenced by components of the diet. **Low glycemic index foods seem to improve attention, memory a**nd functional capacity, while those rich in simple sugars are associated with difficulty in concentration and attention. The brain needs a continuous supply of amino acids for the synthesis of neurotransmitters, especially serotonin and catecholamines. Low levels of serotonin have been linked to decreased learning, reasoning and memory. The quality and type of dietary fat can also affect intellectual and mental capacity. **High saturated fat intake has been related to cognitive deterioration** while the **consumption of polyunsaturated fatty acids (docosahexaenoic acid) has beneficial effects in their prevention.** It is advisable to consume diets with an **adequate ratio (5:1) of omega-6: 3 fatty acids** (Mediterranean diet) given that they are associated with better memory capacity and lower risk of cognitive deterioration. **Vitamins B1, B6, B12, B9 (folic acid) and D, choline, iron and iodine exert neuroprotective effects and improve intellectual performance.** In parallel, antioxidants (**vitamins C, E, A, zinc, selenium, lutein and zeaxanthin) have a very important role in the defense against oxidative**

stress associated with mental deterioration and in the improvement of cognition. Currently, there is a high consumption of diets rich in saturated fats and refined sugars and low intake of fruits, vegetables and water that can negatively affect cognitive ability. Adequate nutrition is necessary to optimize brain function and prevent cognitive decline.
https://pubmed.ncbi.nlm.nih.gov/21539488/ Diet and Alzheimer's disease risk factors or prevention: the current evidence
Elevated saturated fatty acids could have negative effects on age-related cognitive decline and mild cognitive impairment (MCI).
Furthermore, at present, epidemiological evidence suggests a possible association between **fish consumption, monounsaturated fatty acids and polyunsaturated fatty acids (PUFA; in particular, n-3 PUFA) and a reduced risk of cognitive decline** and dementia. cognitive function and an increased risk of vascular dementia (VaD) were found to be associated with a lower consumption of milk or dairy products. However, the consumption o**f whole-fat dairy products may be associated with cognitive decline** in the elderly. **Light-to-moderate alcohol use may be associated with a reduced risk of incident dementia and AD**, while for VaD, cognitive decline and predementia syndromes, the current evidence is only suggestive of a protective effect.
https://pubmed.ncbi.nlm.nih.gov/27933449/ Clearing the fog: a review of the effects of dietary omega-3 fatty acids and added sugars on chemotherapy-induced cognitive deficits
We propose that a **diet rich in long-chain, marine-derived omega-3 fatty acids and low in added sugars may be an ideal pattern for preventing or alleviating neuroinflammation and oxidative stress**, thereby protecting neurons from the toxic effects of chemotherapy.
https://pubmed.ncbi.nlm.nih.gov/27116240/ Nutrient intake, nutritional status, and cognitive function with aging
With respect to nutrients, there is evidence to support the critical role of several B vitamins in particular, but also of vitamin D, antioxidant vitamins (including vitamin E), and **omega-3 fatty acids**, which are preferentially taken up by brain tissue. On the other hand, high intakes of nutrients that contribute to hypertension, atherosclerosis, and poor glycemic control may have negative effects on cognition through these conditions. Collectively, the evidence suggests that considerable slowing and reduction of cognitive decline may be achieved by following a healthy dietary pattern, which **limits intake of added sugars, while maximizing intakes of fish, fruits, vegetables, nuts, and seeds.**
https://pubmed.ncbi.nlm.nih.gov/19203415/ Long-term association of food and nutrient intakes with cognitive and functional decline: a 13-year follow-up study of elderly French women
Recent **cognitive decline was associated with lower intakes of poultry, fish, and animal fats**, as well as **higher intakes of dairy desserts and ice-cream**. IADL impairment was associated with a **lower intake of vegetables**. The odds of recent cognitive decline increased significantly with decreasing intake of soluble dietary fibre and n-3 fatty acids but with increasing intake of retinol. The odds of IADL impairment increased significantly with decreasing intakes o**f vitamins B2, B6 and B12**. These results are consistent with a possible long-term neuroprotective effect of **dietary fibre, n-3 polyunsaturated fats and B-group vitamins**, and support dietary intervention to prevent cognitive decline.
https://pubmed.ncbi.nlm.nih.gov/35701477/ The combined effect of physical activity and fruit and vegetable intake on decreasing cognitive decline in older Taiwanese adults
Trends in cognitive decline were observed over 16 years. The **risk of cognitive decline decreased by 63% when high physical activity and high fruit and vegetable intake were combined (odds ratio 0.37**; 95% confidence interval 0.23-0.59), indicating a potential combined effect of physical activity and fruit and vegetable intake on mitigating cognitive decline. These personal actions are safe, effective, and economical approaches to health promotion and disease prevention.
https://pubmed.ncbi.nlm.nih.gov/34541370/ The effects of twenty-one nutrients and phytonutrients on cognitive function: A narrative review
Ninety-six articles were summarized in this narrative review. In total 21 categories of nutrients and phytonutrients were included, i.e., α-lipoic acid, Bacopa monnieri, B vitamins, cholinergic precursors, vitamin D, vitamin E, Ginkgo biloba, ginseng, lion's mane mushroom, N-acetyl cysteine, omega-3 fatty acids, aloe polysaccharides, Rhodiola rosea, rosemary, saffron, tart cherries, turmeric, wild yam, Withania somnifera, xanthines, and zinc. Particular noteworthy effects on cognition included memory, recollection, attention, intelligence, vocabulary, recognition, response inhibition, arousal, performance enhancement, planning, creative thinking, reaction time, vigilance, task switching, orientation to time, place, and person, reading, writing, comprehension, accuracy, learning, information processing speed, executive function, mental flexibility, daily functioning, decrease in mental fatigue, and freedom from distractibility. Some nutrients and phytonutrients also improved mood and contentedness and reduced anxiety and the need for caregiving. These effects are not completely consistent or ubiquitous across all patient populations or health statuses. Adverse effects were minimal or nonexistent.
https://pubmed.ncbi.nlm.nih.gov/34239993/ The effects of twenty-four nutrients and phytonutrients on immune system function and inflammation: A narrative review
Eighty-seven articles were summarized in this narrative review. In total 24 nutrients and phytonutrients were included in the study, that is, acetyl-L-carnitine, Aloe vera polysaccharides, beta-glucans, bilberry, black seed oil, coenzyme Q10, curcumin (turmeric), frankincense, garlic, ginger, hydrolyzed rice bran, isoflavones, lipoic acid, mistletoe, N-acetyl cysteine, omega-3 fatty acids, resveratrol, selenium, shiitake mushroom and its derivatives, Vitamin B12, Vitamin C, Vitamin D3 (cholecalciferol), Vitamin E (d-alpha- and gamma-tocopherol), and zinc. Some of the noteworthy immune function and anti-inflammatory responses to these interventions included modulation of nuclear factor-Kappa B, tumor necrosis factor-a, interferon-g, interleukin-6, and CD4+ T cells, among others. These findings are not completely consistent or ubiquitous across all patient populations or health status.

Ferulic acid (FA), Polyphenol, (hydroxycinnamic acid)(anti-AChE)

Sources: Popcorn(313mg), cooked sweetcorn(42mg), bamboo(243mg), whole grain rye bread(54mg), oatmeal(25-52mg), rice, citrus fruits
Recommended 150-250mg/day
https://pubmed.ncbi.nlm.nih.gov/34963433/ Therapeutic Potential of Ferulic Acid in Alzheimer's Disease. 2022
Ferulic acid (FA), a high-capacity antioxidant molecule, is naturally synthesized from certain plants. FA has been shown to have different substantial biological properties, such as anticancer, antidiabetic, antimicrobial, **anti-inflammatory, hepatoprotective**, and cardioprotective actions, etc. Furthermore, FA exerts **neuroprotection via preventing Aβ-fibril formation,** acting as an anti-inflammatory agent, and **inhibiting free radical generation and acetylcholinesterase (AChE) enzyme activity**. In this review, we present key biological roles of FA and several FA derivatives in preventing Aβ-induced neurotoxicity, protecting against free radical attacks, and exhibiting enzyme inhibitions and evaluate them as possible therapeutic agents for the treatment of AD.
https://pubmed.ncbi.nlm.nih.gov/33662757/ A review on ferulic acid and analogs based scaffolds for the management of Alzheimer's disease. 2021
Ferulic acid (FA) is a phenol derivative from natural sources and serves as a potential pharmacophore that exerts multiple pharmacological properties such as **antioxidant, neuroprotection, Aβ aggregation modulation, and anti-inflammatory.** Several FA based hybrid analogs are under investigation as a multi-target directed ligand (MTDLs) to develop novel hybrid compounds for the treatment of AD. In the present review article, we are focused on the critical pathogenic factors responsible for the onset of AD followed by the developments of FA pharmacophore-based hybrids compounds as a novel multifunctional therapeutic agent to address the limitations associated with available treatment for AD. The rationale behind the development of these compounds and their pharmacological activities in particular to their **ChE inhibition (ChEI), neuroprotection, antioxidant property, Aβ aggregation modulation, and metal chelation ability**, are discussed in detail. We have also discussed the discovery of caffeic and cinnamic acids based MTDLs for AD.
https://pubmed.ncbi.nlm.nih.gov/36145084/ Recent Advances in the Neuroprotective Properties of Ferulic Acid in Alzheimer's Disease: A Narrative Review. 2022
Emerging evidence highlighted that hyperglycemia and brain insulin resistance represent risk factors for AD development, thus suggesting the existence of an additional AD form, associated with glucose metabolism impairment, named type 3 diabetes. Owing to the limited pharmacological options, novel strategies, especially dietary approaches based on the **consumption of polyphenols, have been addressed to prevent or, at least, slow down AD progression. Among polyphenols, ferulic acid is a hydroxycinnamic acid derivative, widely distributed in nature, especially in cereal bran and fruits, and known to be endowed with many bioactivities, especially antioxidant, anti-inflammatory and antidiabetic, thus suggesting it could be exploited as a possible novel neuroprotective strategy**. Considering the importance of ferulic acid as a bioactive molecule and its widespread distribution in foods and medicinal plants, the aim of the present narrative review is to provide an overview on the existing preclinical and clinical evidence about the neuroprotective properties and mechanisms of action of ferulic acid, also focusing on its ability to **modulate glucose homeostasis**, in order to support a further therapeutic interest for AD and type 3 diabetes.
https://pubmed.ncbi.nlm.nih.gov/36077082/ Combined Treatment with **Curcumin and Ferulic Acid Suppressed the Aβ-Induced Neurotoxicity** More than Curcumin and Ferulic Acid Alone. 2022
. The purpose of this study was thus to evaluate a combination treatment of curcumin (Cur) and ferulic acid (FA) for amyloid-β (Aβ)-induced neuronal cytotoxicity. The effect of Cur or FA on Aβ aggregation using thioflavin T assay was confirmed to be inhibited in a concentration-dependent manner by Cur single or Cur + FA combination treatment. The effects of Cur + FA on the cytotoxicity of human neuroblastoma (SH-SY5Y) cells induced by Aβ exposure were an increase in cell viability, a decrease in ROS and mitochondrial ROS, and repair of membrane damage. Combination treatment showed an overall higher protective effect than treatment with Cur or FA alone. These results suggest that the **combined action mechanisms of Cur and FA may be effective in preventing and suppressing the progression of AD**
https://pubmed.ncbi.nlm.nih.gov/31582657/ The **Additive Effects of Low Dose Intake of Ferulic Acid, Phosphatidylserine and Curcumin**, Not Alone, Improve Cognitive Function in APPswe/PS1dE9 Transgenic Mice. 2019
Thus, in this study, we treated **ferulic acid (FA), phosphatidylserine (PS) and curcumin (Cur)** in combination or alone to APPswe/PS1dE9 transgenic mice and evaluated cognitive function by Y-maze test. Consequently, only the three-ingredient group exhibited a significant improvement in cognitive function compared to the control group. In addition, we determined the amounts of Aβ, brain-derived neurotrophic factor (BDNF), interleukin (IL)-1β, acetylcholine and phosphorylated tau in the mouse brains after the treatment. In the two-ingredient (FA and PS) group, a significant decrease in IL-1β and an increasing trend in acetylcholine were observed. In the Cur group, significant decreases in Aβ and phosphorylated tau and an increasing trend in BDNF were observed. **In the three-ingredient group, all of them were observed.** These results indicate that the intake of multiple active ingredients with different mechanisms of action for the prevention and treatment of AD.
https://pubmed.ncbi.nlm.nih.gov/35892649/ Ferulic Acid as a Protective Antioxidant of Human Intestinal Epithelial Cells. 2022
The intestinal epithelial barrier is the primary and most significant defense barrier against ingested toxins and pathogenic bacteria. When the **intestinal epithelium barrier is breached, inflammatory response is triggered**. Ferulic acid (FA) is a polyphenol that is abundant in plants and has antioxidant and anti-inflammatory properties, although it is unclear whether FA has these effects on the intestine. Therefore, we investigated the effect of FA in vitro and in vivo. It was found that FA suppressed ER stress, nitric oxide (NO) generation, and inflammation in polarized Caco-2 and T84 cells, indicating that the ER stress pathway was implicated in its anti-inflammatory activities. **These results suggest that FA has a protective effect on intestinal tight junctions.** In addition, mouse intestine organoids proliferated significantly more in the presence of FA. Our findings shed light on the molecular mechanism responsible for the antioxidant effects of FA and its protective benefits on the health of the digestive system.
https://pubmed.ncbi.nlm.nih.gov/36065925/ Neuroprotective properties of Ferulic acid in preclinical models of Alzheimer's disease: A systematic literature review. 2022

Ferulic acid (FA), also known as 3-methoxy-4-hydroxycinnamic acid, is an active ingredient in TCM that inhibits β-amyloid (Aβ) aggregation and has antioxidant and anti-inflammatory effects. **FA derivatives have been reported to have low toxicity, high biological activity, and high blood-brain barrier permeability.Conclusion: Previous studies have shown that FA or its derivatives have multiple therapeutic effects on AD models, and can improve the symptoms of AD and resistance of AD cell models. FA and its derivatives have anti-Aβ aggregation, antioxidant, anti-inflammatory, and other effects and are potential drugs for the multi-targeted treatment of AD. The result of our study showed that FA and its derivatives have significant therapeutic effects on animal and cell models of AD, suggesting that they may be potential therapeutic drugs for patients with AD.**

GABA (neurotransmitter known as gamma-aminobutyric acid) (neurotransmitter, calming effect)

caution: GABA and Glutamate are opposite effects as neurotransmitters

Sources: Fermented Food, Cruciferous vegetables (broccoli, cabbage, cauliflower, Brussels sprouts) ,Soy beans,Adzuki beans,Mushrooms,Spinach,Tomatoes,Buckwheat,Peas

supplement dose: 3000-5000mg

https://www.verywellhealth.com/gaba-5095143 Types of Neurotransmitters

Inhibitory neurotransmitters like GABA block certain brain signals and decrease nervous system activity. Another inhibitory neurotransmitter, serotonin, helps to regulate mood and anxiety. Excitatory neurotransmitters have the opposite effect: They promote certain brain signals and increase nervous system activity. An example of an excitatory neurotransmitter is norepinephrine. Research identifies foods that are dietary sources of GABA. They include broccoli and other cruciferous vegetables, certain peas and beans, and oat, wheat, and barley. They also include rice, tomatoes, sweet potatoes, and spinach.14

https://pubmed.ncbi.nlm.nih.gov/26365140 / Treatment Options in Alzheimer´s Disease: The GABA Story 2015

Hence, nowadays research is focused on investigating compounds that could restore cognition and memory in AD patients. **GABA is the primary inhibitory neurotransmitte**r in the central nervous system and GABAergic neurons provide extensive innervation to cholinergic and glutamatergic neurons. It has been shown that **dysfunction of the GABAergic system may contribute to cognitive impairment in humans. Significant reductions in GABA levels have been described in severe cases of AD**, which could be underlying the behavioral and psychological symptoms of AD. This review examines the involvement of the GABAergic system in both cognitive and non-cognitive behavioural symptoms in AD, providing some pointers for rational drug development.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6325366/ Risk of Dementia in Long-Term Benzodiazepine Users: Evidence from a Meta-Analysis of Observational Studies 2019

Benzodiazepines (BDZs) enhance the efficacy of the neurotransmitter gamma-aminobutyric acid (GABA) at the GABA-A receptor so as to induce sedative, hypnotic, anxiolytic, anticonvulsant, and muscle relaxant properties.1 Various studies have been conducted to understand the association between BDZ and dementia.2,3,4,5,6,7,8,9,10,11 A few well-conducted prospective cohort studies have found an **increased risk of dementia in users of long-acting BDZ**, whereas subsequent studies found no such association. This meta-analysis that pooled ten studies has shown that BDZ significantly increases the risk of dementia in the elderly population. The risk is higher in patients taking BDZ with a longer half-life (>20 hours) and for a longer duration (>3 years).

https://onlinelibrary.wiley.com/doi/10.1111/j.1471-4159.2007.04832.x GABAA receptors in aging and Alzheimer's disease 2007

We conclude that although aging- and disease-**related changes in GABAA receptor subunits** may be modest, the mechanisms that compensate for these changes may alter the pharmacokinetic and physiological properties of the receptor. It is therefore crucial to understand the subunit composition of individual GABAA receptors in the diseased brain when developing therapeutics that act at these receptors.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7527439/ Effects of Oral Gamma-Aminobutyric Acid (GABA) Administration on Stress and Sleep in Humans: A Systematic Review 2020

Gamma-aminobutyric acid (GABA) is a non-proteinogenic amino acid and is the **main inhibitory neurotransmitter in the mammalian brain**. **GABA's stress-reducing, and sleep enhancing effects have been established.** In addition to its role as a neurotransmitter, GABA also exists naturally in various foods, such as **tea, tomato, soybean, germinated rice, and some fermented food**s, and could be obtained from a normal diet . On the other hand, much higher concentrations of GABA could be produced by **lactic acid bacteria (LAB) fermentation** (Dhakal et al., 2012). For instance, by using ***Lactobacillus brevis*** NCL912 strain,

https://onlinelibrary.wiley.com/doi/full/10.1002/jmri.24665 Decreased γ-aminobutyric acid levels in the parietal region of patients with Alzheimer's disease 2014

Decreased GABA+/Cr levels were present in the parietal region of patients with AD in vivo, suggesting that abnormalities of the GABAergic system may be present in the pathogenesis of AD

https://my.clevelandclinic.org/health/articles/22857-gamma-aminobutyric-acid-gaba

GABA is known for producing a calming effect. It's thought to play a major role in controlling nerve cell hyperactivity associated with anxiety, stress and fear. Scientists also call GABA a non-protein amino acid neurotransmitter. **GABA and glutamate act like an "on" and "off" switch.** They work in opposite ways. **GABA is the main inhibitory neurotransmitter in your brain,** stopping the chemical messages from passing from nerve cell to nerve cell. Glutamate, on the other hand, is the main excitatory neurotransmitter in your brain, permitting the chemical messages to be carried from nerve cell to nerve cell.

To have a properly functioning brain, a delicate balance must be maintained between the inhibitory effects of GABA and the excitatory effects of glutamate. GABA also works together with another neurotransmitter, serotonin. In fact, many neurotransmitters work together and against each other and must maintain a certain relationship to achieve a properly functioning body and brain.

Ginkgo biloba

https://pubmed.ncbi.nlm.nih.gov/20162004/ Ginkgo biloba extract in Alzheimer's disease: from action mechanisms to medical practice 2010

Standardized extract from the leaves of the Ginkgo biloba tree, labeled EGb761, is one of the most **popular herbal supplements**. Numerous preclinical studies have shown the **neuroprotective effects** of EGb761 and support the notion that it may be effective in the **treatment and prevention of neurodegenerative disorders such as Alzheimer's disease (AD)**. Despite the preclinical promise, the clinical efficacy of this drug remains elusive.

https://www.ncbi.nlm.nih.gov/books/NBK279357/ Alzheimer's disease: Do Ginkgo products help?

The studies showed that taking a higher dose of the **Ginkgo extract (240 mg per day) could improve participants' memory**. There was also an **improvement in their ability to manage activities of daily life, such as doing household chores or washing** themselves. However, these effects varied widely from study to study, so it **isn't possible to draw any clear conclusions** about how many people could actually benefit from Ginkgo and how strong its effect is. The lower dose of the Ginkgo extract (120 mg per day) did not clearly influence the symptoms of Alzheimer's disease.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8833923/ Can We Use Ginkgo biloba Extract to Treat Alzheimer's Disease? Lessons from Preclinical and Clinical Studies 2022

For the clinical trials, eight trials, including 2100 individuals, were conducted. The results show that GBE improved the SKT and ADAS-Cog scores in early-stage AD patients after high doses and long-term administration; (4) Conclusions: **GBE displayed generally consistent anti-AD effects in animal experiments, and it might improve AD symptoms in early-stage AD patients after high doses and long-term administration**. A lack of sample size calculations and the poor quality of the methods are two obvious limitations of the studies.

https://www.sciencedirect.com/science/article/abs/pii/S0378874116322590 Effects of Ginkgo biloba on dementia: An overview of systematic reviews 2017

Overall, the available evidence suggests that GbE has potentially beneficial effects over placebo on cognitive performance, activities of daily living, and clinical global impression in the treatment of dementia at doses greater than 200 mg/day (usually **240 mg/day**) administrated for 22 weeks or longer, and that GbE appears to be safe for human consumption. No sufficient evidence supports the favorable effects of GbE administrated for less than 22 weeks. The available evidence consistently indicates that a dose less than 200 mg/day of GbE may not be adequate to yield clinical relevant effects in the treatment of dementia.

https://pubmed.ncbi.nlm.nih.gov/26268332/ Ginkgo Biloba for Mild Cognitive Impairment and Alzheimer's Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials 2016

Ginkgo biloba is **potentially beneficial for the improvement of cognitive function, activities of daily living**, and global clinical assessment in patients with mild cognitive impairment or Alzheimer's disease. However, due to limited sample size, **inconsistent findings and methodological quality of included trials**, more research are warranted to confirm the effectiveness and safety of ginkgo biloba in treating mild cognitive impairment and Alzheimer's disease.

https://pubmed.ncbi.nlm.nih.gov/34010562/ Evolving Role of Natural Products from Traditional Medicinal Herbs in the Treatment of Alzheimer's Disease 2019

Ginkgo biloba (Gb) has been in the spotlight primarily for its potential role in treating AD. Gb also appears promising as a therapeutic agent for several other chronic and acute forms of diseases. The main pharmacologically active groups of compounds are flavonoids and terpenoids. Almost all clinical studies use Gb extract that contains a combination of flavonoid glycosides, terpene lactones, and ginkgolic acids [50]. **Gb extract has shown beneficial effects in treating Alzheimer's**, cardiovascular diseases, cancer, tinnitus, and other age-associated conditions [49,50].

Ginseng (Herb)

https://pubmed.ncbi.nlm.nih.gov/26268331/ Ginseng for Alzheimer's Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Ginseng is **widely used in the treatment of AD in Asian countries**. This review showed that the **effects of ginseng on AD were still inconclusive**. The main limitations of the available studies were small sample sizes, poor methodological qualities and no placebo controls. Larger, well-designed studies are needed to test the effect of ginseng on AD in the future.
https://pubmed.ncbi.nlm.nih.gov/19584437/ Ginseng for cognitive function in Alzheimer's disease: a systematic review
In conclusion, the **evidence for ginseng as a treatment of AD is scarce and inconclusive**
https://pubmed.ncbi.nlm.nih.gov/18580589/ Panax ginseng enhances cognitive performance in Alzheimer disease
Consecutive AD patients were randomly assigned to the ginseng (n=58) or the control group (n=39), and the ginseng group was treated with Panax ginseng powder (4.5 g/d) for 12 weeks. Cognitive performances were monitored using the mini-mental state examination (MMSE) and Alzheimer disease assessment scale (ADAS) during 12 weeks of the ginseng treatment and at 12 weeks after the ginseng discontinuation. MMSE and ADAS scales showed no baseline difference between the groups. **After ginseng treatment, the cognitive subscale of ADAS and the MMSE score began to show improvements and continued up to 12 weeks** (P=0.029 and P=0.009 vs. baseline, respectively). **After discontinuing ginseng, the improved ADAS and MMSE scores declined to the levels of the control group.** These **results suggest that Panax ginseng is clinically effective in the cognitive performance of AD patients.**
https://pubmed.ncbi.nlm.nih.gov/22780999/ Heat-processed ginseng enhances the cognitive function in patients with moderately severe Alzheimer's disease
In this study, we investigated the **efficacy of a heat-processed form of ginseng** that contains more potent ginsenosides than raw ginseng in the treatment of cognitive impairment in patients with moderately severe Alzheimer's disease (AD). Forty patients with AD were randomized into one of three different dose groups or the control group as follows:
1.5 g/day (n = 10),
3 g/day (n = 10), and
4.5 g/day (n = 10) groups,
or control (n = 10).
The Alzheimer's Disease Assessment Scale (ADAS) and Mini-Mental State Examination (MMSE) were used to assess cognitive function for 24 weeks. **Results:** The treatment groups showed significant improvement on the MMSE and ADAS. Patients with higher dose group (**4.5 g/day) showed improvements in ADAS cognitive, ADAS non-cognitive, and MMSE score as early as at 12 weeks, which sustained for 24-week follow-up.**
https://pubmed.ncbi.nlm.nih.gov/18684311/ An open-label trial of Korean red ginseng as an adjuvant treatment for cognitive impairment in patients with Alzheimer's disease
The trial was designed as a 12-week randomized study. Sixty-one patients (24 males and 37 females) with Alzheimer's disease were randomly assigned to one of the following treatment groups:
low-dose KRG (4.5 g/day, n = 15),
high-dose KRG (9 g/day, n = 15) or
control (n = 31).
The Alzheimer's Disease Assessment Scale (ADAS), Korean version of the Mini-Mental Status Examination (K-MMSE) and Clinical Dementia Rating (CDR) scale were used to assess the change in cognitive and functional performance at the end of the 12-week study period. **Results:** The patients in the **high-dose KRG group showed significant improvement on the ADAS and CDR after 12 weeks of KRG therapy** when compared with those in the control group (P = 0.032 and 0.006 respectively). The KRG treatment groups showed improvement from baseline MMSE when compared with the control group (1.42 vs. -0.48), but this improvement was not statistically significant.
https://pubmed.ncbi.nlm.nih.gov/23717092/ Improvement of cognitive deficit in Alzheimer's disease patients by long term treatment with korean red ginseng
A 24-week randomized open-label study with Korean red ginseng (KRG) showed cognitive benefits in patients with Alzheimer's disease. To further determine long-term effect of KRG, the subjects were recruited to be followed up to 2 yr. Cognitive function was evaluated every 12 wk using the Alzheimer's Disease Assessment Scale (ADAS) and the Korean version of the Mini Mental Status Examination (K-MMSE) with the maintaining dose of **4.5 g or 9.0 g KRG per d.** At 24 wk, there had been a significant improvement in KRG-treated groups. In the long-term evaluation of the efficacy of KRG after 24 wk, the improved MMSE score remained without significant decline at the 48th and 96th wk. ADAS-cog showed similar findings. Maximum improvement was found around week 24. In conclusion, the **effect of KRG on cognitive functions was sustained for 2 yr follow-up, indicating feasible efficacies of long-term follow-up for Alzheimer's disease.**
https://pubmed.ncbi.nlm.nih.gov/34149431/ Neuroprotective Potentials of Panax Ginseng Against Alzheimer's Disease: A Review of Preclinical and Clinical Evidences
Panax ginseng C.A. Mey. is a well-known medicinal plant that **contains ginsenosides, gintonin**, and other components and **has neuroprotective effects** against a series of pathological cascades in AD, including beta-amyloid formation, **neuroinflammation**, oxidative stress, and mitochondrial dysfunction. In this review, we summarize the effects and mechanisms of these major components and formulas containing *P. ginseng* in neuronal cells and animal models. Moreover, clinical findings regarding the prevention and treatment of AD with *P. ginseng* or its formulas are discussed.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3659620/ Effects of fermented ginseng on memory impairment and β-amyloid reduction in Alzheimer's disease experimental models
These findings extract was prepared by steaming and fermenting ginseng. of Aβ42 protein, which **results in enhanced behavioral memory function, thus, suggesting that FG extract may be an effective preventive or treatment for AD.**
https://awakeningfromalzheimers.com/new-ginseng-discovery-may-hold-a-key-%E2%80%A8to-beating-alzheimers/ New Ginseng Discovery May Hold a Key to Beating Alzheimer's
In traditional Chinese medicine the ginseng root is typically used as medicine. But in the soil close to the roots is a complete ecosystem called the rhizosphere, where plants and diverse microorganisms interact. Their efforts led them to find a strain of bacteria called *Streptomyces* which produces a novel compound called rhizolutin. The scientists carried out a series of experiments in cell cultures and in mice with Alzheimer's. The former demonstrated that **rhizolutin** substantially **decreases amyloid-induced inflammation and death in both neurons and in glial cells**, which support and protect neurons. In mice, researchers found **rhizolutin significantly reduced plaques in the hippocampus**.

Glutathione **(note NAC is glutathione precursor) also Gamma-glutamylcysteine, as supplementation with glutathione(GSH) is incapable of increasing GSH levels**

Anti-oxidant, anti-inflammaroty, liver detox

BioAvailble Form: Liposomal Glutathione or Acetyl Glutathione or N Acetylcysteine(not as good) as precursor

Glutamylcysteine is most immediate precursor but does not seem available to buy

- also a heavy metal chelator

Recommended Supplement: 50-600mg/day
https://pubmed.ncbi.nlm.nih.gov/24496077/ The emerging role of glutathione in Alzheimer's disease
This **AD-related increase in oxidative stress has been attributed to decreased levels of the brain antioxidant, glutathione (GSH)**. In this article, we review the role of GSH in AD from a pathological as well as a diagnostic point of view.
https://pubmed.ncbi.nlm.nih.gov/30776003/ Cognitive Improvement with Glutathione Supplement in Alzheimer's Disease: A Way Forward
Oxidative stress is believed to be important player in AD pathology. Glutathione (GSH) is a major antioxidant, and it is already known that **GSH is depleted significantly in the hippocampal regions in mild cognitive impairment (MCI) and AD patients compared to healthy old subjects**. Hence there is a serious discussion to improve the brain GSH level by supplementation.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9473545/ Augmented Glutathione Absorption from Oral Mucosa and its Effect on Skin Pigmentation: A Clinical Review
Various aspects of glutathione bioavailability were examined when administered by oral routes. Absorption of glutathione from the gastrointestinal tract is poor.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6320789/ Overview on the Effects of *N*-Acetylcysteine in Neurodegenerative Diseases
NAC is a glutathione precursor and shows **antioxidant and anti-inflammatory activities**. In addition to the uses quoted in the literature, NAC may be considered helpful in therapies to **counteract neurodegenerative** and mental health diseases. Furthermore, this compound has been evaluated for its neuroprotective potential in the prevention of cognitive aging dementia. As reported in the literature, the single use o**f glutathione (GSH) as oral medication does not sufficiently recover GSH levels.** In fact, in body districts such as liver and intestines, **GSH is quickly hydrolyzed [4] and its capacity to cross through the blood-brain barrier (BBB) is insufficient**. Studies on animal models [10,11], cited in scientific literature, have described that **NAC shows the activity to efficaciously penetrate the BBB increasing the GSH levels in the brain**. In several cellular systems, NAC promotes effects aimed to maintain the survival functions of cells, which also induces the production of intracellular GSH known as the principal antioxidant produced by the body that protects cells from oxidative stress and maintains the redox state inside them . With regards to **anti-inflammatory activity**, several research studies have observed that NAC is able to limit cytokines release in the early state of immune proliferation [13]. NAC can **modulate several key neurotransmitter systems such as glutamate**, which are studied because it is involved in a range of mental illness [27,28]. **NAC showed a protective effect to counteract acrolein, peroxynitrite, hydroxyl radicals, and oxidative damage caused by 3-nitro-propionic acid (3-NP) and GSH augmentation in the brain** and synaptosomes has been observed [69,102,103,104].
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5241507/ A Review on Various Uses of N-Acetyl Cysteine
N**AC is a precursor of L-cysteine that results in glutathione elevation biosynthesis**. During oral administration, deacetylation reaction of NAC happens while passing along the small intestine as well as liver, thus its bioavailability is decreased to 4-10%. NAC stimulates glutathione biosynthesis, promotes detoxification, and acts directly as a scavenger of free radicals. It is a **powerful antioxidant** and a potential treatment option for diseases characterized by the generation of free oxygen radicals (3).
https://clinicaltrials.gov/ct2/show/NCT04740580 Glutathione, Brain Metabolism and Inflammation in Alzheimer's Disease
Alzheimer's disease (AD) is associated with significant, progressive cognitive decline. Key defects in mitochondrial fuel metabolism insulin resistance, inflammation and decreased brain glucose uptake are linked to AD. This trial will investigate the effects of supplementing **glycine and N-acetylcysteine** vs. alanine as placebo on these defects in AD, and examine the effects on cognition.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3654245/
Glutathione is not recommended to be administered orally as it undergoes digestion; however novel modes of delivery such as liposomal and prodrug preparations are emerging [57]
https://www.chiroeco.com/antioxidant-questions/ Direct glutathione supplementation

Until recently, supplementing with active glutathione (GSH) was difficult and expensive, primarily used in an intravenous setting with high out-of-pocket costs to patients. **When it comes to oral glutathione supplementation, many of these supplements end up hydrolyzed into the three amino acids or the glutathione becomes oxidized (GSSG) and further adds to the oxidative burden of the patient.** So, while glutathione is definitely valuable in clinical settings, it needs to be in a form that is both effective and easy for patient adherence. And beyond raising blood levels of active glutathione (GSH) for a healthy ratio to oxidized glutathione (GSSG), it needs to be a one-supplement solution in order to remove the guesswork that seems inherent in NAC supplementation.
Fortunately, there's good news for practitioners and their patients on that front. **French research scientists have developed a way to enhance glutathione's bioavailability in a supplemental form, so it is easy to use and doesn't suffer the oxidizing damage of typical oral supplements. Instead, as a sublingual tablet, the glutathione is protected with additional antioxidants.** This way, the glutathione is transported directly into the bloodstream as it dissolves under the tongue. This capillary-rich sublingual environment is much more conducive to retaining glutathione in an active form than oral supplements that can undergo oxidation in the digestive tract.
In 11 days, this unique sublingual glutathione increased active glutathione in the bloodstream by 38 points. However, the unprotected oral glutathione actually *reduced* the active glutathione amount by 40 points, creating a 78-point difference between the two groups.
This sublingual form also **improved glutathione ratios (the ratio of active glutathione [GSH] to the oxidized form [GSSG]) by 230% compared to unprotected glutathione and 65% better than NAC.** Interestingly, this study was conducted on participants with metabolic syndrome, so the results are promising for many patients today dealing with similar issues.
https://glutathionepro.com/what-is-l-glutathione/ What is L-Glutathione and Why You Need More
Look for supplements using **Reduced Glutathione (L-glutathione), Liposomal Glutathione or Acetyl Glutathione**. The above forms of GSH are the **most bioavailable**, meaning the body will readily absorb them and effectively boost glutathione levels. A quality glutathione complex will not only contain a bioavailable form of GSH, it should also contain the precursors to help produce glutathione naturally. Some of the nutrients capable of increasing GSH levels include N Acetylcysteine (NAC), Alpha Lipoic Acid (ALA), Milk Thistle, B Vitamins (L-methylfolate, Methylcobalamin), Vitamin E (mixed or alpha-tocopherols), Magnesium and Selenium.
https://glutathionepro.com/liposomal-glutathione-vs-acetyl-glutathione-supplements/
Oral Glutathione supplements that include the **bioavailable precursors such as N Acetylcysteine can effectively increase Glutathione production**.
The **more direct ways of supplementing Glutathione include supplements like Liposomal Glutathione or Acetyl Glutathione.** They **protect the Glutathione molecule from being damaged in the intestinal tract,** allowing it to be absorbed intact leaving you with the full benefit.

Liposomal Glutathione

https://pubmed.ncbi.nlm.nih.gov/28853742/ Oral supplementation with liposomal glutathione elevates body stores of glutathione and markers of immune function 2018
Glutathione (GSH) is the most abundant endogenous antioxidant and a critical regulator of oxidative stress. Maintenance of optimal tissues for GSH levels may be an important strategy for the prevention of oxidative stress-related diseases. **Conclusions:** Collectively, these preliminary findings support the **effectiveness of daily liposomal GSH administration at elevating stores of GSH and impacting the immune function and levels of oxidative stress.**
https://www.intelligentlabs.org/liposomal-glutathione/ Liposomal Glutathione: An Ultimate Guide To The Body's Master Antioxidant
The **body's production of glutathione naturally goes down over time**. **Most liposomal GSH products use a 500mg serving**

Glutathione -Cerefolin NAC

https://www.brainpower.org/reviews/cerefolin-nac.html
Cerefolin NAC Ingredients
- 5.6 mg L-methylfolate which is a biologically form of folic acid.
- 2 mg Methylcobalamin which is vitamin B12.
- 600 mg **N-Acetylcysteine** is a form of **glutathione** which is an antioxidant.

https://pubmed.ncbi.nlm.nih.gov/27567825/ CerefolinNAC Therapy of Hyperhomocysteinemia **Delays Cortical and White Matter Atrophy in Alzheimer's Disease** and Cerebrovascular Disease
CFLN was associated with **significantly slowed hippocampal and cortical atrophy rates** in ADRD patients with HHcy, and forebrain parenchymal atrophy rates in CVD patients with HHcy.

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Glutamylcysteine (Gamma-glutamylcysteine, (GGC)) (Glyteine branded form) (raises Glutathione (GSH) levels)

Note: N-acetycysteine is a precursor for L-cysteine to produce glutathione

Glutamylcysteine does not seem available as supplement--- see NAC N-Acetylcysteine

https://www.glutathionereporter.com/gamma-glutamylcysteine-increases-cellular-glutathione/ Gamma-Glutamylcysteine increases cellular glutathione
Gamma-glutamylcysteine, (GGC) is a naturally occurring dipeptide found in all mammalian life and is a key intermediate in the gamma (γ) -glutamyl cycle first described by Meister in the 1970s [1, 2]. It is the **most immediate precursor to the essential antioxidant glutathione (GSH)** [3]. **Supplementation with glutathione (GSH) is incapable of increasing cellular glutathione (GSH)** since the glutathione (GSH) concentration found in the extracellular environment is much lower than that found intracellularly by about a thousand-fold. This large difference means that there is an insurmountable concentration gradient that prohibits extracellular glutathione entering cells and it is only inside the cell where glutathione performs its essential functions. Several review articles have been published regarding the **therapeutic potential of gamma-glutamylcysteine (GGC) to replenish glutathione (GSH) in age related [11] and chronic disease states such as Alzheimer's disease [12]**.
https://pubmed.ncbi.nlm.nih.gov/33276023/ Supplementation with γ-glutamylcysteine (γ-GC) lessens oxidative stress, brain inflammation and amyloid pathology and improves spatial memory in a murine model of AD
Alteration in brain cytokine levels and matrix metalloproteinase enzymes MMP-2 and MMP-9 suggested that **γ-GC may lower inflammation** and enhance Aβ plaque clearance in vivo. **Spatial memory was also improved by γ-GC** as determined using the Morris water maze.
https://pubmed.ncbi.nlm.nih.gov/15678514/ Gamma-glutamylcysteine ethyl ester-induced up-regulation of glutathione protects neurons against Abeta(1-42)-mediated oxidative stress and neurotoxicity: implications for Alzheimer's disease
Taken together, these results suggest that GCEE up-regulates cellular GSH levels which, in turn, **protects neurons against protein oxidation, loss of mitochondrial function**, and DNA fragmentation induced by Abeta(1-42). These results are consistent with the notion that up-regulation of GSH by GCEE may play a viable protective role in the oxidative and neurotoxicity induced by Abeta(1-42) in AD brain.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3316877/ γ-Glutamylcysteine detoxifies reactive oxygen species by acting as glutathione peroxidase-1 cofactor
We found that both mitochondrial-targeted newly synthesized, and endogenous γ-glutamylcysteine, efficiently dispose H_2O_2 by acting as glutathione peroxidase-1 cofactor. These results indicate that **γ-glutamylcysteine is an important player in cellular redox control.**
https://www.sciencedirect.com/science/article/abs/pii/S0197018620303223 Supplementation with γ-glutamylcysteine (γ-GC) lessens oxidative stress, brain inflammation and amyloid pathology and improves spatial memory in a murine model of AD
Highlights
- **Glutathione (GSH) depletion has been linked to cognitive decline and the development of Alzheimer's disease (AD) pathology**.
- **γ-glutamylcysteine (γ-GC), is the immediate precursor and the limiting substrate for GSH biosynthesis.**
- **γ-GC can maintain cellular GSH levels by bypassing the regulation of GSH homeostasis.**
- **Supplementation with γ-GC can reduce brain oxidative stress and neuroinflammation and maintain antioxidant status in an AD mouse model.**
- **Supplementation with γ-GC can reduce amyloid pathology and improve learning and memory deficits in an AD mouse model.**

https://pubmed.ncbi.nlm.nih.gov/25731620/ Therapeutic approaches to modulating glutathione levels as a pharmacological strategy in Alzheimer's disease 2015
Accumulating evidence has suggested the involvement of oxidative stress in the pathogenesis of Alzheimer's disease (AD). The **main endogenous antioxidant, glutathione (GSH), has been shown to decline with ageing and in several age-related degenerative diseases, including AD.** Potential options for replenishing GSH levels as a therapeutic target to treat these conditions include the administration of GSH itself, and low toxicity forms of the limiting amino acid for GSH synthesis; cysteine. **However, passive GSH uptake is limited due to an unfavourable concentration gradient between the plasma and cytosol.** Similarly, cysteine prodrugs have demonstrated limited efficacy to elevate depleted GSH levels in several in vivo and in vitro models of disease. It has been suggested that the decline in GSH levels in AD, may be associated with down regulation of GSH homeostasis rather than substrate limitation. Cellular GSH homeostasis is regulated by non-allosteric feedback inhibition exerted by GSH on **glutamate cysteine ligase (GCL), which is responsible for the synthesis of the GSH precursor γ-glutamylcysteine (GGC).**
https://pubmed.ncbi.nlm.nih.gov/26845022/ Glutamate cysteine ligase and the age-related decline in cellular glutathione: The therapeutic potential of γ-glutamylcysteine 2016

This review focuses on the **suitability of treatment with exogenous γ-GC to raise GSH levels by circumventing the age-related dysregulation** of the rate-limiting step of GSH, providing promise for future research for the treatment of chronic oxidative stress-related diseases.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5284489/ Oral administration of γ-glutamylcysteine increases intracellular glutathione levels above homeostasis in a randomised human trial pilot study 2017
Oral γ-GC is a non-toxic form of cysteine that can be directly taken up by cells and transiently increase lymphocyte GSH above homeostatic levels. Our findings that **γ-GC can increase GSH levels in healthy subjects suggests that it may have potential as an adjunct for treating diseases associated with chronic GSH depletion.**

Gotu Kola (Centella asiatica) anti-oxidant, improve mood, TNF alpha inhibitor, Anti-AChE

Amazon 475mg ($0.09/count) (twice/day?)
https://pubmed.ncbi.nlm.nih.gov/34010562/ Evolving Role of Natural Products from Traditional Medicinal Herbs in the Treatment of Alzheimer's Disease 2019
Gotu Kola (Centella asiatica).
Considered both a nutraceutical and cogniceutical, Gotu kola (Gk) is a staple in Chinese, Indonesian, and Ayurvedic medicine [57]. This medicinal plant is used to strengthen the brain, heal skin issues, and promote liver and kidney health. Gk is considered a rejuvenating herb for nerve and brain cells as it is believed to promote intelligence and improve memory [54,55,56,57].
https://pubmed.ncbi.nlm.nih.gov/27340413/ Effectiveness of Gotu Kola Extract 750 mg and 1000 mg Compared with Folic Acid 3 mg in Improving Vascular Cognitive Impairment after Stroke 2016
his study aimed to determine the effectiveness of gotu kola (Centella asiatica) in improving cognitive function in patients with vascular cognitive impairment (VCI). This study uses a quasi-experimental design. Subjects in this study were patients with poststroke cognitive impairment who were treated at two hospitals in Yogyakarta, Indonesia. The number of subjects was 48: 17 subjects were treated with 1000 mg/day of gotu kola extract, 17 subjects treated with **750 mg/day of gotu kola extract**, and 14 subjects treated with 3 mg/day of folic acid for 6 weeks. A Montreal Cognitive Assessment-Indonesian version (MoCA-Ina) was conducted at the beginning of treatment and after 6 weeks of therapy. It was found that all trials effectively improved poststroke VCI based on MoCA-Ina scores over the course of the study. There is no significant difference in ΔMoCA-Ina (score at the 6th week of treatment - score at the beginning) mean score among the three groups, indicating that gotu kola is as effective as folic acid in improving poststroke VCI. **Gotu kola was shown to be more effective than folic acid in improving memory domain**. This study suggested that gotu kola extract is effective in improving cognitive function after stroke.
https://pubmed.ncbi.nlm.nih.gov/31998466/ *Centella asiatica* (Gotu kola) ethanol extract up-regulates hippocampal brain-derived neurotrophic factor (BDNF), tyrosine kinase B (TrkB) and extracellular signal-regulated protein kinase 1/2 (ERK1/2) signaling in chronic electrical stress model in rats 2019
Impairment of hippocampus function as a center for memory processing occurs due to stress. *Centella asiatica* L. (Gotu kola) is **known to improve memory, intelligence, and neural protection although the precise mechanism is not well understood**. This study aimed to investigate the effects of ethanol extracts of *C. asiatica* toward MAPK expression as down-stream signaling of brain-derived neurotrophic factor (BDNF). **CeA600 group revealed improvement of memory performance as shown by reduction in time and distance parameters compared to control during escape latency test.** This finding associated with significant elevation of hippocampal BDNF protein and mRNA level with up-regulation of TrkB mRNA expression in CeA600 group compared to control. Western-blot analysis showed significant up-regulation of ERK1/2 protein level in CeA600 group ($P<0.05$) compare to control.
https://pubmed.ncbi.nlm.nih.gov/30956976/ *Centella asiatica* Prevents Increase of Hippocampal Tumor Necrosis Factor-α Independently of Its Effect on Brain-Derived Neurotrophic Factor in Rat Model of Chronic Stress 2019
Across all stress conditions, rats receiving the highest dose of CA had the **lowest mean TNF-α** and highest mean BDNF. There were no significant differences in IL-10 and SIRT1 levels between groups. Hippocampal TNF-α did not predict hippocampal BDNF in a regression analysis. In conclusion, lower TNF-α and higher BDNF in the hippocampus support the hypothesis that these factors independently contribute to *Centella asiatica*'s neuroprotective effect in chronically stressed rats.
https://pubmed.ncbi.nlm.nih.gov/32013132/ *Centella asiatica* L. Phytosome Improves Cognitive Performance by Promoting Bdnf Expression in Rat Prefrontal Cortex 2020
Centella asiatica L. is extensively used, not only as anti-inflammatory or antioxidant agent but also as brain tonic. On this basis, the purpose of this study was to evaluate whether the chronic administration of *C. asiatica* L. to adult male rats was able to improve the expression of *Bdnf*, one of the main mediators of brain plasticity. Furthermore, *C. asiatica* L. administration induced an increase of *Bdnf* in the prefrontal cortex, and the administration of the higher dose of the extract was able to improve cognitive performance. Finally, the increase in the preference index in the NOR test was paralleled by a further increase in *Bdnf* expression. Overall, we **highlight the ability of *C. asiatica* L. to affect brain functions by increasing *Bdnf* expression and by enhancing the cognitive performance.**
https://pubmed.ncbi.nlm.nih.gov/28878245/ Effects of Centella asiatica (L.) Urb. on cognitive function and mood related outcomes: A Systematic Review and Meta-analysis 2017
Centella asiatica (L.) Urb. has been used as an herbal brain tonic for mental disorders and enhancing memory, but no review of the overall evidence of C. asiatica and cognitive function has been conducted. This study aims to determine the effects of C. asiatica on cognitive function and its related properties. Meta-analysis indicated that there are **no significant differences in all cognitive function domains of C. asiatica when compared to placebo.** However, it **could improve mood by increasing alert scores [SMD: 0.71 (95% CI; 0.01 to 1.41); I^2 = 30.5%] and decreasing anger scores at 1 hour after treatment** [SMD: -0.81 (95%CI; -1.51 to -0.09); I^2 = 36.6%]. None of the studies reported adverse effects of C. asiatica. In conclusion, there is not strong evidence to support the use of C. asiatica for cognitive function improvement in each cognitive domain. C. asiatica could improve alertness and relieve anger. However, some limitations should be aware including dose regimen, plant preparation, standardization, and product variation.
https://pubmed.ncbi.nlm.nih.gov/18191355/ Positive modulation of cognition and mood in the healthy elderly volunteer following the administration of Centella asiatica 2008
Twenty-eight healthy elderly participants received the plant extract at various doses ranging **250, 500 and 750 mg once daily for 2 months**. **Results:** The results showed that th**e high dose of the plant extract enhanced working memory and increased N100 component amplitude of event-related potential. Improvements of self-rated mood were also found following the Centella asiatica treatment.**
Conclusion: Therefore, the present findings suggest the potential of **Centella asiatica to attenuate the age-related decline in cognitive function and mood disorder in the healthy elderly.** However, the precise mechanism(s) underlying these effects still require further investigation.
https://pubmed.ncbi.nlm.nih.gov/35295926/ Development and Optimization of Nanoemulsion from Ethanolic Extract of Centella asiatica (NanoSECA) Using D-Optimal Mixture Design to Improve Blood-Brain Barrier Permeability 2022
The **evidence on the neuroprotective impact of Centella asiatica (C. asiatica) has been greatly documented in recent years.** However, a **major obstacle that remains to be overcome is the capacity of the active molecules in C. asiatica to cross the blood-brain barrier (BBB)**. In this study, we explored the possibilities of using a D-optimal mixture design to fabricate nanoemulsion of C. asiatica (NanoSECA) for better brain bioavailability. Cell viability was improved in a dose-dependent manner on SH-SY5Y and RAW 264.7 cell lines. In addition, NanoSECA significantly reduced the AChE activity, suppressing the level of proinflammatory mediators and oxidative stress. Moreover, **NanoSECA showed high BBB permeation with a high value of experimental permeability to cross the BBB. Thus, NanoSECA could efficiently potentiate the central nervous system (CNS) therapeutic activities through enhanced penetration of BBB. These nano-delivery systems are crucial to unlock the full potential of C. asiatica for treating numerous CNS disorders.**
https://pubmed.ncbi.nlm.nih.gov/32079355/ Inhibitory Effects of Raw-Extract *Centella asiatica* (RECA) on Acetylcholinesterase, Inflammations, and Oxidative Stress Activities via In Vitro and In Vivo 2020
Centella asiatica (*C. asiatica*) is one of the medicinal plants that has been reported to exert comprehensive neuroprotection in vitro and in vivo. In view of this, the present study was performed to investigate the effect of ethanolic extract of *C. asiatica*, designated as raw-extract of *C. asiatica* (RECA) in **reducing the acetylcholinesterase (AChE),** inflammations, and oxidative stress activities via both in vitro (SH-SY5Y and RAW 264.7 cells) and in vivo (Sprague Dawley rats). Our results elucidated that treatment with RECA **significantly suppressed the level of pro-inflammatory cytokine/mediators and oxidative stress released in a concentration-dependent manner**. Interestingly, these patterns of inhibition were consistent as observed in the LPS-induced neuroinflammation Sprague Dawley rats' model. The **highest concentration used in the two models presented the most significant results. Herein, our findings strongly suggest that RECA may offer therapeutic potential for the treatment of Alzheimer's diseas**e through inhibiting the AChE, inflammation, and oxidative stress activities.
https://pubmed.ncbi.nlm.nih.gov/34267660/ Mitoprotective Effects of *Centella asiatica* (L.) Urb.: Anti-Inflammatory and Neuroprotective Opportunities in Neurodegenerative Disease 2021
Here we appraise the **growing body of evidence that the mitoprotective and antioxidative effects of CA may potentially be harnessed for the treatment of brain aging and neurodegenerative disease.**
https://pubmed.ncbi.nlm.nih.gov/34721056/ Hypoxia-Induced Neuroinflammation in Alzheimer's Disease: Potential Neuroprotective Effects of *Centella asiatica 2021*
Centella asiatica is one of the natural products reported to show neuroprotective effects in various models of CNS diseases. Here, **we review the complex hypoxia-induced neuroinflammation in the pathogenesis of AD and the potential application of *Centella asiatica* as a therapeutic agent in AD or dementia.**
https://pubmed.ncbi.nlm.nih.gov/27540320/ Recent Updates in Neuroprotective and Neuroregenerative Potential of Centella asiatica 2016
Most of the in vivo studies on **neuroprotective effects have focused on Alzheimer's disease**, Parkinson's disease, **learning and memory enhancement, neurotoxicity and other mental illnesses such as depression and anxiety**, and epilepsy. Recent studies have embarked on finding the molecular mechanism of neuroprotection by C. asiatica extract. However, the capability of C. asiatica in enhancing neuroregeneration has not been studied much and is limited to the regeneration of crushed sciatic nerves and protection from neuronal injury in hypoxia conditions. More studies are still needed to identify the compounds and the mechanism of action of C. asiatica that are particularly involved in neuroprotection and neuroregeneration.
https://pubmed.ncbi.nlm.nih.gov/35052625/ *Withania somnifera* and *Centella asiatica* Extracts Ameliorate Behavioral Deficits in an In Vivo *Drosophila melanogaster* Model of Oxidative Stress 2022
The herbs *Withania somnifera* and *Centella asiatica* may be two such alternatives because both have been **connected with reducing oxidative stress** and could therefore ameliorate age-related impairments. To test the effects of these herbs on behavioral phenotypes induced by oxidative stress, we used the *Drosophila melanogaster sniffer* mutant which has high levels of oxidative stress due to reduced carbonyl reductase activity. Effects on cognition and mobility were assessed using phototaxis assays and both, *W. somnifera* and *C. asiatica* water extracts improved phototaxis in *sniffer* mutants. In addition, ***W. somnifera* improved nighttime sleep in male and female *sniffer* flies and promoted a less fragmented sleep pattern in male *sniffer* flies. This suggests that *W. somnifera* and *C. asiatica* can ameliorate oxidative stress-related changes in behavior and that by doing so they might promote healthy aging in humans.**
https://pubmed.ncbi.nlm.nih.gov/34975484/ *Centella asiatica* Alters Metabolic Pathways Associated With Alzheimer's Disease in the 5xFAD Mouse Model of ß-Amyloid Accumulation 2021

Our group has **previously shown that a water extract of *Centella asiatica* (CAW) elicits cognitive-enhancing effects in animal models of aging and Alzheimer's disease**, including a dose-related effect of CAW on memory in the 5xFAD mouse model of *ß*-amyloid accumulation. Here, we endeavor to elucidate the mechanisms underlying the effects of CAW in the brain by conducting a metabolomic analysis of cortical tissue from 5xFAD mice treated with increasing concentrations of CAW. The results are in line with some of our previous findings regarding specific mechanisms of action of CAW (e.g., **improving mitochondrial function, reducing oxidative stress, and increasing synaptic density**). Furthermore, these findings provide new information about additional, potential mechanisms for the cognitive-enhancing effect of CAW, including **upregulation of nicotinamide adenine dinucleotide in the brain and modulation of brain-derived neurotrophic factor.** These metabolic pathways have been **implicated in the pathophysiology of Alzheimer's disease**, highlighting the therapeutic potential of CAW in this neurodegenerative disease.

Grape Seed Extract (iron chelator) (similar to curcumin?)

Supplement dosage: 25-300mg/day

https://pubmed.ncbi.nlm.nih.gov/19384583/ Consumption of grape seed extract prevents amyloid-beta deposition and attenuates inflammation in brain of an Alzheimer's disease mouse 2009

Polyphenols extracted from grape seeds are able to inhibit amyloid-beta (Abeta) aggregation, reduce Abeta production and protect against Abeta neurotoxicity in vitro. We aimed to investigate the therapeutic effects of a **polyphenol-rich grape seed extract (GSE) in Alzheimer's disease (AD) mice. Curcumin also significantly reduced brain Abeta burden and microglia activation.** Conclusively, polyphenol-rich GSE prevents the Abeta deposition and attenuates the inflammation in the brain of a transgenic mouse model, and this thus is promising in delaying development of AD.

https://pubmed.ncbi.nlm.nih.gov/19027755/ **Grape seed polyphenols and curcumin reduce genomic instability** events in a transgenic mouse model for Alzheimer's disease 2009

A significant 10-fold decrease in buccal MN frequency (p=0.01) was found for AD mice fed diets containing curcumin (CUR) or micro-encapsulated grape seed extract (MGSE) and a 7-fold decrease (p=0.02) for AD mice fed unencapsulated grape seed extract (GSE) compared to the AD group on control diet. These results suggest **potential protective effects of polyphenols against genomic instability events in different somatic tissues of a transgenic mouse model for AD.**

https://pubmed.ncbi.nlm.nih.gov/35343876/ The benefits of grape seed extract in neurological disorders and brain aging 2022

Oxidative stress and neuroinflammation play a central role in neuronal damage and neurological diseases induction and progression. In addition, protein homeostasis (proteostasis) impairment occurs in many neurodegenerative diseases, which plays a critical role in the progression of the pathology. **Grape seed contains several flavonoids and non-flavonoids and exerts potent antioxidant and anti-inflammatory effects. In addition, polyphenols and flavanols can maintain cellular proteostasis.**

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7335983/ Grape Seed Oil as a Natural Therapy in Male Rats with Alzheimer's Diseases 2020

this study was carried out to evaluate the efficacy of grape seed oil (GSO) on scopolamine (Scop) induced Alzheimer's in male rats. ***Conclusion:*** The results implied that supplementation of rats with **GSO caused a significant augmentation in spatial memory performance as well as acetylcholine levels** and cell viability in the presence of Scop. This **effect was comparable to that of Don(donepezil)** especially when GSO was used as co-treatment.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3003214/ Grape Seed Extract to Improve Liver Function in Patients with Nonalcoholic Fatty Liver Change 2010

This study describes the **beneficial effect of using grape seed extract for three months i**n patients with nonalcoholic fatty liver disease. These results may improve with a longer period of follow-up.

https://pubmed.ncbi.nlm.nih.gov/31570250/ Protective effects of grape seed proanthocyanidins against iron overload-induced renal oxidative damage in rats 2020

This study was designed to investigate the **protective effects of grape seed proanthocyanidins (GSPAs) against iron overload induced nephrotoxicity in rats**. The roles of GSPAs in chelating iron, antioxidant activity, renal function, pathological section, and apoptosis-related gene expression were assessed. **Conclusions:** GSPAs have protective effects on nephrotoxicity in rats with iron overload.

https://tmu.pure.elsevier.com/en/publications/grape-seed-proanthocyanidin-extract-chelates-iron-and-attenuates- Grape seed proanthocyanidin extract chelates iron and attenuates the toxic effects of 6-hydroxydopamine: Implications for Parkinson's disease 2010

In conclusion, **the iron-chelating activity of GSPE minimizes its pro-oxidant activity** and delays 6-OHDA auto-oxidation to provide cytoprotection.

Huperzia Huperzia saururus, Huperzia selago, Huperzia phlegmaria, Huperzia fargesii, Huperzia serrata, Huperzia reflexa and Huperzia quadrifariata,

- antioxidant, anti-inflammatory and acetylcholinesterase inhibitory(Anti-AChE)

https://pubmed.ncbi.nlm.nih.gov/31778363/ The use of Huperzia species for the treatment of Alzheimer's disease 2019

We found that the **main bioactive compounds of the Huperzia species are alkaloids**, which have shown significant effects on preventing the development of AD. They are new promising compounds against AD due to their **antioxidant, anti-inflammatory and acetylcholinesterase inhibitory** activities in the neural system. Our conclusion from this review is that the Huperzia species are potential source containing various pharmaceutical compounds for the treatment of AD.

https://pubmed.ncbi.nlm.nih.gov/19240260/ Role of huperzine a in the treatment of Alzheimer's disease 2009

Although **use of huperzine A has shown promising results in patients with AD**, data supporting its use are limited by weak study design. Largescale, randomized, placebo-controlled trials are necessary to establish the role of huperzine A in the treatment of AD.

https://pubmed.ncbi.nlm.nih.gov/18230054/ An update on huperzine A as a treatment for Alzheimer's disease 2008

There is evidence that huperzine A may compare favorably in symptomatic efficacy to cholinesterase inhibitors in use. In addition, huperzine A has antioxidant and neuroprotective properties that suggest that it may be useful as a disease-modifying treatment for Alzheimer's disease (AD). The drug is available as a nutriceutical in the US. However, there have been no published controlled clinical trials outside China assessing its toxicity and efficacy. This paper reviews the development of huperzine A as a treatment for AD, including the Phase II trial now under way in the US.

https://pubmed.ncbi.nlm.nih.gov/22941287/ New insights into huperzine A for the treatment of Alzheimer's disease 2012

In addition to its AChE inhibitory effect, potent multifaceted neuroprotective effect through activating cholinergic system and directly acting on mitochondria have been explored. Moreover, in order to **maximize the efficacy and safety of huperzine A therapy, great efforts have been made to optimize drug delivery** system. In the present article, an attempt is made to discuss the current progress and future perspective for huperzine A therapy in AD.

https://pubmed.ncbi.nlm.nih.gov/34770940/ Huperzine A and Its Neuroprotective Molecular Signaling in Alzheimer's Disease 2021

Several studies have evaluated the potential benefits of HupA in human patients. HupA treatment in human subjects suffering from dementia (AD o VaD) shows evidence of improved cognition [4,28,40,41]. It has also been reported that eight weeks of HupA treatment for AD patients improved task switching and alleviated cognitive impairment [42].

A small trial testing the effects of HupA tablets in AD patients showed that the intake of **0.2 mg of HupA improved cognition and memory in 58% of patients** with no severe side effects [43] in later reviews [4], showed significant cognitive enhancement in patients receiving **0.4 mg of HupA twice a day**. **Remarkably, this dose was well tolerated for 24 weeks even though** most AD patients reported being unable to tolerate currently marketed AChEIs for a long period of time [40,44] HupA has **therapeutic benefits for the treatment of AD**, but the understanding of molecular interactions involved in the recovery of neuronal function after HupA treatment is still incomplete. What is known is that AChEI activity is crucial through the regulation of Aβ peptide accumulation by activation of α-secretase cleavage and down-regulation of β/γ-secretase, enhancing BDNF/TrkB signaling as well as PI3K/Akt and PI3K/TrkB/mTOR pathways. **Concomitant reduction of IL-1β, IL-6, TNF-α,** and NF-kB signaling preserves neuronal function.

https://pubmed.ncbi.nlm.nih.gov/24086396/ Huperzine A for Alzheimer's disease: a systematic review and meta-analysis of randomized clinical trials 2013

20 RCTs including 1823 participants were included. The methodological quality of most included trials had a high risk of bias. Compared with placebo, **Huperzine A showed a significant beneficial effect on the improvement of cognitive function** as measured by Mini-Mental State Examination (MMSE) at 8 weeks, 12 weeks and 16 weeks, and by Hastgawa Dementia Scale (HDS) and Wechsler Memory Scale (WMS) at 8 weeks and 12 weeks. Activities of daily living favored Huperzine A as measured by Activities of Daily Living Scale (ADL) at 6 weeks, 12 weeks and 16 weeks. One trial **found Huperzine A improved global clinical assessment as measured by Clinical Dementia Rating Scale (CDR)**. **One trial demonstrated no significant change in cognitive function** as measured by Alzheimer's disease Assessment Scale-Cognitive Subscale (ADAS-Cog) and activity of daily living as measured by Alzheimer's disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL) in Huperzine A group. Trials comparing Huperzine A with no treatment, psychotherapy and conventional medicine demonstrated similar findings.

https://pubmed.ncbi.nlm.nih.gov/26745980/ Isolation, diversity and acetylcholinesterase inhibitory activity of the culturable endophytic fungi harboured in Huperzia serrata from Jinggang Mountain, China 2016

Among them, **22 endophytic fungi strains achieved high inhibitory activity (≥50%) on AChE** which belongs to 13 genera and five incertae sedis strains. Four endophytic fungi designated as JS4 (Colletotrichum spp.), FL14 (Ascomycota spp.), FL9 (Sarcosomataceae spp.) and FL7 (Dothideomycetes spp.) were displayed highly active (≥80%) against AChE, which the inhibition effects were even more intense than the positive control. Our findings highlight that **H. serrata grown in Jinggang Mountain harbors a rich and fascinating endophytic fungus community with potential AChE inhibitory activity, which could further broaden the natural acetylcholinesterase inhibitors resources used for Alzheimer's disease treatment.**

Inositol (little/old information)

Sources: fresh citrus fruits, beans(pinto, peas), grains bran, nuts(almonds or peanut butter), meat, eggs

https://pubmed.ncbi.nlm.nih.gov/8843494/ Inositol treatment of Alzheimer's disease: a double blind, cross-over placebo controlled trial 1996

A double-blind controlled crossover trial of **6 gm of inositol daily vs glucose** for one month each was carried out in 11 Alzheimer patients. 2. Overall CAMCOG scores s**howed a trend for greater improvement with inositol that was not significant**. 3. **Language and orientation improved significantly** more on inositol than on placebo. There were no serious side effects. 4. Higher doses of inositol should be studied in Alzheimer's Disease for longer periods.

Isoflavones (found in soybeans)

https://pubmed.ncbi.nlm.nih.gov/30272840/ Dietary soybean isoflavones in Alzheimer's disease prevention

Soybean isoflavone (SIF) is a type of polyphenol present extensively in legumes. Because of its unique chemical construction and the physiological activity of the phenolic hydroxyl group, SIF exhibits **strong antioxidant activity in antioxidant and nonantioxidant enzyme systems**. Recent studies have suggested that SIF may **alleviate neurodegenerative diseases such as Alzheimer's disease (AD).** Despite the comprehensive research on AD, effective treatments for AD are yet to be established. The early diagnosis and prevention of mild cognitive impairment (MCI) have become crucial for delaying AD development. Several dietary polyphenols have exerted cognitive effects on AD, and the appropriate intake of dietary SIF helps reduce the risk of AD. This study reviews the possible mechanisms of AD pathogenesis and their relationships with SIF intake; the results provide useful insights for AD prevention in the future.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4657545/ Cognitive effects of soy isoflavones in patients with Alzheimer's disease

In a **previous trial, treatment with soy isoflavones was associated with improved nonverbal memory, construction, verbal fluency, and speeded dexterity compared to treatment with placebo in cognitively healthy older men and women**.

The **current trial aimed to examine the potential cognitive benefits of soy isoflavones in patients with Alzheimer's disease.** Sixty-five men and women over the age of 60 were treated with **100mg/day soy isoflavone,** or matching placebo capsules for six months. *APOE* genotype was determined for all participants. Cognitive outcomes and plasma isoflavone levels were measured at Baseline, and at two additional time points. **Six months of 100mg/day treatment with soy isoflavones did not benefit cognition in older men and women with Alzheimer's disease**. However, our results suggest the need to **examine the role of isoflavone metabolism, i.e., the ability to effectively metabolize soy isoflavones by converting daidzen to equol** when attempting fully clarify the cognitive effects of isoflavones.

Ketone Supplements / Ketogenic Diet

- see Caprylic Acid (C8) under Coconut oil for generating Ketones

https://pubmed.ncbi.nlm.nih.gov/31405021/ Ketogenic Diet in Alzheimer's Disease 2019

The ketogenic diet is a very high-fat, low-carbohydrate diet, which has a fasting-like effect bringing the body into a state of ketosis. The presence of **ketone bodies has a neuroprotective impact on aging brain cells.** Moreover, their production may enhance mitochondrial function, reduce the expression of inflammatory and apoptotic mediators. Thus, it has gained interest as a potential therapy for neurodegenerative disorders like Alzheimer's disease.

https://pubmed.ncbi.nlm.nih.gov/36079829/ Ketogenic Diet: A Dietary Intervention via Gut Microbiome Modulation for the Treatment of Neurological and Nutritional Disorders (a Narrative Review) 2022

Gut dysbiosis has been proposed to be involved in those diseases, and **KD can promote gut microbiota remodeling** that may assist in recovery. This review explores the therapeutic applications of KD, the roles of the gut microbiome in neurological diseases and obesity, as well as the effect of KD on the gut microbiome. The present information suggests that KD has significant roles in altering the gut microbiome to improve disease symptoms, mainly by incrementing *Bacteroidetes* to *Firmicutes* (B/F) ratio and reducing *Proteobacteria* in certain cases.

https://pubmed.ncbi.nlm.nih.gov/35718870/ The Ketogenic Diet and Alzheimer's Disease 2022

There is evidence that the **KD and exogenous ketone supplementation may provide treatment benefits in AD patients**. It is unclear whether one method is better than the other. The specific food composition of the KD should be considered, because certain types of fat sources are healthier than others. Many forms of the KD require strict monitoring of carbohydrate intake, which would often fall under the responsibility of the caregiver. Most current studies are small, often uncontrolled, and only look at the short-term effects of ketosis on cognition. Large, long-term, randomized, controlled trials relative to the impact of the KD in patients with cognitive impairment and AD are lacking and thus needed.

https://pubmed.ncbi.nlm.nih.gov/30554068/ The ketogenic diet as a potential treatment and prevention strategy for Alzheimer's disease 2019

The **ketogenic diet could alleviate the effects of impaired glucose metabolism by providing ketones as a supplementary energy source**. In addition, this diet m**ay help to reduce the accumulation of amyloid plaques while reversing amyloid β toxicity**.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8803132/ Efficacy and Safety of Ketone Supplementation or Ketogenic Diets for Alzheimer's Disease: A Mini Review 2021

Glucose usually represents the main fuel for the brain. Glucose metabolism has been related to neuroinflammation, but also with AD lesions. However, in the absence of glucose, the brain may use another fuel: ketone bodies (KB) produced by oxidation of fatty acids. In clinical studies, **KS(supplements) and KD(diet) were associated with better cognition, but also improved brain metabolism and AD biomarkers. In cognitively normal older adults, a high-glycemic diet was previously shown to be associated with cerebral Aβ burden (5)**. Very recently, in a longitudinal analysis over one year, the same research team found greater brain Aβ accumulation in participants with higher daily intake of sugar or carbohydrates (6). AD my also result from insulin resistance, which affects insulin signaling and favors the deposition of brain Aβ and pTau (7). Two different strategies have been considered: first, the i**ntake of medium-chain triglycerides (MCT) resulting in the production of KB after beta-oxidation in the liver.** Thus, KB cross the blood brain barrier and fuel the brain. Second, when glucose is not readily available (e.g., starvation), a metabolic switch occurs in favor of KB usually released by the liver. The diets specifically designed for KB production are called ketogenic diets (KD) (10). The core characteristics of the KD are the association of a high amount of fat, with low carbohydrate intake: usually a macronutrient ratio of fat to protein and carbohydrate combined equal to 3 or 4:1. **When ketosis is achieved, the main fuel used by the body shifts from glucose to favor KB, an adaptation that also occurs with extended fasting.**

Since 2019, we found ten studies, in humans, aiming at improving cognitive performance or biomarkers of AD (See Table 1) (13–22). Among them, seven used KS vs. placebo and three KD vs. control diet. Of note, the most valuable clinical investigation regarding KS included 413 older participants (mean age = 77) with mild to moderate AD, followed-up over 6 months (15). The intervention consisted in 20 g of MCT supplementation, a standard daily dose to produce KB. Finally, Henderson et al. did not observe significant improvements regarding their two main endpoints i.e., cognitive performance and clinician's impression of change. **On the other hand, in older adults with mild cognitive impairment (MCI) Fortier et al. showed that 30 g of MCT supplementation over a 6-month follow, significantly improved three major cognitive functions: episodic memory, executive function and language (19). Three studies in healthy participants used KS over very short intervention windows (0–5weeks) and reported improved cognitive functions and/or brain metabolism (14, 16, 22).**

Intermittent fasting has already been suggested as a therapeutic option for reducing the onset of neurodegenerative disorders (39). As in the KD, fasting induces a metabolic shift where energy results for KB. However, **weight loss due to fasting is likely to accelerate cognitive decline**, whereas maintaining stable weight and nutritional status are mandatory for patients with AD (23).

https://pubmed.ncbi.nlm.nih.gov/36355101/ A Novel Ketone-Supplemented Diet Improves Recognition Memory and Hippocampal Mitochondrial Efficiency in Healthy Adult Mice 2022

Here, we explored the mitochondrial and performative outcomes of a **novel eight-week ketone-supplemented ketogenic (KETO) diet in healthy adult male and female mice**. n a novel object recognition test, KETO mice spent more time with the novel, compared to familiar, object, **indicating an improvement in recognition memory.** High-resolution respirometry on permeabilized hippocampal tissue returned significant reductions in mitochondrial O_2 consumption. No changes in ATP production were observed, yielding a **significantly higher ATP:O_2 ratio, a measure of mitochondrial efficiency.** Together, these findings demonstrate the KETO diet **improves hippocampal mitochondrial efficiency**. They add to a growing body of evidence that suggests ketones and ketogenic diets are neuroprotective and metabolically and cognitively relevant, even in healthy adults.

https://alzres.biomedcentral.com/articles/10.1186/s13195-021-00783-x Randomized crossover trial of a modified ketogenic diet in Alzheimer's disease 2021

This is the first randomized trial to investigate the impact of a ketogenic diet in patients with uniform diagnoses of AD. **High rates of retention, adherence, and safety appear to be achievable in applying a 12-week modified ketogenic diet to AD patients. Compared with a usual diet supplemented with low-fat healthy-eating guidelines, patients on the ketogenic diet improved in daily function and quality of life, two factors of great importance to people living with dementia.**

Lemon Balm (Melissa officinalis) oral oil, aromatherapy, Tea

1600mg

https://pubmed.ncbi.nlm.nih.gov/12888775/ Modulation of mood and cognitive performance following acute administration of single doses of Melissa officinalis (Lemon balm) with human CNS nicotinic and muscarinic receptor-binding properties 2003

Following the in vitro analysis, 20 healthy, young participants received **single doses of 600, 1000, and 1600 mg of encapsulated dried leaf,** or a matching placebo, at 7-day intervals. Cognitive performance and mood were assessed predose and at 1, 3, and 6 h postdose However, no cholinesterase inhibitory properties were detected. The **most notable cognitive and mood effects were improved memory performance and increased 'calmness' at all postdose time points for the highest (1600 mg) dose.** However, while the profile of results was overwhelmingly favorable for the highest dose, decrements in the speed of timed memory task performance and on a rapid visual information-processing task increased with decreasing dose. These results suggest that **doses of Melissa officinalis at or above the maximum employed here can improve cognitive performance and mood and may therefore be a valuable adjunct in the treatment of Alzheimer's disease.** The results also suggest that different preparations derived from the same plant species may exhibit different properties depending on the process used for the sample preparation.

https://pubmed.ncbi.nlm.nih.gov/34449930/ The effects of lemon balm (Melissa officinalis L.) on depression and anxiety in clinical trials: A systematic review and meta-analysis 2021

Based on meta-analysis results, lemon balm **significantly improved mean anxiety and depression scores** compared with the placebo (SMD: -0.98; 95% CI: -1.63 to -0.33; p = 0.003), (SMD: -0.47; 95% CI: -0.73 to -0.21; p = 0.0005) respectively, without serious side effects. Current evidence suggests that lemon balm may be effective in improving anxiety and depressive symptoms, particularly in the acute setting.

https://pubmed.ncbi.nlm.nih.gov/30670268/ A randomised controlled trial of Lavender (Lavandula Angustifolia) and Lemon Balm (Melissa Officinalis) essential oils for the treatment of agitated behaviour in older people with and without dementia 2018

Forty-nine nursing home residents with dementia (n=39) and without dementia (n=10) exhibiting agitation participated in this study. Participants were randomised to a counterbalanced, repeated measures design experiment that tests the treatments Lavender, Lemon Balm, and Placebo (Sunflower oil). Treatments were administered once daily for two-weeks followed by a two-week washout period before commencing the subsequent treatment. Post hoc analysis reports Lemon Balm more effective in reducing NPI agitation (p = .04) and CMAI physical non-aggressive behaviour (PNAB) (p = .02) in residents without dementia. Lemon Balm less effective in reducing NPI irritability (p = 0.01) and Lavender more effective in reducing CMAI PNAB (p = 0.04) in dementia.

https://pubmed.ncbi.nlm.nih.gov/26408043/ A medicinal herb, Melissa officinalis L. ameliorates depressive-like behavior of rats in the forced swimming test via regulating the serotonergic neurotransmitter 2015

The present study shows the serotonergic antidepressant-like activity of WMO. Hence, WMO may offer a serotonergic antidepressant activity to prevent depression and to assist in conventional therapies.

Lion's Mane (Hericium Mushroom)(Monkey head Mushroom) [Active ingredient Ergothioneine/Erinacine?]

https://pubmed.ncbi.nlm.nih.gov/29953363/ Dietary Supplementation of Lion's Mane Medicinal Mushroom, Hericium erinaceus (Agaricomycetes), and Spatial Memory in Wild-Type Mice

Hericium erinaceus is an edible and medicinal mushroom with **potential neuroprotective effects**. The study of H. erinaceus has attracted considerable attention during the past 10 years, particularly with regard to its potential utility in the treatment of motor dysfunction, **Alzheimer disease, and other forms of dementia**. We previously determined that oral supplementation with H. erinaceus results in s**ignificant improvements in novelty-seeking behavior and novel object recognition in mice**. In this study, H. erinaceus was added to the diets of wild-type mice for 2 months, and **effects on spatial memory were evaluated** by means of a Y maze and an object location task. We found that H. erinaceus increased general locomotor activity but had no effect on spatial memory. Thus, oral supplementation with H. erinaceus yields **specific and selective improvements in recognition memory** without altering spatial working memory, which supports the hypothesis that recognition memory can be modeled as a dual process. In this model, the perirhinal cortex supports the recognition of individual items as part of a circuit involved in familiarity with an encountered stimulus, whereas the hippocampus supports recollected associations and relationships between stimuli.

https://pubmed.ncbi.nlm.nih.gov/35334834/ Searching for a Longevity Food, We Bump into *Hericium erinaceus* Primordium Rich in Ergothioneine: The "Longevity Vitamin" Improves Locomotor Performances during Aging

Particularly, *H. erinaceus* primordium (He2) extract contains a **high amount of Ergothioneine (ERGO)**, the longevity vitamin. Herein, we revealed the preventive effect of ERGO-rich He2 extract in a preclinical model, focusing on locomotor decline during ageing monitored through spontaneous behavioral test. This effect was accompanied by a s**ignificant decrease in some oxidative stress markers (NOS2, COX2) paralleled by an increase in P53, showed in cerebellar cortex cells and fibres by immunohistochemistry. In summary, we demonstrated the neuro-protective and preventive effects of He2 extract during aging, probably due to its peculiarly high ERGO content.**

https://pubmed.ncbi.nlm.nih.gov/34203691/ Neuroprotective Metabolites of *Hericium erinaceus* Promote Neuro-Healthy Aging

Frailty is a geriatric syndrome associated with both locomotor and cognitive decline, typically linked to **chronic systemic inflammation**, i.e., *inflammaging*. In the current study, we investigated the effect of a two-month oral supplementation with standardized extracts of *H. erinaceus*, containing a known amount of Erinacine A, Hericenone C, Hericenone D, and L-ergothioneine, on locomotor frailty and cerebellum of aged mice. Locomotor performances were monitored comparing healthy aging and frail mice. Cerebellar volume and cytoarchitecture, **together with inflammatory and oxidative stress pathways**, were assessed focusing on senescent frail animals. *H. erinaceus* partially **recovered the aged-related decline of locomotor performances**. Histopathological analyses paralleled by immunocytochemical evaluation of specific molecules strengthened the neuroprotective role of *H. erinaceus* able to ameliorate cerebellar alterations, i.e., milder volume reduction, slighter molecular layer thickness decrease and minor percentage of shrunken Purkinje neurons, also d**iminishing inflammation and oxidative stress in frail mice while increasing a key longevity regulator and a neuroprotective molecule.**

https://pubmed.ncbi.nlm.nih.gov/35892581/ The Monkey Head Mushroom and Memory Enhancement in Alzheimer's Disease

Alzheimer's disease (AD) is a neurodegenerative disorder, and no effective treatments are available to treat this disorder. Therefore, **researchers have been investigating *Hericium erinaceus*, or the monkey head mushroom, an edible medicinal mushroom, as a possible treatment for AD**. In conclusion, *Hericium erinaceus* has **therapeutic potential and may facilitate memory enhancement in patients with AD**.

https://pubmed.ncbi.nlm.nih.gov/34829535/ Key Mechanisms and Potential Implications of *Hericium erinaceus* in NLRP3 Inflammasome Activation by Reactive Oxygen Species during Alzheimer's Disease

Altered antioxidant systems and inflammation have an important role in the etiology of neurodegenerative disorders. In this study, we evaluated the effects of *Hericium erinaceus*, a nutritional mushroom with **important antioxidant effects, in a rat model of AD**. Animals were injected with 70 mg/Kg of AlCl3 daily for 6 weeks, and *Hericium erinaceus* was administered daily by gavage. Before the experiment's end date, behavioral test training was performed. At the end of the study, behavioral changes were assessed, and the animals were euthanized. Brain tissues were harvested for further analysis. AlCl3 mainly accumulates in the hippocampus, the principal region of the brain involved in memory functions and learning. ***Hericium erinaceus* administration reduced behavioral changes and hippocampal neuronal degeneration. Additionally, it reduced phosphorylated Tau levels, aberrant APP overexpression, and β-amyloid accumulation. Moreover, *Hericium erinaceus* decreased the pro-oxidative and pro-inflammatory hippocampal alterations induced by AD. In particular, it reduced the activation of the NLRP3 inflammasome components, usually activated by increased oxidative stress during AD.** Collectively, our results showed that ***Hericium erinaceus* has protective effects on behavioral alteration and histological modification associated with AD due to the modulation of the oxidative and inflammatory pathways, as well as regulating cellular brain stress**.

https://pubmed.ncbi.nlm.nih.gov/34204787/ *Hericium erinaceus* (Bull.) Pers. Ethanolic Extract with Antioxidant Properties on Scopolamine-Induced Memory Deficits in a Zebrafish Model of Cognitive Impairment

The **ethanolic extract from the fungal biomass of *H. erinaceus*** was previously obtained using an ultrasonic extraction method (UE). The administration of *H. erinaceus* extract to zebrafish, with a pattern of AD induced by scopolamine, showed an **improvement in memory evaluated by behavioral and biochemical tests on brain tissue.** These results suggest that *H. erinaceus* has **preventive and therapeutic potentials in managing memory deficits and brain oxidative stress in zebrafish with AD.**

https://pubmed.ncbi.nlm.nih.gov/34688684/ Structural characterization of polysaccharide purified from Hericium erinaceus fermented mycelium and its pharmacological basis for application in Alzheimer's disease: Oxidative stress related calcium homeostasis

The **purified polysaccharides from Hericium erinaceus fermented mycelium entitled with PHEB** was analyzed and it was mainly composed of six glycosidic bonds. It has been **confirmed to show the relieving activity against Alzheimer's Disease (AD)** . **PHEB alleviated the oxidative stress in brains of AD mice** via regulation the Nrf2 and its downstream kinase, which further improved the cholinergic system function. Proteomics and bioinformatics analysis showed that the therapeutic effect of PHEB is achieved by **regulating calcium homeostasis mediated by oxidative stress**. Furthermore, PHEB regulated the CaMK II/IV to achieve the calcium homeostasis in brains; and ultimately to show the anti-AD property.

https://pubmed.ncbi.nlm.nih.gov/27350344/ Erinacine A-enriched Hericium erinaceus mycelium ameliorates Alzheimer's disease-related pathologies in APPswe/PS1dE9 transgenic mice

The fruiting body of **Hericium erinaceus has been demonstrated to possess anti-dementia activity in mouse model of Alzheimer's disease and people with mild cognitive impairment.** However, the therapeutic potential of Hericium erinaceus mycelia on Alzheimer's disease remains unclear. In this study, the effects of **erinacine A-enriched Hericium erinaceus mycelia (HE-My)** on the pathological changes in APPswe/PS1dE9 transgenic mouse model of Alzheimer's disease are studied. After a 30 day oral administration to 5 month-old female APPswe/PS1dE9 transgenic mice, we found that HE-My and its **ethanol extracts (HE-Et)** attenuated cerebral Aβ plaque burden. These results highlight the therapeutic potential of HE-My and HE-Et on Alzheimer's disease. Therefore, the effective **components of HE-My and HE-Et are worth to be developed to become a therapeutic drug for Alzheimer's disease.**

https://pubmed.ncbi.nlm.nih.gov/35877305/ Lion's Mane (*Hericium erinaceus*) Exerts Anxiolytic Effects in the rTg4510 Tau Mouse Model

Alzheimer's disease (AD) significantly impairs the life of an individual both cognitively and behaviorally. Tau and beta-amyloid (Aβ) proteins are major contributors to the etiology of AD. This study used mice modeling AD through the presence of tau pathology to assess the effects of *Hericium erinaceus* (*H. erinaceus*), also known as Lion's mane, on cognitive and non-cognitive behaviors. **Mice given *H. erinaceus* spent significantly more time in the open arms of and made more head dips in the elevated zero maze** (EZM) (*p* < 0.05). While *H. erinaceus* had anxiolytic effects, **no improvements were seen in spatial memory or activities of daily living**. These findings provide additional **support for the anxiolytic effects of *H. erinaceus* and point to its potential benefit as a therapeutic for anxiety in AD.**

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5987239/ Neurohealth Properties of *Hericium erinaceus* Mycelia Enriched with Erinacines

Hericium erinaceus, an ideal culinary-medicinal mushroom, has become a well-established candidate in promoting positive brain and nerve health-related activities by inducing the nerve growth factor from its bioactive ingredient. Among its active compounds, only **erinacine** A has confirmed pharmacological actions in the central nervous system in rats. preclinical studies have shown that there can be improvements in ischemic stroke, **Parkinson's disease, Alzheimer's disease, and depression** if *H. erinaceus* mycelia enriched with erinacines are included in daily meals. **Erinacine A**, the main representative of the erinacine group, not only has an enhancing effect on NGF synthesis *in vitro* [12] but also can increase NGF and catecholamine content in the locus coeruleus and hippocampus of rats after administration (8 mg/kg body weight) As the **fruiting body was reported to contain no erinacines** [26], the best option would be to enhance erinacine production in *H. erinaceus* mycelia via submerged fermentation under constantly controlled culture parameters.

Collectively, these findings raise the possibility that prevention with **erinacine A-enriched *H. erinaceus* mycelia could be an effective therapeutic strategy for managing Alzheimer's disease.**

https://pubmed.ncbi.nlm.nih.gov/34010562/ Evolving Role of Natural Products from Traditional Medicinal Herbs in the Treatment of Alzheimer's Disease 2019

Lion's mane (Lm) is an edible mushroom that is predominant in North America, Europe, and Asia. It is widely used in traditional Chinese medicine for its **neuroprotective, anti-cancer, and anti-inflammatory properties** [59]. These benefits are attributed to the two principal constituents of Lm, namely hericenones and erinacines [127,128].

l-theanine [unique non-protein amino acid found in tea (Camellia sinensis)] (tea maybe linked with aluminum and iron bioavailability?)

https://pubmed.ncbi.nlm.nih.gov/30527255/ The combination of luteolin and l-theanine improved Alzheimer disease-like symptoms by potentiating hippocampal insulin signaling and decreasing neuroinflammation and norepinephrine degradation in amyloid-β-infused rats 2018

Luteolin and l-theanine have anti-inflammatory, antioxidant, and possible antidiabetic activities, and they may synergistically protect against dementia. Here, we hypothesized that a combination of luteolin and l-theanine would synergistically act to improve memory function and glucose disturbances in rats infused with amyloid-β, and the mechanisms underlying these actions were investigated. In conclusion, the hypothesis of the study was accepted. The combination of luteolin and l-theanine prevented Alzheimer disease-like symptom, possibly by improving hippocampal insulin signaling, norepinephrine metabolisms, and decreasing neuroinflammation. The **combination of luteolin and l-theanine may be a useful therapeutic option for preventing and/or delaying the progression of memory dysfunction.**

https://pubmed.ncbi.nlm.nih.gov/19766184/ l-Theanine, an **amino acid in green tea**, attenuates beta-amyloid-induced cognitive dysfunction and neurotoxicity: reduction in oxidative damage and inactivation of ERK/p38 kinase and NF-kappaB pathways 2009

Amyloid beta (Abeta)-induced neurotoxicity is a major pathological mechanism of Alzheimer disease (AD). In this study, we investigated the inhibitory effect of l-theanine, a component of green tea (Camellia sinensis), on Abeta(1-42)-induced neuronal cell death and memory impairment. Oral treatment of l-theanine (**2 and 4 mg/kg) for 5 weeks** in the drinking water of mice, followed by injection of Abeta(1-42) (2 microg/mouse, icv), significantly attenuated Abeta(1-42)-induced memory impairment. l-Theanine also significantly reduced oxidative protein and lipid damage and the elevation of glutathione levels in the brain. These **data suggest that the positive effects of l-theanine on memory** may be mediated by suppression of ERK/p38 and NF-kappaB as well as the reduction of macromolecular oxidative damage. **Thus, l-theanine may be useful in the prevention and treatment of AD.**

https://pubmed.ncbi.nlm.nih.gov/21735448/ L-Theanine: properties, synthesis and isolation from tea 2011

Theanine is a non-protein amino acid that occurs naturally in the tea plant (Camellia sinensis) and contributes to the favourable taste of tea. It is also associated with effects such as the enhancement of relaxation and the **improvement of concentration and learning ability**. While theanine has been chemically and biologically synthesised, techniques to isolate theanine from natural sources remain an important area of research. In this review article, the properties and health benefits of theanine are summarised and the synthesis and isolation of theanine are reviewed and discussed.

https://pubmed.ncbi.nlm.nih.gov/21735551/ Optimum conditions for the water extraction of L-theanine from green tea 2011

The results showed that temperature, extraction time, ratio of water-to-tea and tea particle sizes had significant impacts on the extraction yield of theanine. The optimal conditions for extracting theanine from green tea using water were found to be extraction at **80 °C for 30 min with a water-to-tea ratio of 20:1 mL/g and a tea particle size of 0.5-1 mm.**

https://pubmed.ncbi.nlm.nih.gov/28429900/ Theanine: the unique amino acid in the tea plant as an oral hepatoprotective agent 2017

Recently, multiple lines of evidence have proven its **beneficial effects on hepatic and immune functions**. One possible mechanism for its biological activity involves the **downregulation of the inflammatory response through the induction of nitric oxide production and glutathione synthesis**. In this review, we summarize published results describing the potential mechanisms for these beneficial health effects and provide new insight into how theanine can be t**herapeutic for liver injury and chronic liver disease**.

https://pubmed.ncbi.nlm.nih.gov/34562208/ A Randomized, Triple-Blind, Placebo-Controlled, Crossover Study to Investigate the Efficacy of a Single Dose of AlphaWave® L-Theanine on Stress in a Healthy Adult Population 2021

This study was conducted during the coronavirus pandemic, which has had a rapid and significant effect on both physical and mental health around the world. A single dose of AlphaWave® L-Theanine had significant positive effects on brainwaves, salivary cortisol, and self-reported state anxiety compared to the placebo in response to an acute stress challenge. These changes are indicative of **relaxation in the brain and suggest a calming response** in a moderately stressed but otherwise healthy population. AlphaWave® L-Theanine was found to be safe and well tolerated by participants.

https://pubmed.ncbi.nlm.nih.gov/21477654/ Neuroprotective effects of theanine and its preventive effects on cognitive dysfunction 2011

Theanine (γ-glutamylethylamide) characteristically present in tea leaves (Camellia sinensis). It has a **similar chemical structure to glutamate,** which is a neurotransmitter related to memory. Theanine **passes through the blood-brain barrier** and has been shown to have a **cerebroprotective effect** and a preventive effect on neuronal cell death after transient cerebral ischemia. The neuroprotective effect is partly due to the antagonistic action of theanine on glutamate receptor subtype AMPA and kainate receptors, but the affinity is very low. Theanine also acted on glutamine (Gln) transporter strongly and inhibited the incorporation of extracellular Gln into neurons, which in turn suppressed the conversion of Gln to glutamate by glutaminase, a reaction required for condensation into synaptic vesicles to form a neurotransmitter pool responsible for subsequent exocytotic release upon stimuli. In an investigation of elderly persons with normal or slight cognitive dysfunction, volunteers who ingested powdered green tea containing a high theanine concentration (equivalent to **47.5mgday**(-1) of theanine) s**howed significantly lower decline in cognitive function compared with that of the placebo group**. This result suggested that theanine might have improved a slight cognitive dysfunction in elderly persons.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8080935/ Effects of l-Theanine on Cognitive Function in Middle-Aged and Older Subjects: A Randomized Placebo-Controlled Study 2021

l-theanine (γ-glutamylethylamide), an amino acid in green tea, has been shown to affect brain functions by **relieving stress disorders, improving mood, and maintaining normal sleep**. However, the c**ognitive functions for which theanine is effective are unclear**. This study aimed to clarify which cognitive functions are positively affected by intake of l-theanine. A double-blind, randomized, placebo-controlled study was conducted. The subjects were Japanese men and women aged 50–69 years. Mini Mental State Examination-Japanese version score was 24 or higher. Cognitrax was used as a test battery for cognitive function. Evaluations were performed before the intervention, after a single dose of l-theanine, and after 12 weeks of regular intake. The single dose of l-theanine reduced the reaction time to attention tasks (Stroop test, Part 1), and it increased the number of correct answers and decreased the number of omission errors in working memory tasks (4-Part continuous performance test, Part 4). **In conclusion, our study indicated that l-theanine may contribute to improving attention, thus enhancing working memory and executive functions**. Clinical Trial No.: UMIN000033812.

https://www.alzdiscovery.org/cognitive-vitality/ratings/l-theanine L-THEANINE 2017

L-theanine is an **amino acid structurally similar to glutamate and GABA, two neurotransmitters? important for brain function.** It is contained in **green, black, and oolong teas**, which are all derived from Camellia sinensis, a perennial evergreen shrub. L-theanine is traditionally used to **promote relaxation** without sedative effects. Research suggests it is s**afe and has positive effects on cognitive function when combined with caffeine**, but the effects of L-theanine alone appear to be modest and short-term. No studies have tested whether it can prevent dementia or cognitive decline. L-theanine supplements are available in both capsule and powder forms. A single cup (200 ml) of tea can contain 5 to 85 mg of L-theanine depending on the type, quality, and preparation of tea. Clinical trials examining the effects of L-theanine on cognitive function have used doses ranging from 12–250 mg/day, with the majority of studies using **200 mg/day** [2][15][16].

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6836118/ Effects of L-Theanine Administration on Stress-Related Symptoms and Cognitive Functions in Healthy Adults: A Randomized Controlled Trial 2019

This randomized, placebo-controlled, crossover, and double-blind trial aimed to examine the possible effects of four weeks L-theanine administration on stress-related symptoms and cognitive functions in healthy adults. Participants were 30 individuals (nine men and 21 women; age: 48.3 ± 11.9 years) who had no major psychiatric illness. **L-theanine (200 mg/day)** or placebo tablets were randomly and blindly assigned for four-week administration. Our findings suggest that **L-theanine has the potential to promote mental health in the general population with stress-related ailments and cognitive impairments.**

Lycopene (see tomatoes) (anti-oxidant in the carotenoid family)

Sources: SunDried Tomatoes(45.9mg), Guave(5.2mg), Watermelon(4.5mg), Fresh Tomatoes(3mg), Papaya(1.8mg), Ketchup(10-14mg/100grams)
Recommended intake: 8-21mg

https://pubmed.ncbi.nlm.nih.gov/24247062/ Serum lycopene, lutein and zeaxanthin, and the risk of Alzheimer's disease mortality in older adults 2014

High serum levels of lycopene and lutein+zeaxanthin are associated with a lower risk of AD mortality in adults. Our findings suggest that a high intake of lycopene- or lutein+zeaxanthin-rich food may be important for reducing the AD mortality risk.

https://pubmed.ncbi.nlm.nih.gov/32551202/ Lycopene alleviates oxidative stress via the PI3K/Akt/Nrf2pathway in a cell model of Alzheimer's disease

Conclusion: **Lycopene possibly prevents Aβ-induced damage** by activating the PI3K/Akt/Nrf2 signaling pathway and reducing the expression of BACE in M146L cells.

Melissa officinalis(Lemon balm)

https://pubmed.ncbi.nlm.nih.gov/12810768/ Melissa officinalis extract in the treatment of patients with mild to moderate Alzheimer's disease: a double blind, randomised, placebo controlled trial 2003

To assess the efficacy and safety of Melissa officinalis extract using a fixed dose (**60 drops/day)** in patients with mild to moderate Alzheimer's disease. **Results:** At four months, Melissa officinalis extract produced a **significantly better outcome on cognitive function than placebo** (ADAS-cog: df = 1, F = 6.93, p = 0.01; CDR: df = 1, F = 16.87, p < 0.0001). There were no significant differences in the two groups in terms of observed side effects except agitation, which was more common in the placebo group (p = 0.03).

Conclusions: **Melissa officinalis extract is of value in the management of mild to moderate Alzheimer's disease and has a positive effect on agitation in such patients.**

Moringa oleifera Quercetin source

https://pubmed.ncbi.nlm.nih.gov/29710724/ Moringa Oleifera Alleviates Homocysteine-Induced Alzheimer's Disease-Like Pathology and Cognitive Impairments 2018

Due to the complexity of AD, many attempted single therapy treatments, like Aβ immunization, have generally failed. Therefore, there is a need for drugs with multiple benefits. Naturally occurring phytochemicals with **neuroprotective, anti-amyloidogenic, antioxidative, and anti-inflammatory** properties could be a possible way out. In this study, the effect of Moringa oleifera (MO), a naturally occurring plant with high antioxidative, anti-inflammatory, and neuroprotective effects, was evaluated on hyperhomocysteinemia (HHcy) induced AD-like pathology in rats. Homocysteine (Hcy) injection for 14 days was used to induce AD-like pathology. Simultaneous MO extract gavage followed the injection as a preventive treatment or, after injection completion, MO gavage was performed for another 14 days as a curative treatment. **MO was found to not only prevent but also rescue the oxidative stress and cognitive impairments induced by Hcy treatment.** Moreover, MO recovered the decreased synaptic proteins PSD93, PSD95, Synapsin 1 and Synaptophysin, and i**mproved neurodegeneration**. Interestingly, MO decreased the Hyc-induced tau hyperphosphorylation at different sites including S-199, T-231, S-396, and S-404, and at the same time **decreased Aβ production** through downregulation of BACE1. These effects in HHcy rats were accompanied by a decrease in calpain activity under MO treatment, supporting that calpain activation might be involved in AD pathogenesis in HHcy rats. Taken together, our data, for the first time, provided evidence that **MO alleviates tau hyperphosphorylation and Aβ pathology in a HHcy AD rat model.** This and previous other studies support MO as a **good candidate for, and could provide new insights into, the treatment of AD and other tauopathies.**

https://pubmed.ncbi.nlm.nih.gov/36296969/ Moringa Oleifera Alleviates Aβ Burden and Improves Synaptic Plasticity and Cognitive Impairments in APP/PS1 Mice 2022

Alzheimer's disease is a global public health problem and the most common form of dementia. Due to the failure of many single therapies targeting the two hallmarks, Aβ and Tau, and the multifactorial etiology of AD, there is now more and more interest in nutraceutical agents with multiple effects such as *Moringa oleifera* (MO) that have strong anti-oxidative, anti-inflammatory, anticholinesterase, and neuroprotective virtues. In this study, we treated APP/PS1 mice with a methanolic extract of MO for four months and evaluated its effect on AD-related pathology in these mice using a multitude of behavioral, biochemical, and histochemical tests. Our data revealed that **MO improved behavioral deficits such as anxiety-like behavior and hyperactivity and cognitive, learning, and memory impairments.** MO treatment abrogated the Aβ burden to wild-type control mice levels via decreasing BACE1 and AEP and upregulating IDE, NEP, and LRP1 protein levels. Moreover, MO improved synaptic plasticity by improving the decreased GluN2B phosphorylation, the synapse-related proteins PSD95 and synapsin1 levels, the quantity and quality of dendritic spines, and neurodegeneration in the treated mice. **MO is a nutraceutical agent with promising therapeutic potential that can be used in the management of AD and other neurodegenerative diseases.**

https://pubmed.ncbi.nlm.nih.gov/36192762/ Effects of Moringa oleifera on working memory: an experimental study with memory-impaired Wistar rats tested in radial arm maze 2022

Thus, the **study concludes that M. oleifera can prevent ketamine-induced memory impairment in Wistar rats.**

https://pubmed.ncbi.nlm.nih.gov/34843254/ *Moringa oleifera*: A Tree of Life as a Promising Medicinal Plant for Neurodegenerative Diseases 2021

Moringa oleifera, popularly known as a **miracle tree or tree of life**, has been extensively used as a functional food and nutritional asset worldwide. Ethnomedicinal and traditional uses of *M. oleifera* indicate that this plant might have a pleiotropic therapeutic efficacy against most human ailments. In fact, *M. oleifera* is reported to have several pharmacological activities, including **antioxidant, antibacterial, antifungal, antidiabetic, antipyretic, antiulcer, antispasmodic, antihypertensive, antitumor, hepatoprotective**, and cardiac stimulant properties. Recently, a few experimental studies reported the **neuroprotective effects of *M. oleifera* against Alzheimer's disease, dementia,** Parkinson's disease, stroke, and neurotoxicity-related symptoms. In addition, several neuroprotective phytochemicals have been isolated from *M. oleifera*, which signifies that it can have promising neuroprotective effects. Therefore, **this review aimed to explore the current updates and future prospective of neuroprotective efficacies of *M. oleifera*.**

https://pubmed.ncbi.nlm.nih.gov/35163945/ Characterization, Large-Scale HSCCC Separation and Neuroprotective Effects of Polyphenols from *Moringa oleifera* Leaves 2022

The phenolic composition in *Moringa oleifera* leaves was first analyzed qualitatively and quantitatively by UPLC-Q-Exactive Orbitrap/MS and UPLC-QqQ/MS, respectively, indicating that **quercetin** and **kaempferol** derivatives, **phenolic acid** and **apigenin** are the main polyphenols in *Moringa oleifera* leaves, with **quercetin and kaempferol derivatives predominating**. Furthermore, the conditions of HSCCC for large-scale separation of polyphenols from *Moringa oleifera* leaves were optimized, which included the selection of the solvent system, flow rate and the sample load. Only by one-step HSCCC separation (within 120 min) under the optimized conditions, six quercetin and kaempferol derivatives, a phenolic acid and an apigenin could be individually isolated at a large scale (yield from 10% to 98%), each of which possessed high purity. Finally, the i**solated polyphenols and phenolic extract from *Moringa oleifera* leaves (MLPE) were verified to have strong neuroprotective activities against H_2O_2-induced oxidative stress in PC-12 cells, suggesting that these compounds would contribute to the main beneficial effects of *Moringa oleifera* leaves.**

https://pubmed.ncbi.nlm.nih.gov/34206952/ Nutritional Value of *Moringa oleifera* Lam. Leaf Powder Extracts and Their Neuroprotective Effects via Antioxidative and Mitochondrial Regulation 2021

The aim of this work is to investigate the neuroprotective role of methanol extracts of *Moringa oleifera* leaf powder on antioxidant/oxidant imbalance and mitochondrial regulation in a H_2O_2-induced oxidative stress model in human neuroblastoma cells. On nutritional analysis, results showed that moringa contained **28.50% carbohydrates**, **25.02% proteins**, **10.42% fat**, **11.83% dietary fiber**, **1.108 mg β-carotene**, **326.4 μg/100 g vitamin B1** and **15.2 mg/100 g vitamin C**. In-vitro assays revealed that **moringa methanol extracts had more phenolic content and higher antioxidant activity than acetone extracts.** Moreover, pretreatments with methanol extracts showed a protective effect against H_2O_2-induced oxidative damage through increasing cell viability and reducing free radicals. Furthermore, the extract decreased lipid peroxidation and enhanced glutathione levels and antioxidant enzyme activity. Finally, moringa also prevented mitochondrial dysfunction by **regulating calcium levels** and increasing mitochondrial membrane potential. The most active concentration was 25 μg/mL. In summary, the nutritional and functional properties of *Moringa oleifera* as a neuroprotective agent could be beneficial to protect against oxidative stress and provide necessary nutrients for a healthy diet.

https://pubmed.ncbi.nlm.nih.gov/24454988/ Moringa oleifera mitigates memory impairment and neurodegeneration in animal model of age-related dementia 2013

Therefore, our data suggest that M. oleifera leaves extract is the **potential cognitive enhancer and neuroprotectant.** The possible mechanism might occur partly via the decreased oxidative stress and the enhanced cholinergic function.

https://pubmed.ncbi.nlm.nih.gov/24367723/ Cerebroprotective effect of Moringa oleifera against focal ischemic stroke induced by middle cerebral artery occlusion 2013

The protective effect of medium and low doses of extract in all areas occurred mainly **via the decreased oxidative stress**. The protective effect of the high dose extract in striatum and hippocampus occurred via the same mechanism, whereas other mechanisms might play a crucial role in cortex.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5745501/ Bioactive Components in *Moringa Oleifera* Leaves Protect against Chronic Disease 2017

Fresh leaves from *MO* are a good source of **vitamin A [**22].

MO leaves also contain **200 mg/100 g of vitamin C**, a concentration greater than what is found in oranges [22,25]

The dried leaves of *MO* are a great source of **polyphenol compounds, such as flavonoids and phenolic acids**. The main flavonoids found in *MO* leaves are **myrecytin, quercetin and kaempferol, in concentrations of 5.8, 0.207 and 7.57 mg/g,** respectively [31,32].

Quercetin is found in dried *MO* leaves, at concentrations of **100 mg/100 g, as quercetin**-3-*O*-β-d-glucoside (iso-quercetin or isotrifolin) [33,34]. Quercetin is a strong antioxidant, with multiple therapeutic properties [35].

Phenolic acids are a sub-group of phenolic compounds, derived from **hydroxybenzoic acid and hydroxycinnamic acid**, naturally present in plants, and these compounds have antioxidant, anti-inflammatory, antimutagenic and anticancer properties [40,41] In dried leaves, **Gallic acid is the most abundant, with a concentration of 1.034 mg/g** of dry weight.

Chlorogenic acid (CGA) is an ester of dihydrocinnamic acid and a major phenolic acid in *MO* [44]. CGA has a role in glucose metabolism.

Alkaloids are a group of chemical compounds, which contain mostly basic nitrogen atoms. Several of these compounds, including *N*,α-l-rhamnopyranosyl vincosamide, phenylacetonitrile pyrrolemarumine,4′-hydroxyphenylethanamide-α-l-rhamnopyranoside and its glucopyranosyl derivative, have been isolated from *Moringa Oleifera* leaves [49,50].

Glucosinolates are a group of secondary metabolites in plants [51]. Both glucosinolates and isothiocyanates have been found to have important health-promoting properties [52].

Tannins are water-soluble phenolic compounds that precipitate alkaloids, gelatin and other proteins. Their concentrations in dried leaves range between 13.2 and 20.6 g tannin/kg [53] being a little higher in freeze-dried leaves [54]. Tannins have been reported to have anti-cancer, antiatherosclerotic, anti-inflammatory and anti-hepatoxic properties [55].

MO leaves are also a good source of **saponins**, natural compounds made of an isoprenoidal-derived aglycone, covalently linked to one or more sugar moieties [56].

https://link.springer.com/article/10.1007/s11011-021-00855-9 *Moringa oleifera*-supplemented diet protect against cortico-hippocampal neuronal degeneration in scopolamine-induced spatial memory deficit in mice: role of oxido-inflammatory and cholinergic neurotransmission pathway 2021

These results suggest that ***Moringa oleifera*-supplemented diet may serve a potential therapeutic and possible pharmacological macromolecule for preventing loss of neuronal cells and management of Alzheimer's disease.**

https://pubmed.ncbi.nlm.nih.gov/25808883/ Review of the Safety and Efficacy of Moringa oleifera 2015

Moringa oleifera leaves, seeds, bark, roots, sap, and flowers are widely used in traditional medicine, and the **leaves and immature seed pods are used as food products in human nutrition**. **Leaf extracts exhibit the greatest antioxidant activity, and various safety studies in animals involving aqueous leaf extracts indicate a high degree of safety**. No adverse effects were reported in association with human studies. Five human studies using powdered whole leaf preparations of M. oleifera have been published, which have demonstrated anti-hyperglycemic (antidiabetic) and anti-dyslipidemic activities. These activities have been confirmed using extracts as well as leaf powders in animal studies. A rapidly growing number of published studies have shown that aqueous, hydroalcohol, or alcohol extracts of M. oleifera leaves possess a wide range of additional biological activities **including antioxidant, tissue protective (liver, kidneys, heart, testes, and lungs),** analgesic, antiulcer, antihypertensive, radioprotective, and immunomodulatory actions. **A wide variety of polyphenols and phenolic acids as well as flavonoids, glucosinolates, and possibly alkaloids is believed to be responsible for the observed effects.**

https://pubmed.ncbi.nlm.nih.gov/25183111/ Protective effects of Moringa oleifera Lam. leaves against arsenic-induced toxicity in mice 2014

Conclusions: The results indicate that the leaves of M. oleifera may be **useful in reducing the effects of arsenic-induced toxicity**.

https://www.prevention.com/food-nutrition/a21201466/moringa-benefits/ How to use moringa powder

"I would recommend adding the powder to smoothies, muffins, protein or granola bars, or quick bread. It has a strong vegetal flavor that works well in savory dishes or in recipes with natural sweetness," says Moore. It can also be steeped as a tea or sprinkled into soups and salad dressings.

If you're curious about incorporating moringa powder into your diet, whipping up this tropical green smoothie is a good place to start.

Moringa Smoothie Recipe

- 1/2 frozen banana
- 1/2 cup frozen peaches
- 1/3 cup plain Greek yogurt
- 1/2 cup milk (dairy, soy or nut)
- 1/2 cup coconut water
- 1 tablespoon moringa

MSM Methylsulfonylmethane (34% elemental sulfur)(herbal product)

Generally Recognized as Safe Possible Interactions: aspirin, warfarin, NSAIDS

Supplement dosage: 500mg 2-3times/day

https://pubmed.ncbi.nlm.nih.gov/11641045/ Methylsulfonylmethane (MSM) is a widely available 'alternative' medicine. In vivo magnetic resonance spectroscopy (MRS) was used to detect and quantify MSM in the brains of four patients with memory loss and in three normal volunteers all of who had ingested **MSM at the recommended doses of 1-3 g daily**. MSM was detected in all subjects at concentrations of 0.42-3.40 mmole/kg brain and was equally distributed between gray and white matter. MSM was undetectable in drug-naïve normal subjects (N=25), patients screened for 'toxic exposure' (N=50) or patients examined with 1H MRS for the diagnosis of probable Alzheimer Disease (N=520) between 1991 and 2001. No adverse clinical or neurochemical effects were observed. **Appearance of MSM in significant concentrations in the human brain indicates ready transfer across the intact blood-brain barrier**, of **a compound with no known medical benefits**.

https://pubmed.ncbi.nlm.nih.gov/28300758/ Methylsulfonylmethane: Applications and Safety of a Novel Dietary Supplement

Methylsulfonylmethane (MSM) has become a **popular dietary supplement** used for a variety of purposes, including its most common use as an **anti-inflammatory agent.** It has been well-investigated in animal models, as well as in human clinical trials and experiments. A variety of health-specific outcome measures are improved with MSM supplementation, including **inflammation, joint/muscle pain, oxidative stress, and antioxidant capacity**. Initial evidence is available regarding the dose of MSM needed to provide benefit, although additional work is underway to determine the precise dose and time course of treatment needed to provide optimal benefits. As a **Generally Recognized As Safe (GRAS) approved substance, MSM is well-tolerated** by most individuals at dosages of up to four grams daily, with few known and mild side effects. This review provides an overview of MSM, with details regarding its common uses and applications as a dietary supplement, as well as its safety for consumption.

https://pubmed.ncbi.nlm.nih.gov/32926927/ Modulatory effect of methylsulfonylmethane against BPA/γ-radiation induced neurodegenerative alterations in rats: Influence of TREM-2/DAP-12/Syk pathway

Whereas, MSM treatment improved histopathological insults and a**meliorated level of oxidative stress, neuroinflammation and AD markers** as well as modulated TREM-2/DAP-12/Syk pathway.

https://pubmed.ncbi.nlm.nih.gov/32083522/ Beauty from within: Oral administration of a **sulfur-containing** supplement methylsulfonylmethane improves signs of skin ageing

Methylsulfonylmethane (MSM) is an organosulfur compound with known benefits for joint health, sports nutrition, immune function, and anti-aging formulations and is gaining popularity as a nutritional supplement for the support of hair, skin and nails.

Results: Part I of the study clearly indicates that oral ingestion of MSM (3 g/d) **reduces signs of ageing** like facial wrinkles ($p < 0.05$) and skin roughness ($p < 0.05$) as compared to placebo. Detailed analysis in Part II instrumentation assessments showed a significant ($p < 0.05$) improvement from baseline in the severity of facial wrinkles, as well as improved skin firmness, elasticity and hydration with MSM. Some of these parameters exhibited a good dose-response indicating that the higher **(3 g/d) o**f the supplement was more effective than the lower dose of 1 g/d, but generally the lower dose of 1 g/d appeared to be sufficiently effective in reducing the facial signs of ageing. Conclusion: This study indicated that MSM is effective in reducing visual signs of skin ageing even at a low dose of 1 g/d.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5097813/ The Influence of Methylsulfonylmethane on Inflammation-Associated Cytokine Release before and following Strenuous Exercise

Inflammation is associated with strenuous exercise and methylsulfonylmethane (MSM) has been shown to have **anti-inflammatory properties**. MSM appears to **dampen the release of inflammatory molecules in response to exercise**, resulting in a less incendiary environment, allowing cells to still have the capacity to mount an appropriate response to an additional stimulus after exercise.

Methylsulfonylmethane (MSM) is an **organosulfur compound that is widely used as a dietary supplement for inflammatory conditions such as osteoarthritis**

In vitro studies indicate that the **anti-inflammatory activity of this compound is mediated by the inhibition of the proinflammatory nuclear factor kappa beta** (NF-κβ) signaling pathway and attenuation of the NLR family pyrin domain containing 3 (NLRP3) inflammasome activation, **resulting in decreased release of the proinflammatory cytokines such as interleukins IL-1β, IL-6, and IL-8** [6–8]. In addition to pathological conditions, MSM supplementation also alleviates markers of oxidative stress and muscle damage following acute bouts of exercise in a healthy population [9–12]. However, as strenuous exercise also induces an inflammatory response, it is not known what effect MSM has on the inflammatory cytokine production.

https://pubmed.ncbi.nlm.nih.gov/16309928/#:~:text=Methylsulfonylmethane%20%28MSM%29%20is%20a%20popular%20dietary%20supplement%20used,Methods%3A%20A%20randomized%2C%20double-blind%2C%20placebo-controlled%20trial%20was%20conducted.

Efficacy of methylsulfonylmethane (MSM) in osteoarthritis pain of the knee: a pilot clinical trial

Results: Compared to placebo, MSM produced **significant decreases in WOMAC pain and physical function impairment** ($P<0.05$). No notable changes were found in WOMAC stiffness and aggregated total symptoms scores. MSM also produced **improvement in performing activities of daily living** when compared to placebo on the SF-36 evaluation ($P<0.05$).

Conclusion: MSM **(3g twice a day) i**mproved symptoms of pain and physical function during the short intervention without major adverse events.

https://nutrientssolutions.com/5-ways-msm-transforms-your-health/ 5 Ways MSM Transforms Your Health

MSM (short for methylsulfonylmethane) is a white crystalline powder that offers the **most biologically active form of the element sulfur**. Sulfur is found in plants and almost all living organisms, and it plays a vital role in every cell of the human body. According to the Weston Price Foundation, U.S. soils are depleted of sulfur because of over-farming. Sulfur in foods is also destroyed when food is pasteurized, heated at high temperatures or frozen.

https://pubmed.ncbi.nlm.nih.gov/11641045/ Accumulation of methylsulfonylmethane in the human brain: identification by multinuclear magnetic resonance spectroscopy

Methylsulfonylmethane (MSM) is a widely available 'alternative' medicine. In vivo magnetic resonance spectroscopy (MRS) was used to detect and quantify MSM in the brains of four patients with memory loss and in three normal volunteers all of who had ingested MSM at the recommended doses of **1-3 g daily.** MSM was detected in all subjects at concentrations of 0.42-3.40 mmole/kg brain and was equally distributed between gray and white matter. MSM was undetectable in drug-naïve normal subjects (N=25), patients screened for 'toxic exposure' (N=50) or patients examined with 1H MRS for the diagnosis of probable Alzheimer Disease (N=520) between 1991 and 2001. No adverse clinical or neurochemical effects were observed. Appearance of MSM in significant concentrations in the human brain **indicates ready transfer across the intact blood-brain barrier**, of a compound with no known medical benefits.

https://pubmed.ncbi.nlm.nih.gov/28300758/ Methylsulfonylmethane: Applications and Safety of a Novel Dietary Supplement

Methylsulfonylmethane (MSM) has become a **popular dietary supplement** used for a variety of purposes, including its most common use as an **anti-inflammatory agent**. It has been well-investigated in animal models, as well as in human clinical trials and experiments. A variety of health-specific outcome measures are improved with MSM supplementation, including inflammation, joint/muscle pain, oxidative stress, and antioxidant capacity. Initial evidence is available regarding the dose of MSM needed to provide benefit, although additional work is underway to determine the precise dose and time course of treatment needed to provide optimal benefits. As a **Generally Recognized As Safe (GRAS)** approved substance, MSM is well-tolerated by most individuals at dosages of **up to four grams daily**, with few known and mild side effects.

https://clubalthea.com/2017/11/16/msm-powder-benefits-alzheimer-is-a-sulfur-deficiency/ MSM powder benefits – Alzheimer is a sulfur deficiency

has information, but no references.

https://www.sciencedirect.com/science/article/pii/S0028390816304749 DMSO modulates CNS function in a preclinical Alzheimer's disease model

Here we examined the brain structure and function following chronic exposure to low DMSO dose at a paradigm with flawed synaptic connectivity in a preclinical transgenic mouse model for Alzheimer's disease . **DMSO exhibited clear influence on the behavior of this mouse line by enhancing hippocampal-dependent spatial memory accuracy**, modulating hippocampal-independent olfactory habituation and displaying anxiolytic effect.

https://pubmed.ncbi.nlm.nih.gov/33613018/ Sulfur-containing therapeutics in the treatment of Alzheimer's disease

A lot of research has been conducted on sulfur-containing compounds in the context of AD due to their innate antioxidant potential and some are currently being evaluated in clinical trials.

https://pubmed.ncbi.nlm.nih.gov/35887282/ Is There a Connection between the Metabolism of Copper, Sulfur, and Molybdenum in Alzheimer's Disease? New Insights on Disease Etiology

We found significant evidence in the literature of a new potential mechanism linking **Cu imbalance to Mo and S abnormalities in AD etiology:** under certain circumstances, the accumulation of Cu not bound to ceruloplasmin might affect the transport of Mo outside the blood vessels, causing a mild Mo deficiency that might lowerthe activity of Mo and S enzymes essential for neuronal activity.

https://pubmed.ncbi.nlm.nih.gov/32083522/ Beauty from within: Oral administration of a sulfur-containing supplement methylsulfonylmethane improves signs of skin ageing 2022

Methylsulfonylmethane (MSM) is an organosulfur compound with **known benefits for joint health, sports nutrition, immune function, and anti-aging formulations** and is gaining popularity as a nutritional supplement for the support of hair, skin and nails. Detailed analysis in Part II instrumentation assessments showed a significant ($p < 0.05$) improvement from baseline in the severity of facial wrinkles, as well as improved skin firmness, elasticity and hydration with MSM. Some of these parameters exhibited a good dose-response indicating that the higher (3 g/d) of the supplement was more effective than the lower dose of 1 g/d, but generally the lower dose o**f 1 g/d appeared to be sufficiently effective in reducing the facial signs of ageing.** *Conclusion*: This study indicated that MSM is effective in reducing visual signs of skin ageing even at a low dose of 1 g/d.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5097813/ The Influence of Methylsulfonylmethane on Inflammation-Associated Cytokine Release before and following Strenuous Exercise 2016

Results. LPS stimulation of whole blood after MSM supplementation resulted in decreased induction of IL-1*β*, with **no effect on IL-6, TNF-α, or IL-8**. After exercise, there was a reduced response to LPS in the placebo, but **MSM resulted in robust release of IL-6 and TNF-α.** A small decrease in resting levels of proinflammatory cytokines was noted with MSM, while an acute postexercise increase in IL-10 was observed with MSM. *Conclusion*. Strenuous exercise causes a robust inflammatory reaction that precludes the cells from efficiently responding to additional stimuli. **MSM appears to dampen the release of inflammatory molecules in response to exercise**, resulting in a less incendiary environment, allowing cells to still have the capacity to mount an appropriate response to an additional stimulus after exercise.

Mucuna pruriens (Fabaceae) (source of L-dopa) anti-oxidant and metal cheltor

Supplement dosage: 500mg/day

https://pubmed.ncbi.nlm.nih.gov/35380400/ Neuroprotection by Mucuna pruriens in Neurodegenerative Diseases 2022

The medicinal plant Mucuna pruriens (Fabaceae) is widely known for its **anti-oxidative and anti-inflammatory** properties. It is a well-established drug in Ayurveda and has been widely used for the **treatment of neurological disorders** and male infertility for ages. The seeds of the plant have potent medicinal value and its extract has been tested in different models of neurodegenerative diseases, especially Parkinson's disease (PD). Apart from PD, Mucuna pruriens is now being studied in models of other nervous systems disorders such as Alzheimer's disease (AD), Amyotrophic lateral sclerosis (ALS) and stroke because of its neuroprotective importance. This review briefly discusses the pathogenesis of PD, AD, ALS and stroke.

https://pubmed.ncbi.nlm.nih.gov/35630617/ Mucuna pruriens Seed Aqueous Extract Improved Neuroprotective and Acetylcholinesterase Inhibitory Effects Compared with Synthetic L-Dopa 2022

L-dopa, a dopaminergic agonist, is the gold standard for the treatment of Parkinson's disease. However, due to the long-term toxicity and adverse effects of using L-dopa as the first-line therapy for Parkinson's disease, a search for alternative medications is an important current challenge. Traditional Ayurvedic medicine has suggested the use of Mucuna pruriens Linn. (Fabaceae) as an anti-Parkinson's agent. The present study aimed to quantify the amount of L-dopa in M. pruriens seed extract by HPLC analysis. The cytotoxicity and neuroprotective properties of M. pruriens aqueous extract were investigated by two in vitro models including the serum deprivation method and co-administration of hydrogen peroxide assay. The results showed the s**ignificant neuroprotective activities of M. pruriens seed extracts at a concentration of 10 ng/mL.** In addition, the effects of L-dopa and M. pruriens seed extract on in vitro acetylcholinesterase activities were studied. M. pruriens seed extract demonstrated acetylcholinesterase inhibitory activity, while synthetic L-dopa enhanced the activity of the enzyme. It can be concluded that the administration of M. pruriens seed might be effective in **protecting the brain against neurodegenerative disorders such as Parkinson's and Alzheimer's diseases.** M. prurience seed extract containing L-dopa has shown less acetylcholinesterase activity stimulation compared with L-dopa, suggesting that the extract might have a superior benefit for use in the treatment of Parkinson's disease.

https://pubmed.ncbi.nlm.nih.gov/30131460/ Levodopa-Reduced Mucuna pruriens Seed Extract Shows Neuroprotective Effects against Parkinson's Disease in Murine Microglia and Human Neuroblastoma Cells, Caenorhabditis elegans, and Drosophila melanogaster 2018

Mucuna pruriens (Mucuna) has been prescribed in Ayurveda for various brain ailments including 'kampavata' (tremors) or Parkinson's disease (PD). While **Mucuna is a well-known natural source of levodopa (L-dopa)**, published studies suggest that other bioactive compounds may also be responsible for its anti-PD effects. To investigate this hypothesis, an L-dopa reduced (<0.1%) M. pruriens seeds extract (MPE) was prepared and evaluated for its anti-PD effects in cellular (murine BV-2 microglia and human SH-SY5Y neuroblastoma cells), Caenorhabditis elegans, and Drosophila melanogaster models. Therefore, **MPE contains bioactive compounds, beyond L-dopa, which may impart neuroprotective effects against PD**.

https://pubmed.ncbi.nlm.nih.gov/30179419/ Comparative evaluation of extract of Bacopa monnieri and Mucuna pruriens as neuroprotectant in MPTP model of Parkinson's disease 2016

Treatment of PD has been shifted recently towards **herbal medicines.Bacopa monnieri (L.) Wettst. (BM) and Mucuna pruriens (L.) DC (MP)** are traditional herbal plants known to have neuroprotective effects due to the presence of bacosides in whole plant extract of Bacopa monnieri (BME) and L-DOPA in MP seed extract (MPE). In this study, the comparative effect of BME and MPE in Parkinsonian mice induced by chronic exposure to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) was evaluated. Treatment with BME or MPE for one month significantly decreased the elevated levels of oxidative stress found in Parkinsonian mice. In **behavioral tests, comparative analysis of BME and MPE showed a significant increase in spontaneous locomotor activity and grip strength test. Moreover, it was found that the use of BME considerably improved the tyrosine hydroxylase activity, caspase-3 and expression of neurogenic gene in the substantia nigra region of the brain. The results suggest that BME may provide a better platform for future drug discoveries and novel treatment strategies for PD as compared to MPE.**

https://pubmed.ncbi.nlm.nih.gov/24716148/ The Magic Velvet Bean of Mucuna pruriens 2012

Mucuna pruriens (Fabaceae) is an established herbal drug used for the management of male infertility, nervous disorders, and also as an aphrodisiac. It has been shown that its seeds are potentially of substantial medicinal importance. The ancient Indian medical system, Ayurveda, traditionally used M. pruriens, even to treat such things as Parkinson's disease. M. pruriens has been shown to have anti-parkinson and **neuroprotective** effects, which may be related to **its anti-oxidant activity**. In addition, anti-oxidant activity of M. pruriens has been also demonstrated in vitro by its ability to scavenge DPPH radicals and reactive oxygen species. In this review the medicinal properties of M. pruriens are summarized, taking in consideration the studies that have used the seeds extracts and the leaves extracts.

https://pubmed.ncbi.nlm.nih.gov/18064727/ Antiparkinson drug--Mucuna pruriens shows **antioxidant and metal chelating activity** 2008

Oxidative stress plays an important role in the pathophysiology of Parkinson's disease. The ancient Indian medical system, Ayurveda, traditionally uses Mucuna pruriens to treat Parkinson's disease. In our earlier studies, Mucuna pruriens has been shown to possess antiparkinson and neuroprotective effects in animal models of Parkinson's disease. The antioxidant activity of Mucuna pruriens was demonstrated by its ability to scavenge DPPH radicals, ABTS radicals and reactive oxygen species. Mucuna pruriens significantly inhibited the oxidation of lipids and deoxyribose sugar. **Mucuna pruriens exhibited divalent iron chelating activity** and did not show any genotoxic/mutagenic effect on the plasmid DNA. These results suggest that the **neuroprotective and neurorestorative effect of Mucuna pruriens may be related to its antioxidant activity** independent of the symptomatic effect. In addition, the **drug appears to be therapeutically safe in the treatment of patients with Parkinson's disease.**

https://pubmed.ncbi.nlm.nih.gov/35046433/ Administration of mucuna beans (Mucuna pruriences (L.) DC. var. utilis) improves cognition and neuropathology of 3 × Tg-AD mice 2022

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by the accumulation of extracellular amyloid-beta peptides (Aβ) resulting in senile plaques and intracellular hyperphosphorylated tau protein resulting in neurofibrillary tangles (NFTs). Mucuna beans (Mucuna pruriences (L.) DC. var. utilis) are unique plants containing 3-9% L-3,4-dihydroxyphenylalanine (L-DOPA). Here we investigated the effect of the administration of Mucuna beans on AD prevention by feeding triple-transgenic mice (3 × Tg-AD mice) with a diet containing Mucuna beans for 13 months. The levels of Aβ oligomers and detergent-insoluble phosphorylated tau decreased in the brain of mice fed with Mucuna beans (Mucuna group) compared to those of the Control group. Aβ accumulation and phosphorylated tau accumulation in the brain in the Mucuna group were also reduced. In addition, administration of Mucuna beans improved cognitive function. **These results suggest that administration of Mucuna beans may have a preventive effect on AD development in 3 × Tg-AD mice.**

https://www.ehealthme.com/ds/mucuna-pruriens/dementia-of-the-alzheimer-s-type-with-delirium/ Mucuna pruriens and Dementia of the alzheimer's type, with delirium - a phase IV clinical study of FDA data

We study 54 people who take Mucuna pruriens or have Dementia of the alzheimer's type, with delirium. **No report of Dementia of the alzheimer's type, with delirium is found in people who take Mucuna pruriens.**

L-Dopa

https://pubmed.ncbi.nlm.nih.gov/19894644/ Establishing the probable mechanism of L-DOPA in Alzheimer's disease management 2009

Clinical data suggest the **role of L-DOPA in Alzheimer's Disease (AD) though its mechanism of action in AD is not clear**. No change was observed in the brain or the circulating SOD activity. Hence, it is derived that protective role of L-DOPA in AD management is not exerted through its antioxidant property and may be manifested due to its involvement in other pathways.

https://pubmed.ncbi.nlm.nih.gov/18594753/ L-dopa modulates motor cortex excitability in Alzheimer's disease patients 2008

In Alzheimer's disease (AD), transcranial magnetic stimulation (TMS) studies have shown abnormalities of motor cortical excitability, such as a decreased intra-cortical inhibition (ICI) and changes in resting motor threshold (rMT). We studied the effects of L-dopa on rMT and ICI in a cohort of moderate AD patients after paired-pulse TMS. Results were compared with a control group of healthy subjects. As expected, AD patients showed a significant reduction in ICI and a lower rMT. **L-dopa administration (soluble form, melevodopa 200 mg) promptly reversed the ICI impairment up to normalization.** This effect was specific, since it was not mimicked in control subjects. These results indicate a possible role of dopamine in modulating AD cortical excitability, thus suggesting an interaction between dopaminergic ascending pathways and endogenous intracortical transmitters. In addition, considering that L-dopa showed a pharmacological profile similar to the one of cholinomimetics, **L-dopa might represent a reliable tool to study new therapeutic perspective and strategies for AD**.

https://www.nature.com/articles/s41598-020-62172-y Effects of daily L-dopa administration on learning and brain structure in older adults undergoing cognitive training: a randomised clinical trial 2020

We investigated whether supplementation with the dopamine-precursor L-dopa improves effects of cognitive training on performance. Sixty-three participants for this randomised, parallel-group, double-blind, placebo-controlled trial were recruited via newspaper advertisements. Compared to the placebo group, **subjects receiving L-dopa improved less in spatial intelligence** (−0.267 SDs; 95%CI [−0.498, −0.036]; p = 0.024). Change in verbal intelligence did not significantly differ between the groups (−0.081 SDs, 95%CI [−0.242, 0.080]; p = 0.323). **Subjects receiving L-dopa also progressed slower through the training** and the groups displayed differential volumetric changes in the midbrain. The **results speak against early pharmacological interventions in older healthy adults to improve broader cognitive functions by targeting the dopaminergic system and provide no support for learning-enhancing properties of L-dopa supplements in the healthy elderly.**

Naringin (see ref in Manganese)

N-acetylcysteine (NAC) [see also Glutathione Liposomal Glutathione or Acetyl Glutathione for possible better supplement]

-Glutathione precursor

https://www.alzdiscovery.org/cognitive-vitality/ratings/n-acetylcysteine N-acetylcysteine

N-acetylcysteine is a precursor of an amino acid (L-cysteine), which is itself a component of an **antioxidant**. It may help protect against oxidative stress by maintaining or increasing antioxidant levels in the body. Some clinical trials testing **formulations that included N-acetylcysteine have found modest improvements in cognitive function**, but **clinical trials testing it alone have shown less robust results**. N-acetylcysteine supplements are generally regarded as safe when taken at recommended doses.

https://pubmed.ncbi.nlm.nih.gov/28411131/ Influence of N-acetyl cysteine on beta-amyloid-induced Alzheimer's disease in a rat model: A behavioral and electrophysiological study

The purpose of this study was to evaluate the protective effect of N-acetyl cysteine (NAC) on learning and memory in an Aβ-induced Alzheimer's disease model in adult male rats. Administration of **NAC in rats receiving Aβ alleviated the Aβ-induced deficits** in comparison to the Aβ-only group. The results of this study suggest that NAC shows potential for treatment of Alzheimer's disease.

https://pubmed.ncbi.nlm.nih.gov/28499986/ N-acetylcysteine treatment attenuates the cognitive impairment and synaptic plasticity loss induced by streptozotocin

In conclusion, NAC treatment prevented the cognitive impairment induced by STZ, normalizing the AChE activity and rescuing the synaptic plasticity loss. Our results suggest that **NAC is a promising therapeutic strategy for the treatment of AD.**

https://www.researchgate.net/publication/311583479_N-Acetylcysteine_A_Natural_Antidote_for_Alzheimer's_Disease N-Acetylcysteine: A Natural Antidote for Alzheimer's Disease

The present paper proposes that **cysteinet** is impaired in Alzheimer's disease resulting in a functional and structural deregulation of the matrix of interconnected cysteine-containing proteins that result in misfolding, aggregation and accumulation of specific toxic proteins. In this context, **the role of N-acetylcysteine to prevent and restore cysteinet deregulation in AD development and progression is discussed**.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6320789/ Overview on the Effects of *N*-Acetylcysteine in Neurodegenerative Diseases

NAC is a glutathione precursor and shows **antioxidant and anti-inflammatory activities**. In addition to the uses quoted in the literature, NAC may be considered helpful in therapies to **counteract neurodegenerative** and mental health diseases. Furthermore, this compound has been evaluated for its neuroprotective potential in the prevention of cognitive aging dementia. As reported in the literature, the single use of **glutathione (GSH) as oral medication does not sufficiently recover GSH levels.** In fact, in body districts such as liver and intestines, **GSH is quickly hydrolyzed [4] and its capacity to cross through the blood-brain barrier (BBB) is insufficient**. Studies on animal models [10,11], cited in scientific literature, have described that **NAC shows the activity to efficaciously penetrate the BBB increasing the GSH levels in the brain**. In several cellular systems, NAC promotes effects aimed to maintain the survival functions of cells, which also induces the production of intracellular GSH known as the principal antioxidant produced by the body that protects cells from oxidative stress and maintains the redox state inside them . With regards to **anti-inflammatory activity**, several research studies have observed that NAC is able to limit cytokines release in the early state of immune proliferation [13]. NAC can **modulate several key neurotransmitter systems such as glutamate**, which are studied because it is involved in a range of mental illness [27,28]. **NAC showed a protective effect to counteract acrolein, peroxynitrite, hydroxyl radicals, and oxidative damage caused by 3-nitro-propionic acid (3-NP) and GSH augmentation in the brain** and synaptosomes has been observed [69,102,103,104].

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5241507/ A Review on Various Uses of N-Acetyl Cysteine

N**AC is a precursor of L-cysteine that results in glutathione elevation biosynthesis**. During oral administration, deacetylation reaction of NAC happens while passing along the small intestine as well as liver, thus its bioavailability is decreased to 4-10%. NAC stimulates glutathione biosynthesis, promotes detoxification, and acts directly as a scavenger of free radicals. It is a **powerful antioxidant** and a potential treatment option for diseases characterized by the generation of free oxygen radicals (3).

https://www.cambridge.org/core/journals/cns-spectrums/article/abs/lmethylfolate-methylcobalamin-and-nacetylcysteine-in-the-treatment-of-alzheimers-diseaserelated-cognitive-decline/5D859237FD82CDAB7361921709393DDB

L-Methylfolate, Methylcobalamin, and N-Acetylcysteine in the Treatment of Alzheimer's Disease-Related Cognitive Decline

This review considers the **rationale for a combined B-vitamin and antioxidant supplement (Cerefolin NAC)** in treating and slowing AD-related cognitive decline. **Vitamin B12 and folate deficiencies are associated with various cognitive disorders, including dementia**.

https://clinicaltrials.gov/ct2/show/NCT04740580 Glutathione, Brain Metabolism and Inflammation in Alzheimer's Disease

Alzheimer's disease (AD) is associated with significant, progressive cognitive decline. Key defects in mitochondrial fuel metabolism insulin resistance, inflammation and decreased brain glucose uptake are linked to AD. This trial will investigate the effects of supplementing **glycine and N-acetylcysteine** vs. alanine as placebo on these defects in AD, and examine the effects on cognition.

https://www.ucsf.edu/news/2005/12/97790/key-brain-antioxidant-linked-alzheimers-and-parkinsons Key Brain Antioxidant Linked to Alzheimer's and Parkinson's

A study conducted at the San Francisco VA Medical Center has identified a protein found in both mice and humans that appears to play a key role in protecting neurons from **oxidative stress, a toxic process linked to neurodegenerative** illnesses including Alzheimer's and Parkinson's diseases. The study, led by Raymond Swanson, MD, chief of neurology and rehabilitation services at SFVAMC, **identified the protein - known as EAAC1 in mice and as EAAT3 in humans** - as the main mechanism through which the amino acid cysteine is transported into neurons. **Cysteine is an essential component of glutathione, which Swanson terms "the most important antioxidant in the brain."** Antioxidants such as glutathione provide protection from oxidative stress, which kills cells through the "uncontrolled reaction of lipids in the cells with oxygen-basically, burning them out," says Swanson. Since the **brain uses a lot of oxygen** and is "chock full of lipids," it is particularly **vulnerable to oxidative stress,** he notes. This demonstrated that brains of mice unable to produce EAAC1 were ten times as vulnerable to oxidative stress as mice with the ability to produce EAAC1. The researchers also found that the **neurons of the EAAC1-deficient mice contained lower levels of the antioxidant glutathione compared to those of the normal mice**. In the final part of the study, Swanson and his team investigated whether oxidative stress in **EAAC1-deficient mice might be reversible**.

For several days, a group of gene-deficient mice were **fed N-acetylcysteine, an oral form of cysteine** that is readily taken up by neurons. When their neuron slices were compared with slices from untreated gene-deficient mice, it was found that **N-acetylcysteine "had completely corrected the biochemical defect" in their neurons**, recounts Swanson. "**Their glutathione levels were normal, their ability to withstand hydrogen peroxide toxicity was normal, and the oxidants we saw in the** neurons **in response to oxidative challenges were normal."**

https://content.iospress.com/articles/journal-of-alzheimers-disease/jad00733 Lipoic Acid and N-acetyl Cysteine Decrease Mitochondrial-Related Oxidative Stress in Alzheimer Disease Patient Fibroblasts

In this study, we evaluated the effect of **lipoic acid (LA) and N-acetyl cysteine (NAC) on oxidative** [4-hydroxy-2-nonenal, Nε-(carboxymethyl)lysine and heme oxygenase-1] and apoptotic (caspase 9 and Bax) markers in fibroblasts from patients with Alzheimer disease (AD) and age-matched and young controls. AD fibroblasts showed the highest levels of oxidative stress, and the antioxidants, lipoic acid (1 mM) and/or N-acetyl cysteine (100 μM) exerted a **protective effect as evidenced by decreases in oxidative stress and apoptotic markers**. Furthermore, we observed that the **protective effect of LA and NAC was more pronounced when both agents were present simultaneously**. AD-type changes could be generated in control fibroblasts using N-methylprotoporphyrin to inhibit cytochrome oxidase assembly indicating that the the oxidative damage observed was associated with mitochondrial dysfunction. The effects of N-methylprotoporphyrine were reversed or attenuated by both lipoic acid and N-acetyl cysteine. These data suggest mitochondria are important in oxidative damage that occurs in AD. As such, **antioxidant therapies based on lipoic acid and N-acetyl cysteine supplementation may be promising.**

https://www.kidneycoach.com/kidney-nutrients/can-n-acetyl-cysteine-prevent-kidney-damage/ Can N-acetyl Cysteine Prevent Kidney Damage?

NAC was introduced in the 1960s as a mucolytic drug used to thin mucous in conditions like cystic fibrosis. After that it was discovered that NAC is an effective **antioxidant that increases the production of glutathione** in the body prompting its use as an antidote to acetaminophen/paracetamol overdose and toxicity to protect the liver and kidneys from damage. NAC itself has **direct antioxidant activity but primarily acts as a precursor to glutathione which is known as the 'master' antioxidant** and found in every cell of the body. NAC supplementation has been shown to **significantly decrease the frequency of influenza type episodes as well as reduce the severity of symptoms**. So, not only are you less likely to get the flu but if you do, the symptoms aren't as severe and don't tend to last as long. Another thing that was really interesting in the study was that only 25% of those in the group that were taking NAC developed any symptoms from infection with the influenza virus, whilst 75% of the placebo group were symptomatic. The therapeutic dose of NAC is usually **600mg-1200mg a day and is best taken in divided doses**.

https://www.researchgate.net/publication/13989914_Attenuation_of_influenza-like_symptomatology_and_improvement_of_cell-mediated_immunity_with_long-term_N-acetylcysteine_treatment

Attenuation of influenza-like symptomatology and improvement of cell-mediated immunity with long-term N-acetylcysteine treatment

They were randomized to receive either placebo or **NAC tablets (600 mg) twice daily for 6 months**. Frequency of seroconversion towards A/H1N1 Singapore 6/86 influenza virus was similar in the two groups, but only 25% of virus-infected subjects under NAC treatment developed a symptomatic form, versus 79% in the placebo group. Evaluation of cell-mediated immunity showed a progressive, significant shift from anergy to normoergy following NAC treatment. Administration of N-acetylcysteine during the winter, thus, appears to provide a significant attenuation of influenza and influenza-like episodes, especially in elderly high-risk individuals. **N-acetylcysteine did not prevent A/H1N1 virus influenza infection but significantly reduced the incidence of clinically apparent disease.**

https://slowaging.org/n-acetyl-cysteine-support-body/ Contraindications

An N-acetyl cysteine supplement may contraindicate with the following medications:

- Nitroglycerin and isosorbide
- Activated charcoal
- Medications that suppress the immune system , including azathioprine (Imuran), cyclophosphamide (Cytoxan) or prednisone (Deltasone)
- Oxiconazole

https://www.livestrong.com/article/485221-daily-dosage-of-n-acetyl-cysteine/ Daily Dosage of N-Acetyl Cysteine

The University of Maryland Medical Center suggests starting with **500 mg daily** and slowly increasing with your doctor's supervision. It reports doses higher than **7,000 mg could cause toxicity**.

Nitrate (NO)(nitric oxide) Beet root juice

https://pubmed.ncbi.nlm.nih.gov/28329785/ Beet Root Juice: An Ergogenic Aid for Exercise and the Aging Brain

Older adults who exercised and consumed **BRJ demonstrated greater consistency within the motor community** and fewer secondary connections with the insular cortex compared with those who exercised without BRJ. The exercise + BRJ group had brain networks that more closely resembled those of younger adults, showing the potential enhanced neuroplasticity conferred by combining exercise and BRJ consumption

https://pubmed.ncbi.nlm.nih.gov/32292042/ The benefits and risks of beetroot juice consumption: a systematic review

BRJ contains high concentrations of nitrate, which can be **converted into nitric oxide (NO) after consumption**. NO has various functions in the human body, including a vasodilatory effect, which reduces blood pressure and increases oxygen- and nutrient delivery to various organs. These effects indicate that BRJ may have relevant applications in prevention and treatment of cardiovascular disease. Furthermore, the consumption of BRJ also has an impact on oxygen delivery to skeletal muscles, muscle efficiency, tolerance and endurance and may thus have a positive impact on sports performances. Aside from the beneficial aspects of BRJ consumption, there may also be potential health risks. **Drinking BRJ may easily increase nitrate intake above the acceptable daily intake, which is known to stimulate the endogenous formation of N-nitroso compounds (NOC's), a class of compounds that is known to be carcinogenic and that may also induce several other adverse**

https://pubmed.ncbi.nlm.nih.gov/25875121/ The potential benefits of red beetroot supplementation in health and disease

Beetroot is also being considered as a promising therapeutic treatment in a range of **clinical pathologies associated with oxidative stress and inflammation**

https://www.j-alz.com/content/researchers-find-possible-environmental-causes-alzheimer%E2%80%99s-diabetes – A new study by researchers at Rhode Island Hospital has found a substantial link between increased levels of nitrates in our environment and food with increased deaths from diseases, including Alzheimer's, diabetes mellitus and Parkinson's. The study was published in the Journal of Alzheimer's Disease (Volume 17:3 July 2009

Nitrosamines are formed by a chemical reaction between nitrites or other proteins. **Sodium nitrite** is deliberately added to meat and fish to prevent toxin production; it is also used to preserve, color and flavor meats. Ground beef, cured meats and bacon in particular contain abundant amounts of amines due to their high protein content. **Because of the significant levels of added nitrates and nitrites, nitrosamines are nearly always detectable in these foods. Nitrosamines are also easily generated under strong acid conditions, such as in the stomach, or at high temperatures associated with frying or flame broiling. Reducing sodium nitrite content reduces nitrosamine formation in foods**

https://www.ironsageconsulting.com/blog/nitrates BEETS TO BACON: ARE NITRATES HEALTHY OR HARMFUL? WHAT ATHLETES NEED TO KNOW

Nitrates (NO3) have 1 nitrogen atom and 3 oxygen atoms. They are converted into Nitrites (NO2) in the body after one oxygen atom gets plucked off. **Nitrites can turn into 1 of 2 things 1) nitric oxide (beneficial for the body) or 2) nitrosamines, which can be harmful**. They're naturally occurring compounds in the human body and some foods such as vegetables. Manufacturers also use them as a preservative.

Nitrites can become hazardous if they form nitrosamines, which form if you cook nitrates/nitrites at high heat or have a bad gut microbiome profile from poor food choices. Cook meat and vegetables at lower heat and avoid charring. Also, check the ingredient list. I recommend **staying away from sodium nitrate, sodium nitrite, potassium nitrate, potassium nitrite. Bacon is the highest source, so limit your intake and don't cook at high temperatures**

https://pubmed.ncbi.nlm.nih.gov/19542621/#:~:text=Streptozotocin%20%28STZ%29%20is%20a%20nitrosamine-related%20compound%20that%20causes,impairment%2C%20brain%20insulin%20resistance%2C%20and%20brain%20insulin%20deficiency

Mechanisms of nitrosamine-mediated neurodegeneration: potential relevance to sporadic Alzheimer's disease

Streptozotocin (STZ) is a nitrosamine-related compound that causes Alzheimer's disease (AD)-type neurodegeneration with cognitive impairment, brain insulin resistance, and brain insulin deficiency. Nitrosamines and STZ mediate their adverse effects by causing DNA damage, oxidative stress, lipid peroxidation, pro-inflammatory cytokine activation, and cell death, all of which occur in AD. **We tested the hypothesis that exposure to N-nitrosodiethylamine (NDEA), which is widely present in processed/preserved foods, causes AD-type molecular and biochemical abnormalities in central nervous system (CNS) neurons.** NDEA treatment of cultured post-mitotic rat CNS neurons (48 h) produced dose-dependent impairments in ATP production and mitochondrial function, and increased levels of 8-hydroxy-2'-deoxyguanosine, 4-hydroxy-2-nonenal, phospho-tau, amyloid-beta protein precursor-amyloid-beta (A beta PP-A beta), and ubiquitin immunoreactivity. These effects were associated with decreased expression of insulin, insulin-like growth factor (IGF)-I, and IGF-II receptors, and choline acetyltransferase. **Nitrosamine exposure causes neurodegeneration** with a number of molecular and biochemical features of AD including impairments in energy metabolism, insulin/IGF signaling mechanisms, and acetylcholine homeostasis, together with increased levels of oxidative stress, DNA damage, and A beta PP-A beta immunoreactivity. These results suggest that **environmental exposures and food contaminants may play critical roles in the pathogenesis of sporadic AD**.

https://pubmed.ncbi.nlm.nih.gov/30099096/ Effects of dietary nitrate supplementation, from beetroot juice, on blood pressure in hypertensive pregnant women: A randomised, double-blind, placebo-controlled feasibility trial

Conversion of nitrate to **nitrite critically involves oral bacterial nitrate reductase activities**. We speculate that **differences in efficacy of nitrate supplementation relate to differences in the oral microbiome**, which will be investigated in future studies.

https://pubmed.ncbi.nlm.nih.gov/27872324/#:~:text=Subsequently%2C%20the%20oral%20bacterial%20species%20located%20at%20the,convert%20nitrate%20to%20NO%20as%20the%20first%20step.

From Nitrate to Nitric Oxide: The Role of Salivary Glands and Oral Bacteria

Subsequently, the oral bacterial species located at the posterior part of the tongue reduce nitrate to nitrite, as catalyzed by nitrate reductase enzymes. These bacteria use nitrate and nitrite as final electron acceptors in their respiration and meanwhile help the host to convert nitrate to NO as the first step.

https://pubmed.ncbi.nlm.nih.gov/8939344/ Modulation of nitrate-nitrite conversion in the oral cavity

The use of an a**ntiseptic mouthwash with active antibacterial constituent chlorhexidine resulted in an almost complete decrease of the mean percentage of reduced nitrate, to 0.9 +**/- 0.8%. Mouthwash solutions with antibacterial component triclosan or antimicrobial enzymes amyloglucosidase and glucose oxidase did not affect the reduction of nitrate into nitrite. A toothpaste with active components triclosan and zinc citrate with synergistic antiplaque activity was also without effect. Use of a pH-regulating chewing gum resulted in a rise in the pH in the oral cavity from 6.8 to 7.3. At 30 min after nitrate ingestion, this rise was accompanied by a significant increase in the salivary nitrite concentration, which might be explained by the pH being close to the optimal pH for nitrate reductase of 8. In conclusion, a limited number of possibilities of modulation of the conversion of nitrate into nitrite in the oral cavity are available.

https://pubmed.ncbi.nlm.nih.gov/25359409/ **Antibacterial mouthwash blunts oral nitrate reduction and increases blood pressure** in treated hypertensive men and women

Relative to control, 3-day antibacterial mouthwash use resulted in decreased oral nitrate to nitrite reduction (P = 0.02), decreased salivary nitrite (P = 0.01) and increased salivary nitrate (P < 0.001), and there was a trend toward a decrease in plasma nitrite concentration (P = 0.09). Use of antibacterial mouthwash over 3 days also resulted in higher systolic blood pressure (2.3mm Hg; 95% CI: 0.5, 4.0; P = 0.01), but not diastolic blood pressure (P = 0.4) or plasma cGMP (P = 0.7), relative to contro

https://pubmed.ncbi.nlm.nih.gov/31709856/ Over-the-counter mouthwash use, nitric oxide and hypertension risk

Short-term clinical trials have shown that **antibacterial mouthwash deplete oral nitrate-reducing bacteria, and decrease systemic nitric oxide bioavailability**. Our previous publication from the San Juan Overweight Adults Longitudinal Study (SOALS) was the first to show frequent over-the-counter mouthwash use was independently associated with increased risk of prediabetes/diabetes. This manuscript evaluates whether over-the-counter mouthwash was associated with increased risk of hypertension

https://www.researchgate.net/publication/266763051_Effects_of_Fluorides_in_Toothpastes_on_Oral_Nitrite_Formation **Effects of Fluorides in Toothpastes on Oral Nitrite Formation**

No influence of dental health status on nitrite formation was observed. Conclusion: Toothbrushing two times daily for two weeks prior to alimentary uptake of nitrate in a vegetable juice with toothpastes containing amine fluorides or monosodium fluoride did not result in differential salivary nitrite formation.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7522554/pdf/fmicb-11-555465.pdf Isolation and Characterization of Nitrate-Reducing Bacteria as Potential Probiotics for Oral and Systemic Health

The pH at which most nitrate was reduced differed between strains. However, acidic **pH 6 always stimulated the reduction of nitrite compared to neutral pH 7 or slightly alkaline pH 7.5** ($p < 0.01$). Nitrate-reducing oral bacteria, including representatives of Neisseria, Rothia, Veillonella, Actinomyces, Corynebacterium, Haemophilus, and Kingella reduce nitrate to nitrite (Grant and Payne, 1981; Doel et al., 2005; Hyde et al., 2014). Human cells cannot reduce nitrate, but there are several enzymatic and non-enzymatic processes that convert nitrite into nitric oxide (Hezel and Weitzberg, 2015). For example, **in the acidic gastric juice, nitrite is decomposed to nitrogen oxides, such as nitric oxide (NO), which is essential for the antimicrobial activity of the stomach** (Lundberg and Govoni, 2004). It should be noted that **anti-oxidants and polyphenols in vegetables and fruits prevent the formation of carcinogenic N-nitroso compounds from nitrite, while stimulating nitric oxide production** (Ward, 2009; Kobayashi et al., 2015).

Nitric Oxide Benefits:

https://pubmed.ncbi.nlm.nih.gov/15265275/ Nitric oxide pathways in Alzheimer's disease and other neurodegenerative dementias

Nitric oxide (NO) is an enzymatic product of nitric oxide synthase (NOS). NO has significant physiological functions and an increasing body of evidence **suggests that NO pathways are implicated in a number of neurological disorders, including Alzheimer's disease (AD) and other neurodegenerative dementias.**

https://pubmed.ncbi.nlm.nih.gov/20698819/ Nitric oxide: target for therapeutic strategies in Alzheimer's disease

There is d**ata implicating nitric oxide (NO) in the progression of the disease**. The three isoforms of the NO-synthesizing enzyme **(NOS) operate as central mediators of amyloid beta-peptide (Aβ) action**, giving rise to **elevated levels of NO that contributes to the maintenance, self-perpetuation and progression of the disease**. Reducing Aβ production and the cholinergic deficit is a goal in the treatment of AD.

https://pubmed.ncbi.nlm.nih.gov/23745722/ Endothelial nitric oxide deficiency promotes Alzheimer's disease pathology

Aging and the presence of cerebrovascular disease are associated with increased incidence of Alzheimer's disease. A common feature of aging and cerebrovascular disease is d**ecreased endothelial nitric oxide (NO)**. These **data suggest that chronic loss of endothelial NO may be an important contributor to both Aβ related pathology and cognitive decline**

https://pubmed.ncbi.nlm.nih.gov/12652163/ Statins and the role of nitric oxide in chronic heart failure

However, **statins increase nitric oxide synthase activity.** Some statins have proven to lower plasma levels of C-reactive protein, which is induced by pro-inflammatory cytokines. Other statins have been demonstrated to directly **inhibit pro-inflammatory cytokine** induction. Finally, some data suggest that statins might be able to counterbalance an increased production of oxygen free radicals.

Since chronic heart failure is accompanied not only by endothelial dysfunction, but also by pro-inflammatory cytokine activation and enhanced formation of oxygen free radicals, it is **tempting to speculate that statins might be an ideal candidate to treat certain features of this disease**.
https://pubmed.ncbi.nlm.nih.gov/31782366/ Alzheimer's Disease: A Contextual Link with Nitric Oxide Synthase
Further, this review provides convergent **evidence that NO could provide a therapeutic avenue in AD** via modulation of the relevant NOS expression
https://pubmed.ncbi.nlm.nih.gov/15974915/ Nitric oxide mimetic molecules as therapeutic agents in Alzheimer's disease
A survey of current research indicates that **NO mimetics will provide a combined neuroprotective and cognition-enabling approach to anti-neurodegenerative therapy**.
https://pubmed.ncbi.nlm.nih.gov/11245887/ Say NO to Alzheimer's disease: the putative links between nitric oxide and dementia of the Alzheimer's type
Nitric oxide (NO) is an enzymatic product of nitric oxide synthase, which **exists in three isoforms**. In addition to its vasoactive and immunological properties, **NO has significant neurophysiological functions**. However, **NO can also be neurotoxic primarily due to its free radical properties, and it has been implicated in neurodegenerative diseases**. Interestingly, there is increasing evidence that NO may have a role in the aforementioned AD pathogenetic mechanisms, and **putative links between NO and AD are beginning to be recognized.** This review focuses on these issues highlighting the possible relevance of NO in AD, **either as a neuroprotective** or **neurotoxic agent**.
https://aor.ca/nitric-oxide-alzheimers-disease/ The Link Between Nitric Oxide & Alzheimer's disease
Lack of NO production by endothelial cells due to too much ABP aggregate formation and/or free radical generation only contributes to pathology of AD. Researchers have argued that if the NO production could be assured then AD would be significantly halted in its track. To test this hypothesis, researchers at the Mayo Clinic looked into the link between NO and AD through a number of elegant experiments and came to the following conclusions:

- When NO production is inhibited by using a known **inhibitor, there was increased endothelial damage with ABP levels rising as expected accompanied by AD**
- When NO production was increased by use of a known **stimulator of NO production in an animal model of AD, the levels of ABP decreased and there was a significant improvement in memory of animals.**
- Using **genetic mice that cannot produce NO, the ABP levels rose in the brain tissue and there was significant brain damage compared to those mice that could naturally produce NO and were clear of AD**
- .NO seems to affect the production of ABP but does not affect its clearance suggesting that NO donors may work as preventative of AD rather than reversing AD

These findings provide further support that keeping NO levels optimal may be beneficial strategy for prevention of AD and that NO donors like the inorganic nitrates may be useful.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4677236/ Getting to NO Alzheimer's Disease: Neuroprotection versus Neurotoxicity Mediated by Nitric Oxide
Nitric oxide (NO) has long been considered part of the neurotoxic insult caused by neuroinflammation in the Alzheimer's brain. The **primary pharmaceuticals currently available to AD patients are cholinesterase inhibitors (Donepezil, Rivastigmine, and Galantamine) and NMDA receptor antagonists (Memantine). These drugs have been shown to reduce memory loss and slow disease progression temporarily in some patients** **Harnessing the protective role of NO and related signaling pathways could provide a therapeutic avenue that prevents synapse loss early in disease.**
There are deficits in the cerebrovasculature, characterized by the breakdown of the blood-brain barrier, as well as increased inflammatory signaling and alterations in neuronal signaling, all key components of AD [21]. **Each of the three NOS isoforms has been postulated to play a role in either AD progression or prevention**, leading to a seemingly **conflicting message about the role of NO in AD and whether NO is neuroprotective or neurotoxic.** An area of controversy in regard to the involvement of NO in AD pathogenesis is the extent to which the molecule is neuroprotective or neurotoxic [29–31]. **Several studies have demonstrated that NO holds neuroprotective properties** through its induction of the cGMP pathway [32–34]. This triggers vasodilation and consecutive increases in the cerebral blood supply to neurons, reducing the potential for oxidative stress, in addition to minimizing excess Ca2+ influx through inhibition of NMDA receptors at glutamatergic synapses [32–34]. **Discrepancies could be due in part to the challenges of measuring NO and peroxynitrite concentration**s in situ (half-life < 3 s and half-life < 1 s, resp.), which prevents a clear distinction of the formation of neurotoxic peroxynitrite at the expense of protective NO [26].
https://pubmed.ncbi.nlm.nih.gov/20817920/ Nitric oxide signaling in brain function, dysfunction, and dementia
Abnormal NO signaling could therefore contribute to a variety of neurodegenerative pathologies such as stroke/excitotoxicity, Alzheimer's disease, multiple sclerosis, and Parkinson's disease.
http://ijshr.com/IJSHR_Vol.6_Issue.3_July2021/IJSHR055.pdf Nitric Oxide: The Common Link in Different Forms of Dementia
The existing medical literature shows both **neuroprotective** and **neurotoxic** effects of nitric oxide. The present article intends to delve into this topic and provide a lucid understanding of the role of nitric oxide in dementia
There are epidemiological evidences in favour of both. However, those in favour of r**educed nitric oxide being associated with dementia appear to be slightly more**, especially if we consider its effect on vascular smooth muscle and anti-atherosclerotic effect. Given its beneficial as well as detrimental effects, a unanimous consensus on the exact role of nitric oxide in the pathogenesis is yet to emerge, but it can be definitely concluded that **nitric oxide is a vital connecting link between the different types of dementia**.

OILS

Coconut oil caprylic acid (C8), capric acid (C10), (0.02g Omega3, 1.68g Omega6)

https://pubmed.ncbi.nlm.nih.gov/28421789/ How does coconut oil affect cognitive performance in alzheimer patients?
44 patients with Alzheimer's in region of Ribera (Valencia), of which half was selected to receive during 21 days, 40 ml coconut oil daily divided between breakfast (20 ml) and food (20 ml). Before and after administration of the oil, they were evaluated through cognitive test Mini-Mental State Examination to determine possible changes. Results: It was observed in patients who received coconut oil, that **cognitive improvement after completion of the intervention, statistically significant improved** in the orientation and language-construction areas. Conclusions: Coconut oil appears to improve cognitive abilities of Alzheimer's patients, with different intensity depending on the cognitive area.
https://pubmed.ncbi.nlm.nih.gov/26667739/ COCONUT OIL: NON-ALTERNATIVE DRUG TREATMENT AGAINST ALZHEIMER´S DISEASE
study was conducted in patients with Alzheimer's dementia, with a control and an intervention group which was administered 40 ml/day of extra virgin coconut oil. it was observed in subjects taking the product, a statistically **significant increase in test score MECWOLF and therefore an improvement in cognitive status**, improving especially women's, those without diabetes mellitus type II, and severe patients.
https://curealz.org/news-and-events/myth-busting-why-coconut-oil-is-not-a-cure-for-alzheimers-disease/
Scientists are learning more and more about how **saturated fats like coconut oil a**re digested. As an important note, **fatty acids cannot pass the blood-brain-barrier**, but the product they are **broken down into, ketone bodies, can serve as an alternative fuel source for the brain**. The brain favors glucose as its energy source, but in times of starvation or glucose deficiency, it will use ketone bodies. fats can accumulate on artery walls and if introduced in excess can increase the risk of cardiovascular and metabolic disorders.

Caprylic Acid (C8)

500 to 1,000 milligrams, three times a day in capsule form (1tsp(6ml) = 15g C8=130 calories) Study uses 20g
can be used in coffee 473ml $33, (79 servings)
https://pubmed.ncbi.nlm.nih.gov/36342577/ Potential of Capric Acid in Neurological Disorders: An Overview. 2022
To solve the restrictions of a classical ketogenic diet, a modified medium-chain triglyceride diet was introduced which required only around 60% of dietary energy. Capric acid (CA), a small molecule, is one of the main components because its metabolic profile offers itself as an alternate **source of energy to the brain in the form of ketone bodies**. This is possible with the combined **capability of CA to cross the blood-brain barrier and achieve a concentration of 50% concentration in the brain** more than any other fatty acid in plasma. Natural sources of CA include vegetable oils such as palm oil and coconut oil, mammalian milk and some seeds. Several studies have shown that CA has varied action on targets that include AMPA receptors, PPAR-γ, inflammatory/oxidative stress pathways and gut dysbiosis. Based on these lines of evidence, CA has proved to be effective in the amelioration of neurological diseases such as epilepsy, affective disorders and **Alzheimer's disease.**
https://www.alz.org/alzheimers-dementia/treatments/alternative-treatments#:~:text=The%20body%20breaks%20down%20caprylic%20acid%20into%20substances,Alzheimer%E2%80%99s.%20Glucose%20is%20the%20brain%E2%80%99s%20chief%20energy%20source .
Caprylic acid and coconut oil
Caprylic acid — clinically tested as Ketasyn (AC-1202), marketed as a "medical food" called Axona® — is the active ingredient of Axona, which is marketed as a "medical food." **Caprylic acid is a medium-chain triglyceride (fat) produced by processing coconut oil or palm kernel oil.** The body breaks down **caprylic acid into substances called "ketone bodies."** The theory behind Axona is that the ketone bodies derived from caprylic acid may provide an alternative energy source for brain cells that have lost their ability to use glucose (sugar) as a result of Alzheimer's. Glucose is the brain's chief energy source. Some people with Alzheimer's and their caregivers have turned to coconut oil as a less expensive, over-the-counter source of caprylic acid. A few people have reported that coconut oil helped the person with Alzheimer's, but there's never been any clinical testing of coconut oil for Alzheimer's, and there's no scientific evidence that it helps.
https://www.dropanfbomb.com/blogs/articles-resources/c8-mct-oil
caprylic acid (C8) and 40% capric acid (C10).
Caprylic Acid (C8) has been shown to increase energy, **boost ketone production**, and facilitate weight loss [*][*][*]. It possesses cancer-fighting and antimicrobial properties [*][*][*].
Capric Acid (C10) has many of the same properties of caprylic acid (C8) (e.g., boosts ketones, is antimicrobial, and can help reduce body fat [*], but generally takes a bit longer for the body to process into ketones [*]. **C8 products are a refined version of MCT oils that have had the capric acid (C10) and lauric acid (C12) removed. This leaves only caprylic acid as the fatty acid**

component. This improves gut tolerability, a common issue with MCT oil. GI distress, indigestion, and diarrhoea can result in those new to MCT oils or if doses are over a tablespoon. C8 increases ketones by approximately 3 times more than C10.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4099555/ Effects of Caprylic Triglyceride on Cognitive Performance and Cerebral Glucose Metabolism in Mild Alzheimer's Disease: A Single-Case Observation
AD subjects with normal controls and found significant **diminished cerebral glucose metabolism (DCGM) in AD patients**. In these studies, significant correlations were found between DCGM and worsening performance on measures of cognitive function (de Leon et al., 1983). Subsequent studies have revealed that DCGM in AD is not simply a global decrease in glucose use across the brain, but rather maps to specific regions found in the posterior cingulate and parietal, temporal, and prefrontal cortices. Longitudinal studies have demonstrated the progression of DCGM over the course of AD. DCGM can be observed in preclinical AD and progressively worsens as patients proceed from mild cognitive impairment (MCI) to AD (Mosconi et al., 2009).
Given the realization that AD begins decades before onset of clinical signs of dementia, it is important to investigate and develop low risk interventions that can intervene early in the course of cognitive decline. **One low risk attempt to address the DCGM in AD is to induce ketosis.** Ketosis is the elevation of circulating ketone bodies, namely beta-hydroxybutyrate (BHB), acetoacetate, and acetone. Ketone bodies (KB) are normally produced from the incomplete oxidation of fatty acids under conditions of low glucose availability and are readily metabolized by the brain to serve as an alternative to glucose (Owen et al., 1967). Ketosis has traditionally been induced by adherence to a ketogenic diet. Ketogenic diets were developed to mimic fasting, and have been used for decades to reduce seizure frequency in pediatric epilepsy (Freeman et al., 2006).
It is possible to induce ketosis without dietary modification with special fats called medium chain triglycerides (MCTs). Reger et al. (2004) studied the effects of a specific MCT called caprylic triglyceride (CT) to induce ketosis in 20 mild to moderate probable AD subjects [mean age 74.7; mean mini mental state exam (MMSE) score 22.0]. This study used a crossover design to examine the effects of acute elevation of serum KB levels on cognitive performance. A single 40 g dose of CT induced mild ketosis and a significant positive correlation between performance on the paragraph recall task and serum BHB concentration was found. In addition, significant improvement was demonstrated in the Alzheimer's disease assessment scale-cognitive subscale (ADAS-Cog) scores in subjects who were non-carriers of APOE4 [APOE4(−)] compared to those who were carriers [APOE4(+)].
In a follow-up study, Henderson et al. (2009) induced ketosis in mild to moderate AD subjects (mean MMSE of 23) by daily dosing of 20 g of CT for 90 days. This study was a randomized, double-blind, placebo-controlled, multicenter trial conducted at 23 clinical sites within the United States. Consistent with the earlier acute dosing study, subjects who were APOE4(−) demonstrated a significant change in ADAS-Cog scores compared to placebo at both days 45 and 90. As with the earlier study, post-dose serum BHB levels correlated with improvement in ADAS-Cog scores, suggesting the induction of ketosis may be beneficial to AD patients, particularly if they lack an APOE4 allele
The CT formulation was provided in sachets containing a dry powder composed of 50% CT. The graduated dosing schedule began with the patient taking 10 g of materia**l (5 g CT) for the first 2 days** and then the dose was increased by **10 g (5 g of CT) every 2 days**, until after 7 days, the patient was consuming the full 40 g dose (20 g CT). For the remaining 102 days, the CT formulation was administered at 40 g **(20 g).**
Over the 109 day course of the study, the patient's MoCA increased by four points and the MMSE increased by five points
https://pubmed.ncbi.nlm.nih.gov/21830350/ Caprylic acid in the effective treatment of intractable medical problems of frequent urination, incontinence, chronic upper respiratory infection, root canalled tooth infection, ALS, etc., caused by asbestos & mixed infections of Candida albicans, Helicobacter pylori & cytomegalovirus with or without other microorganisms & mercury 2011
Thus, **Caprylic acid is superior to & less expensive than Diflucan, & has potential application for anti-cancer, anti-aging, anti-Alzheimer's disease,** anti-Autism, anti-infection, & general circulatory improvement.
https://pubmed.ncbi.nlm.nih.gov/24187498/ Retrospective case studies of the efficacy of caprylic triglyceride in mild-to-moderate Alzheimer's disease 2013
Under **normal conditions, the adult human brain is fueled primarily by glucose**. A prominent feature of Alzheimer's disease (AD) is region-specific decreases in cerebral glucose metabolism. **Ketone bodies are a group of compounds produced from fat stores during periods of low glucose availability that can provide an alternative to glucose for brain metabolism**. **Consumption of sufficient quantities of caprylic triglyceride (CT) increases plasma concentrations of ketone bodies and may be beneficial in conditions of compromised glucose metabolism, such as AD.** The present study describes the use of CT in mild-to-moderate AD in routine clinical practice. Case records from eight patients with extensive monitoring of cognitive function using the Mini-Mental State Examination (MMSE) and who had received CT for ≥6 months were reviewed. All were outpatients aged ≥50 years, cared for in standard practice, had a diagnosis of probable AD of mild-to-moderate severity (MMSE 14-24), and had received CT for at least 6 months in addition to other approved pharmacotherapy for AD. Response to CT administration as measured by MMSE scores varied by patient. However, the **rate of decline in MMSE scores appeared slower than previously published reports for patients treated with pharmacotherapy alone**.
https://pubmed.ncbi.nlm.nih.gov/24187497/ Retrospective cohort study of the efficacy of caprylic triglyceride in patients with mild-to-moderate alzheimer's disease 2013
A total of 55 patients were included. The physician's overall assessment indicated that ~80% of patients who had CT added to ongoing pharmacotherapy were stable or improved. Mini-Mental State Examination scores also remained stable over 15 months of therapy. **Conclusion:** Results from this chart review indicate that **addition of CT to pharmacotherapy was associated with stable disease or improvement over a follow-up period of 18.8 months.**
https://pubmed.ncbi.nlm.nih.gov/31870908/ Medium Chain Triglycerides induce mild ketosis and may improve cognition in Alzheimer's disease. A systematic review and meta-analysis of human studies 2020
The brain in Alzheimer's disease shows glucose hypometabolism but may utilize ketones for energy production. **Ketone levels can potentially be boosted through oral intake of Medium Chain Triglycerides (MCTs)**. **Conclusions:** In this meta-analysis, we **demonstrated that MCTs can induce mild ketosis and may improve cognition in patients with mild cognitive impairment and Alzheimer's disease.** However, risk of bias of existing studies necessitates future trials.
https://pubmed.ncbi.nlm.nih.gov/27547436/ Lauric acid-rich medium-chain triglycerides can substitute for other oils in cooking applications and may have limited pathogenicity 2016
Recently, medium-chain triglycerides (MCTs) containing a **large fraction of lauric acid (LA) (C12)-about 30%-have been introduced commercially for use in salad oils and in cooking applications**. As compared to the long-chain fatty acids found in other cooking oils, the medium-chain fats in MCTs are far less likely to be stored in adipose tissue, do not give rise to 'ectopic fat' metabolites that promote insulin resistance and inflammation, and may be less likely to activate macrophages. When ingested, medium-chain fatty acids are rapidly oxidised in hepatic mitochondria; the resulting glut of acetyl-coenzyme A drives ketone body production and also provokes a thermogenic response. Hence, studies in animals and humans indicate that MCT ingestion is less obesogenic than comparable intakes of longer chain oils. Although LA tends to raise serum cholesterol, it has a more substantial impact on high density lipoprotein (HDL) than low density lipoprotein (LDL) in this regard, such that the ratio of total cholesterol to HDL cholesterol decreases. LA constitutes about 50% of the fatty acid content of coconut oil; south Asian and Oceanic societies which use coconut oil as their primary source of dietary fat tend to be at low cardiovascular risk. Since **ketone bodies can exert neuroprotective effects**, the moderate ketosis induced by regular MCT ingestion may have neuroprotective potential. As compared to traditional MCTs featuring C6-C10, laurate-rich MCTs are more feasible fo**r use in moderate-temperature frying** and tend to produce a lower but more sustained pattern of blood ketone elevation owing to the more gradual hepatic oxidation of ingested laurate.
https://pubmed.ncbi.nlm.nih.gov/35719157/ Applications of Medium-Chain Triglycerides in Foods 2022
Recently, MCTs have also been shown to promote protein anabolism and inhibit catabolism, and applied research has been conducted into the **prevention of frailty in the elderly**. In addition, a r**elatively large ingestion of MCTs can be partially converted into ketone bodies**, which can be used as a component of "ketone diets" in the dietary treatment of patients with intractable epilepsy, or in the nutritional support of terminally ill cancer patients. The possibility of **improving cognitive function in dementia patients** and mild cognitive impairment is also being studied.

Oil Avocado

https://pubmed.ncbi.nlm.nih.gov/27651262/ Avocado as a Major Dietary Source of Antioxidants and Its Preventive Role in Neurodegenerative Diseases 2016
Avocados have a high content of phytochemicals especially **antioxidants with potential neuroprotective effect**. Aging is the major risk factor for neurodegenerative diseases such as Alzheimer's and Parkinson's diseases. A large body of evidence indicates that oxidative stress is involved in the pathophysiology of these diseases. 2011
Thus, Caprylic acid is superior to & less expensive than Diflucan, & has potential application for anti-cancer, anti-aging, anti-Alzheimer's disease, anti-Autism, anti-infection, & general circulatory improvement.

Oil Olive

https://pubmed.ncbi.nlm.nih.gov/31521394/ Extra-virgin olive oil for potential prevention of Alzheimer disease 2019
The authors base their hypothesis on meta-analyses of epidemiological data, numerous experimental studies, and a comprehensive review of the mechanisms of action of extra-virgin olive oil and its components in the prevention of vascular disease. In addition, extra-virgin olive oil has had positive effects on experimental animal models of Alzheimer disease. **We therefore propose that extra-virgin olive oil is a promising tool for mitigating the effects of adverse vascular factors and may be utilized for potential prevention of late-onset Alzheimer disease**.
https://pubmed.ncbi.nlm.nih.gov/33979140/ Natural Compound from Olive Oil Inhibits S100A9 Amyloid Formation and Cytotoxicity: Implications for Preventing Alzheimer's Disease
Polyphenolic compounds in the Mediterranean diet have received increasing attention due to their protective properties in amyloid neurodegenerative and many other diseases. Here, we have demonstrated for the first time that **polyphenol oleuropein aglycone (OleA), which is the most abundant compound in olive oil,** has multiple potencies for the inhibition of amyloid self-assembly of pro-inflammatory protein S100A9 and the mitigation of the damaging effect of its amyloids on neuroblastoma SH-SY5Y cells. OleA may effectively mitigate the pathological consequences of the S100A9-dependent **amyloid-neuroinflammatory cascade as well as provide protection from neurodegeneration**, if used within the Mediterranean diet as a potential preventive measure.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5553230/ Extra-virgin olive oil ameliorates cognition and neuropathology of the 3xTg mice: role of autophagy
Consumption of extra virgin olive oil (EVOO), a major component of the Mediterranean diet, has bee**n associated with reduced incidence of Alzheimer's disease** (AD).
https://worldolivecenter.com/en/alzheimers-and-high-phenolic-olive-oils/ Alzheimer's and High Phenolic Olive Oils 2022

For the first time, high phenolic olive oils rich in **oleocanthal and oleacein** were associated with a significant improvement in mental functions in humans. The effect of daily **ingestion of high phenolic olive oils was found to be dose-dependent according to the concentration of phenolic c**ompounds compounds. Positive results were achieved within 3 months.

Oil Vegetable (ω-6 PUFA-rich vegetable oils such as rapeseed (canola), soybean, sunflower, and corn oils)

https://pubmed.ncbi.nlm.nih.gov/32623461/ Intake of ω-6 Polyunsaturated Fatty Acid-Rich Vegetable Oils and Risk of Lifestyle Diseases

Although excessive consumption of **deep-fried foods** is regarded as 1 of the most **important epidemiological factors of lifestyle diseases such as Alzheimer's disease**, type 2 diabetes, and obesity, the exact mechanism remains unknown. his review aims to discuss whether heated cooking oil-derived peroxidation products **cause cell degeneration/death** for the occurrence of lifestyle diseases. Deep-fried foods cooked in ω-6 PUFA-rich vegetable oils such as rapeseed (canola), soybean, sunflower, and corn oils, already contain or intrinsically generate "hydroxynonenal" by peroxidation. As demonstrated previously, **hydroxynonenal promotes carbonylation of heat-shock protein 70.1 (Hsp70.1), with the resultant impaired ability of cells to recycle damaged proteins and stabilize the lysosomal membrane.** Until now, the implication of lysosomal/autophagy failure due to the daily consumption of ω-6 PUFA-rich vegetable oils in the progression of cell degeneration/death has not been reported. Since the "calpain-cathepsin hypothesis" was formulated as a cause of ischemic neuronal death in 1998, its **relevance to Alzheimer's neuronal death has been suggested with particular attention to hydroxynonenal.**

Omega-3 polyunsaturated fatty acid

Three main different Types:

1. alpha-linolenic acid (ALA) -18 carbons

2. eicosapentaenoic acid (EPA) – 20 carbons

3. docosahexaenoic acid (DHA) – 22 carbons

https://ods.od.nih.gov/factsheets/Omega3FattyAcids-HealthProfessional/ Omega-3 Fatty Acids: Fact Sheet for Health Professionals

ALA can be converted into EPA and then to DHA, but the conversion (which occurs primarily in the liver) is very limited, with reported rates of less than 15% [3]. Therefore, **consuming EPA and DHA directly from foods and/or dietary supplements is the only practical way to increase levels of these fatty acids in the body.** Because both classes of fatty acids compete for the same desaturation enzymes, ALA is a competitive inhibitor of linoleic acid metabolism and vice versa [8]. Similarly, EPA and DHA can compete with arachidonic acid for the synthesis of eicosanoids. Thus, **higher concentrations of EPA and DHA than arachidonic acid tip the eicosanoid balance toward less inflammatory activity** [9]. Some researchers propose that the relative intakes of omega-6s and omega-3s—the **omega-6/omega-3 ratio—may have important implications** for the pathogenesis of many chronic diseases, such as cardiovascular disease and cancer [8], but the optimal ratio—if any—has not been defined [10]. Others have concluded that **such ratios are too non-specific and are insensitive to individual fatty acid levels** [11-13]. **Most agree that raising EPA and DHA blood levels is far more important than lowering linoleic acid or arachidonic acid levels**.

The potential health benefits of consuming omega-3s are the focus of a great deal of scientific research. By far, the **majority of research has focused on EPA and DHA from foods (e.g., fish) and/or dietary supplements (e.g., fish oil)** as opposed to ALA from plant-based foods.

Some, but not all, observational studies suggest that diets high in LC omega-3s are associated with a reduced risk of cognitive decline, Alzheimer's disease, and dementia [131,132]. Because DHA is an essential component of cellular membrane phospholipids in the brain, researchers hypothesize that LC omega-3s might protect cognitive function by helping to maintain neuronal function and cell-membrane integrity within the brain [132]. This hypothesis is supported by findings from case-control studies indicating that patients with Alzheimer's disease have lower serum levels of DHA than cognitively healthy people [133,134]. Lower serum DHA levels are also associated with more cerebral amyloidosis (build-up of protein deposits called amyloids) in healthy older adults, whereas higher DHA is correlated with preservation of brain volume [135].

Several observational studies have examined the effects of fish, EPA, and/or DHA intakes on cognitive function in healthy older adults. In a prospective cohort study involving 210 healthy men aged 70–89, fish consumption was **associated with less cognitive decline at follow-up 5 years later** [136]. In addition, a dose-response relationship was observed between tertiles of dietary EPA plus DHA intake and subsequent 5-year cognitive decline. Similarly, in the Rotterdam Study, a population-based prospective study of people aged 55 or older who were free from dementia at baseline, higher fish consumption among 5,386 study participants was associated with a 60% lower risk of dementia and a 70% lower risk of Alzheimer's disease over an average of 2.1 years [137]. Subsequent follow-up 6 years after baseline, however, found **no associations between omega-3 intakes and incidence of dementia or Alzheimer's disease** [138]. The authors suggest that the discrepancy might be explained by the short follow-up period in the first analysis and the small number of patients who developed dementia. A higher omega-3 index was associated with a greater hippocampal volume in the Women's Health Initiative Memory Study [139] and with a larger brain volume and improved cognitive test scores in the Framingham Offspring cohort [140]. A 2016 dose-response meta- analysis of 21 cohort studies found that increased intakes of fish and dietary DHA were both inversely associated with the risks of dementia and Alzheimer's disease [141]. Specifically, a **100 mg/day incremental increase in DHA intake was associated with a 14% lower risk of dementia and a 37% lower risk of Alzheimer's disease**.

Results from clinical trials, however, suggest that LC omega-3 supplementation does not affect cognitive function in older adults who have no cognitive impairment. In a trial in the United Kingdom, 748 cognitively healthy adults aged 70–79 years received either 500 mg DHA and 200 mg EPA or placebo daily for 24 months [142]. Cognitive function did not differ significantly between the two groups, although cognitive function did not decline in either group. In the AREDS2 study, treatment with 350 mg DHA and 650 mg EPA for 5 years did not have a significant effect on cognitive function in 3,501 older adults (mean age 72.7 years) with AMD [133].

Clinical trial results also suggest that LC omega-3 supplementation does not benefit patients with Alzheimer's disease, although it might help patients with mild cognitive impairment. For example, daily supplementation with 2 g DHA for 18 months did not slow the rate of cognitive decline compared to placebo in 295 participants (mean age 76 years) with mild to moderate Alzheimer's disease [143]. In the OmegaAD trial, daily supplementation with 1,700 mg DHA and 600 mg EPA for 6 months in 174 older adults with mild to moderate Alzheimer's disease also failed to slow down the rate of cognitive decline compared to placebo [144]. However, a subgroup of patients with very mild impairment experienced a significant reduction in the rate of cognitive decline. In a small trial in Malaysia, fish oil supplementation (1,290 mg DHA and 450 mg EPA daily) for 12 months improved memory—particularly short-term, working, and verbal memory—and delayed recall compared to placebo in 35 older adults with mild cognitive impairment [145].

Several systematic reviews and meta-analyses, including a Cochrane review, have assessed the effects of omega-3 supplementation on cognitive function and dementia in healthy older adults and those with Alzheimer's disease or cognitive impairment [131,146-148]. Overall, the findings indicate that LC omega-3 supplementation does not affect cognitive function in healthy older adults or in people with Alzheimer's disease compared to placebo. For people with mild cognitive impairment, omega-3s may improve certain aspects of cognitive function, including attention, processing speed, and immediate recall [148]. However, these findings need to be confirmed in additional clinical trials.

https://www.forbes.com/sites/alicegwalton/2017/09/11/why-the-omega-3s-in-walnuts-are-not-the-same-as-the-ones-in-fish-and-algae/?sh=27abbb3d6e06

Why The Omega-3s In Walnuts Are Not The Same As The Ones In Fish And Algae

The variety of omega-3s in plants is α-linolenic acid (ALA). The omega-3s in fish are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Humans aren't able to make EPA or DHA from scratch; we need either to eat them or to form them from shorter fatty acids (like ALA). The **body *is* able to convert ALA into EPA and DHA through a chain of chemical reactions that generally take place in the liver.** In this sequence of events, DHA is the final product, arriving a couple of steps after EPA. (For a detailed breakdown of all the reactions needed to take ALA to DHA, see this.) The problem is that the conversion isn't very efficient, with **only a small percentage of ALA making it all the way to DHA**. This is partly due to competition from omega-6 fatty acids, which people tend to eat in higher quantities than omega-3s in general.

Table 2: ALA, EPA, and DHA Content of Selected Foods [29]

Food	Grams per serving		
	ALA	DHA	EPA
Flaxseed oil, 1 tbsp	7.26		
Chia seeds, 1 ounce	5.06		
English walnuts, 1 ounce	2.57		
Flaxseed, whole, 1 tbsp	2.35		
Salmon, Atlantic, farmed cooked, 3 ounces		1.24	0.59
Salmon, Atlantic, wild, cooked, 3 ounces		1.22	0.35
Herring, Atlantic, cooked, 3 ounces*		0.94	0.77
Canola oil, 1 tbsp	1.28		
Sardines, canned in tomato sauce, drained, 3 ounces*		0.74	0.45
Mackerel, Atlantic, cooked, 3 ounces*		0.59	0.43
Salmon, pink, canned, drained, 3 ounces*	0.04	0.63	0.28
Soybean oil, 1 tbsp	0.92		
Trout, rainbow, wild, cooked, 3 ounces		0.44	0.40
Black walnuts, 1 ounce	0.76		
Mayonnaise, 1 tbsp	0.74		
Oysters, eastern, wild, cooked, 3 ounces	0.14	0.23	0.30
Sea bass, cooked, 3 ounces*		0.47	0.18
Edamame, frozen, prepared, ½ cup	0.28		
Shrimp, cooked, 3 ounces*		0.12	0.12
Refried beans, canned, vegetarian, ½ cup	0.21		
Lobster, cooked, 3 ounces*	0.04	0.07	0.10
Tuna, light, canned in water, drained, 3 ounces*		0.17	0.02
Tilapia, cooked, 3 ounces*	0.04	0.11	
Scallops, cooked, 3 ounces*		0.09	0.06
Cod, Pacific, cooked, 3 ounces*		0.10	0.04
Tuna, yellowfin, cooked 3 ounces*		0.09	0.01
Kidney beans, canned ½ cup	0.10		
Baked beans, canned, vegetarian, ½ cup	0.07		
Ground beef, 85% lean, cooked, 3 ounces**	0.04		
Bread, whole wheat, 1 slice	0.04		
Egg, cooked, 1 egg		0.03	
Chicken, breast, roasted, 3 ounces		0.02	0.01
Milk, low-fat (1%), 1 cup	0.01		

https://pubmed.ncbi.nlm.nih.gov/28466678/ Omega-3 fatty acids' supplementation in Alzheimer's disease: A systematic review
The effects of omega-3 fatty acids supplementation in mild AD corroborate epidemiological observational studies showing that omega-3 fatty acids may be beneficial in disease onset, when there is slight impairment of brain function. Although some studies have shown changes in scales of cognitive function in more severe cases, they are not enough to support omega-3 fatty acids supplementation in the treatment of AD.
https://www.nccih.nih.gov/health/providers/digest/dietary-supplements-and-cognitive-function-dementia-and-alzheimers-disease-science#omega-3-fatty-acid-supplements
Among the nutritional and dietary factors studied to prevent cognitive decline in older adults, the most consistent positive research findings are for omega-3 fatty acids, often measured as how much fish people consumed. However, a 2016 Cochrane review of 3 randomized, placebo-controlled trials involving a total of 632 participants found no convincing evidence for the efficacy of omega-3 polyunsaturated fatty acid supplements in the treatment of mild-to-moderate Alzheimer's disease.
https://pubmed.ncbi.nlm.nih.gov/27933449/ Clearing the fog: a review of the effects of dietary omega-3 fatty acids and added sugars on chemotherapy-induced cognitive deficits
We propose that a diet rich in long-chain, **marine-derived omega-3 fatty acids** and low in added sugars may be an ideal pattern **for preventing or alleviating neuroinflammation and oxidative stress**, thereby protecting neurons from the toxic effects of chemotherapy.
https://pubmed.ncbi.nlm.nih.gov/29259181/ Comparison of the effect of omega-3 supplements and fresh fish on lipid profile: a randomized, open-labeled trial
Results: Data from 48 patients in fish oil group and 47 patients from fish group was used for final analysis. **In both groups, total cholesterol, non-HDL cholesterol, triglyceride (TG) levels, and Castelli I index (total cholesterol/HDL ratio) were reduced significantly** following the treatment; **however, dietary-fish intake had a more pronounced effect** (-85.08 ± 74.82 vs. -30.75 ± 89.00, P < 0.001; 75.06 ± 35.43 vs. -16.93 ± 40.21, P < 0.001; -66.55 ± 30.79 vs. -12.7 ± 35.48, P = 0.003; and -0.77 ± 1.39 vs. -3.02 ± 1.85, P < 0.001; respectively). HDL level was increased in both groups with a higher effect in dietary fish group (4.47 ± 7.83 vs. 8.51 ± 8.79, P = 0.022). Atherogenic (Log [TG/HDL ratio]) and Castelli II (**LDL/HDL ratio) indices did not change in fish oil group while were reduced significantly by fresh fish consumption** (-0.04 ± 0.27 vs. -0.26 ± 0.17, P < 0.001; and 0.15 ± 0.7 vs. -1.32 ± 1.15, P < 0.001, respectively). LDL level was increased in the supplementation group, while it was **significantly reduced in the dietary-fish group** (+18.7 ± 24.97 vs. -22.75 ± 27.28, P < 0.001).
https://pubmed.ncbi.nlm.nih.gov/26184297/ What Is the Most Effective Way of Increasing the Bioavailability of Dietary Long Chain Omega-3 Fatty Acids--Daily vs. Weekly Administration of Fish Oil?
These unexpected findings show that a **large dose of n-3 LC-PUFA once per week is more effective in increasing whole body n-3 LC-PUFA content in rats compared with a smaller dose delivered daily**.
https://pubmed.ncbi.nlm.nih.gov/30773210/ Association of reported fish intake and supplementation status with the omega-3 index
Conclusions: Current AHA recommendations are unlikely to produce a desirable O3I. Consuming **at least 3 fish servings per week** plus taking an EPA+DHA supplement markedly increases the likelihood of achieving this target level.

Omega-6 (Linoleic acid C18:2n-6, and Arachidonic Acid C20:4n-6)

-note raising Omega 3 EPA and DHA is more important that reducing Omega 6 intake, ie ratio is more important

https://pubmed.ncbi.nlm.nih.gov/29610056/ Omega-6 fatty acids and inflammation
Hence, it is **commonly believed that increasing dietary intake of the omega-6 fatty acids ARA or its precursor linoleic acid (LA) will increase inflammation**. However, studies in healthy human adults have **found that increased intake of ARA or LA does not increase the concentrations of many inflammatory markers. Epidemiological studies have even suggested that ARA and LA may be linked to reduced inflammation**. Contrastingly, **there is also evidence that a high omega-6 fatty acid diet inhibits the anti-inflammatory and inflammation-resolving effect of the omega-3 fatty acids**. Thus, the interaction of omega-3 and omega-6 fatty acids and their lipid mediators in the context of inflammation is complex and still not properly understood.
https://pubmed.ncbi.nlm.nih.gov/33008950/ Anti-Inflammatory and Proresolving Effects of the Omega-6 Polyunsaturated Fatty Acid Adrenic Acid
Our findings are, to our knowledge, the first to indicate that the *n*-6 fatty acid AdA effectively blocks production of LTB_4 by neutrophils and could play a role in resolution of inflammation in vivo.
https://openheart.bmj.com/content/5/2/e000946 *Importance of maintaining a low omega–6/omega–3 ratio for reducing inflammation*
Decreasing the omega-6/3 ratio seems to reduce the inflammatory response to a high-fat meal. For example, one study looked at responses in men with metabolic syndrome to an oral fat tolerance test (OFTT) by adjusting the omega-6/3 ratio. Patients ingested two high-saturated fat OFTTs (1 g fat/kg body weight) with either a high omega-6/3 ratio (~18:1) or a low omega-6/3 ratio (~3:1) and a

water control in a randomised crossover design. Reducing the omega-6/3 ratio caused a lower release of the proinflammatory cytokine IL-6 at hours 6 and 8.28 Additionally, Nelson and Hickey performed a study showing that an isocaloric replacement of LA with ALA for just 4 days leads to a reduction in soluble IL-6 receptor.29 These studies suggest that replacing omega-6 with omega-3 reduces inflammation.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4424767/ The impact of specific fatty acids on inflammation may be central to how dietary fats affect health.
Three key fatty acid–inflammation interactions are briefly described. First, the evidence suggests that **saturated fatty acids induce inflammation** in part by mimicking the actions of LPS. Second, the often-repeated **claim that dietary linoleic acid promotes inflammation was not supported** in a recent systematic review of the evidence. Third, an explanation is offered for why **omega-3 (n–3) polyunsaturated fatty acids are so much less anti-inflammatory in humans than in mice**. The article closes with a cautionary tale from the genomic literature that illustrates why extrapolating the results from inflammation studies in mice to humans is problematic.
However, there is no consensus regarding which inflammatory biomarker is best. Clearly, not all fats under all circumstances promote postprandial inflammation. There are insufficient data to predict when and how specific fat sources will affect inflammatory status in people. One possible explanation for the discrepancies in the literature is the **variability in the types of microbes in the gastrointestinal tract** of individuals being studied in these postprandial fat challenge studies.
Whether **dietary fats substantially affect inflammatory status of people by altering their gut microflora remains untested**, but with the rapid advances in the field, answers should be forthcoming.
Linoleic acid (LA; 18:2n−6, octadecadienoic acid) is an n–6 PUFA and an essential nutrient (38). LA comprises ≥50% of the most widely consumed vegetable oils in Western societies. For many decades it has been known that LA helps reduce blood cholesterol concentrations and that substituting LA for SFAs lowers the risk of heart disease (39). Therefore, current recommendations from numerous expert bodies, including the Institute of Medicine and the American Heart Association, are that people should consume between 5% and 10% of total energy as LA for a heart-healthy diet (40
However, a **few members of the lipid research community have expressed concerned that LA-rich diets are unhealthy and promote inflammation** (41, 42). The theoretical basis for this concern over LA's proinflammatory actions involve a number of putative interrelated metabolic processes, including the following: 1) dietary LA promoting tissue arachidonic acid (AA; 20:4n−6, eicosatetraenoic acid) accumulation, 2) enhanced synthesis of proinflammatory eicosanoids derived from AA, 3) reduced conversion of α-linolenic acid (ALA; 18:3n−3, octadecatrienoic acid) into EPA (eicosapentaenoic acid; 20:5n–3) and/or DHA, and 4) diminished synthesis of anti-inflammatory eicosanoids from EPA and DHA. The experimental evidence supporting each step of this paradigm originated primarily from rodent and cell culture studies. More recently, and in contrast with the multistep process described above, it was **suggested that various oxidized forms of LA are directly responsible for stimulating inflammation**

Phenolic Compounds (curcumin, ferulic acid, rosmarinic acid, Quercetin, hydroxycinnamic acids, Pterostilbene, anthocyanins)
- see individual component for more details
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7278806/ A Reference List of Phenolic Compounds (Including Stilbenes) in Grapevine (*Vitis vinifera* L.) Roots, Woods, Canes, Stems, and Leaves 2020
phenolic compounds have been identified, including **78 stilbenes (23 monomers, 30 dimers, 8 trimers, 16 tetramers, and 1 hexamer), 15 hydroxycinnamic acids, 9 hydroxybenzoic acids, 17 flavan-3-ols (of which 9 are proanthocyanidins), 14 anthocyanins, 8 flavanones, 35 flavonols, 2 flavones, and 5 coumarins**.
https://pubmed.ncbi.nlm.nih.gov/19893028/ Phenolic compounds prevent Alzheimer's pathology through different effects on the amyloid-beta aggregation pathway 2009
Inhibition of amyloid-beta (Abeta) aggregation is an attractive therapeutic strategy for Alzheimer's disease (AD). Certain phenolic compounds have been reported to have anti-Abeta aggregation effects in vitro. This study systematically investigated the effects of phenolic compounds on AD model transgenic mice (Tg2576). Mice were fed five phenolic compounds (**curcumin, ferulic acid**, myricetin, nordihydroguaiaretic acid (NDGA), and **rosmarinic acid (RA)**) for 10 months from the age of 5 months. In the **curcumin**- and myricetin-treated groups, changes in the Abeta profile were similar to those in the RA-treated group, but Abeta plaque deposition was not significantly decreased. In the ferulic acid-treated group, there was no significant difference in the Abeta profile. These results showed that **oral administration of phenolic compounds prevented the development of AD pathology by affecting different Abeta aggregation pathways** in vivo. Clinical trials with these compounds are necessary to confirm the anti-AD effects and safety in humans.

Phosphatidylserine (bovine{NA} or plant sources)(TNF inhibitor) (works with Omega 3)
Sources: Soy, **Egg Yolks(1.3g/100g?)**, organ means, white beans, sunflower Lecithin
Average intake: 75-184mg/day
https://pubmed.ncbi.nlm.nih.gov/1609044/ Effects of phosphatidylserine in Alzheimer's disease
We studied 51 patients meeting clinical criteria for probable Alzheimer's disease (AD). Patients were treated for 12 weeks with a formulation of bovine cortex phosphatidylserine (BC-PS; 100 mg t.i.d.) or placebo, and those treated with the drug improved on several cognitive measures relative to those administered placebo. Differences between treatment groups were most apparent among patients with less severe cognitive impairment. **Results suggest that phosphatidylserine may be a promising candidate for study in the early stages of AD.**
https://pubmed.ncbi.nlm.nih.gov/8038871/ Long-term effects of phosphatidylserine, pyritinol, and cognitive training in Alzheimer's disease. A neuropsychological, EEG, and PET investigation
This 6-month study in four groups of patients with Alzheimer's disease indicated that phosphatidylserine treatment has an effect on different measures of brain function. Since neuropsychological improvements were best documented after 8 and 16 weeks and faded towards the end of the treatment period, it must be concluded that this symptomatic therapy is mainly of **short-term benefit** and was overcome by the progressive pathological changes at the end of the treatment period.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2981104/ The effect of phosphatidylserine-containing omega-3 fatty acids on memory abilities in subjects with subjective memory complaints: a pilot study
PS-omega-3 supplementation resulted in **42% increase in the ability to recall words in the delayed condition.**
http://www.nlm.medscape.idmu.unboundmedicine.unboundmedicine.com/medline/citation/31915963/
Phosphatidylserine_modulates_response_to_oxidative_stress_through_hormesis_and_increases_lifespan_via_DAF_16_in_Caenorhabditis_elegans_
Phosphatidylserine modulates response to oxidative stress through hormesis and increases lifespan via DAF-16 in Caenorhabditis elegans.
Supplementation with phosphatidylserine significantly suppressed amyloid beta-induced toxicity in Alzheimer's disease model.
https://pubmed.ncbi.nlm.nih.gov/3290936/ Phosphatidylserine in the treatment of Alzheimer's disease: results of a multicenter study
https://pubmed.ncbi.nlm.nih.gov/2690093/ Double-blind study with phosphatidylserine (PS) in parkinsonian patients with senile dementia of Alzheimer's type (SDAT)
Acute and long-term CEEG results--till 18 months--showed that the so-called Theta anteriorisation can be reduced or even abolished; this is replaced by Alpha waves. Even in preclinical cerebral changes this method open the possibility to show incipient alterations of the brain metabolism. **Preliminary therapeutic results leads to this and not prooven hypothesis that prevention or retardation of cerebral ageing might be possible.**
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7402346/ Neuroprotective Effect of Bean Phosphatidylserine on TMT-Induced Memory Deficits in a Rat Model
We analyzed the neuroprotective effects of soybean-derived phosphatidylserine (Bean-PS) on cognitive function, changes in the central cholinergic systems, and neural activity in TMT-induced memory deficits in a rat model. Results: Treatment with Bean-PS **enhanced memory function in the Morris water maze (MWM) test.** Consistent with the behavioral results, treatment with Bean-PS diminished the damage to cholinergic cells in the hippocampus, in contrast to those of the TMT group. The TMT+Bean-PS group showed **elevated glucose uptake in the frontal lobe of the rat brain**. Conclusion: T**hese results demonstrate that Bean-PS protects against TMT-induced learning and memory impairment.**
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3921088/ Cognitive effects of a dietary supplement made from extract of *Bacopa monnieri*, astaxanthin, phosphatidylserine, and vitamin E in subjects with mild cognitive impairment: a noncomparative, exploratory clinical study
A prospective cohort, noncomparative, multicenter trial was conducted to explore the potential of a phytotherapeutic compound, available as a dietary supplement and containing extracts of ***Bacopa monnieri*** **and** ***Haematococcus pluvialis*** **(astaxanthin) plus phosphatidylserine and vitamin E**, in improving cognition in subjects diagnosed with mild cognitive impairment. In conclusion, dietary supplementation with the tested compound **shows potential for counteracting cognitive impairment in subjects with mild cognitive impairment** and warrants further investigation in adequately controlled, longer-term studies.
https://www.foundhealth.com/alzheimer-s-disease/alzheimers-disease-and-phosphatidylserine Effect of Phosphatidylserine on Alzheimer's Disease
Phosphatidylserine (PS), in studies of severe mental decline, appears to have been equally effective whether the cause was Alzheimer's disease or something entirely unrelated, such as multiple small strokes. This certainly suggests that PS may have a positive impact on the brain that is not specific to any one condition. From this observation, it is not a great leap to suspect that it might be useful for much less severe problems with memory and mental function, such as those that seem to occur in nearly all of us who are older than 40. Indeed, one double-blind study did find that **animal-source phosphatidylserine could improve mental function in individuals with relatively mild age-related memory loss**.[18] However, plant-sources PS did not show the same level of effectiveness.[7,47] However, **all these studies involved cow-brain PS**; studies of **plant-source PS for dementia have not been reported.**
PS is sometimes taken with ginkgo because they both appear to enhance mental function. However, some caution might be in order: Ginkgo is a "blood thinner," and PS might be one as well. PS is known to enhance the effect of heparin, a very strong prescription blood thinner. [3] It is possible that combined use of PS and any drug or supplement that thins the blood could interfere with normal blood clotting enough to cause problems. Some medications and supplements to consider include warfarin (Coumadin), aspirin, pentoxifylline (Trental), clopidogrel (Plavix), ticlopidine (Ticlid), garlic, ginkgo, and vitamin E.
https://pubmed.ncbi.nlm.nih.gov/8323999/ Cognitive decline in the elderly: a double-blind, placebo-controlled multicenter study on efficacy of phosphatidylserine administration

Statistically **significant improvements in the phosphatidylserine-treated group** compared to placebo were observed both in terms of **behavioral and cognitive parameters.** In addition, clinical evaluation and laboratory tests demonstrated that BC-PS was well tolerated.
https://safeaccess.unboundmedicine.com/medline/citation/25414047/
Positive_effects_of_soy_lecithin_derived_phosphatidylserine_plus_phosphatidic_acid_on_memory_cognition_daily_functioning_and_mood_in_elderly_patients_with_Alzheimer's_disease_and_dementia_
PS is efficiently absorbed after oral consumption. A **positive influence of PS+PA on memory, mood, and cognition was demonstrated** among elderly test subjects. Short-term supplementation with PS+PA in patients with AD showed a stabilizing effect on daily functioning, emotional state and self-reported general condition. The data encourage long-term studies with PS+PA in AD patients and other elderly with memory or cognition problems.
https://pubmed.ncbi.nlm.nih.gov/11201936/ An open trial of **plant-source derived phosphatydilserine** for treatment of age-related cognitive decline
We assessed whether the efficacy of plant-source derived phosphatydilserine (one of the phospholipids which play an important functional role in membrane-related processes in the brain) for treatment of age related cognitive decline is consistent with previous (placebo controlled) positive findings with bovine derivative of PS (BC-PS). These results are encouraging. However, they await double-blind controlled verification in a large sample before suggesting that this may be a **viable approach to the treatment of age-related cognitive decline, without exposing the patients to possible hazards involved in the treatment with bovine derivative of PS (BC-PS).**
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3665496/ The effect of **soybean-derived phosphatidylserine** on cognitive performance in elderly with subjective memory complaints: a pilot study
To evaluate the efficacy and safety of soybean-derived phosphatidylserine (SB-PS) (300 mg/day) in improving cognitive performance in elderly with memory complaints, following a short duration of 12 weeks' SB-PS administration. The computerized test results showed that SB-PS supplementation **significantly increased the following cognitive parameters: memory recognition (*P* = 0.004), memory recall (*P* = 0.006), executive functions (*P* = 0.004), and mental flexibility** (*P* = 0.01). The Rey-AVLT indicated that, following SB-PS administration, total learning and immediate recall improved significantly (*P* = 0.013 and *P* = 0.007, respectively). **Unexpected results from the safety tests suggested that SB-PS significantly reduces both systolic (*P* = 0.043) and diastolic (*P* = 0.003) blood pressure.** SB-PS consumption was **well tolerated and no serious adverse events** were reported during the study. This exploratory study demonstrates that SB-PS may have favorable effects on cognitive function in elderly with memory complaints. In addition, the study suggests that **SB-PS is safe for human consumption and may serve as a safe alternative to phosphatidylserine extracted from bovine cortex.** These results encourage further extended studies in order to establish the safety and efficacy of SB-PS treatment. However, safety concerns due to the risk of bovine spongiform encephalopathy, commonly known as **mad cow disease,[17] brought an end to the use of BC-PS** and encouraged a search for safe alternative sources.
In the mid-1990s, soybean-derived PS (SB-PS) replaced BC-PS and was examined as a safer alternative.[18] A few preclinical studies suggested that administration of SB-PS could benefit cognitive performance in rodents.[19–21] To date, some clinical trials have shown that SB-PS is safe for human consumption and may potentially improve cognitive performance. According to Jorissen et al[22] and Kato-Kataoka et al,[23] Gindin et al was the first to examine the effect of SB-PS on cognitive function of elderly volunteers.[24] In addition, based on a preliminary open-label trial,[25] Kato-Kataoka et al[23] conducted a double-blind clinical trial on **78 elderly Japanese with memory complaints and examined the effect of SB-PS (100 and 300 mg/day) following 6 months of administration and at 3 months' follow-up. The results of this study demonstrate that SB-PS has a positive effect on cognitive performance**, which was especially evident in a subgroup of subjects who had low pretreatment scores. Interestingly, this subgroup demonstrated a significant influence of SB-PS on cognitive function following 6 months' administration versus baseline, and, at 3-month posttreatment follow-up, there was a **significant difference between the SB-PS group and placebo**.[23] The efficacy of SB-PS was also examined by Schreiber et al.[26] In this open-label study, the authors tested the effect of **300 mg/day SB-PS on 18 healthy elderly volunteers**, meeting Age Associated Memory Impairment (AAMI) inclusion and exclusion criteria.[3] **The study showed that those treated with SB-PS had a significant improvement on recall and immediate memory parameters following 6 weeks' administration**, an effect that was maintained following an additional 6 weeks of supplementation.[26] **In contrast to these clinical trials, a double-blind study conducted by Jorissen et al, which evaluated the effect of SB-PS (300–600 mg/day) administration on 81 subjects with AAMI, failed to find any significant improvement in cognitive skills.[22]**
https://www.phosphatidylserine.net/blog/compare_soy_bovine_phosphatidylserine.html Which Source of PhosphatidylSerine (PS) Works Best? Soy? Bovine?
Website implies Soy based works best!
https://pubmed.ncbi.nlm.nih.gov/35992593/ Phosphatidylserine, inflammation, and central nervous system diseases. 2022
Phosphatidylserine (PS) is an anionic phospholipid in the eukaryotic membrane and is abundant in the brain. Accumulated studies have revealed that PS is involved in the multiple functions of the brain, such as **activation of membrane signaling pathways, neuroinflammation, neurotransmission, and synaptic refinement.** Those functions of PS are related to central nervous system (CNS) diseases. In this review, we discuss the metabolism of PS, the anti-inflammation function of PS in the brain; the alterations of PS in different CNS diseases, and the possibility of PS to serve as a therapeutic agent for diseases. Clinical studies have showed that PS has no side effects and is well tolerated. Therefore, **PS and PS liposome could be a promising supplementation for these neurodegenerative and neurodevelopmental diseases.**
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4425170/ **Egg Phospholipids** and Cardiovascular Health 2015
Eggs are a major source of phospholipids (PL) in the Western diet. Dietary PL have emerged as a potential source of bioactive lipids that may have widespread effects on pathways related to inflammation, cholesterol metabolism, and high-density lipoprotein (HDL) function. Based on pre-clinical studies, egg phosphatidylcholine (PC) and sphingomyelin appear to regulate cholesterol absorption and inflammation. **Consuming three eggs per day for 12 weeks resulted in a reduction in plasma C-reactive protein (CRP)** and an increase in adiponectin in overweight men; changes which were not observed with yolk-free egg substitute [80]. In combination with moderate carbohydrate restriction, the addition o**f three eggs per day led to decreases in plasma TNFα** and serum amyloid A in men and women with MetS, whereas no changes were observed in subjects consuming a yolk-free egg substitute [81].
https://pubmed.ncbi.nlm.nih.gov/8423880/ Phosphatidylserine, a putative inhibitor of tumor necrosis factor, prevents autoimmune demyelination 1993
We tested the effect of bovine cortex phosphatidylserine (BC-PS), a membrane phospholipid known to inhibit the release of the cytokine tumor necrosis factor (TNF), in SJL/J mice sensitized for adoptively transferred experimental autoimmune encephalomyelitis (EAE) Cultures of lymph node cells or SC from BC-PS-treated and control animals **showed an 80 to 90% reduction in TNF production** in the BC-PS-treated group.
https://pubmed.ncbi.nlm.nih.gov/26266022/ The Effects of Phosphatidylserine and Omega-3 Fatty Acid-Containing Supplement on Late Life Depression 2015
They took a supplement containing **PS 100 mg, DHA 119 mg and EPA 70 mg three times a day for 12 weeks**. The effects of the supplement were assessed using the 17-item Hamilton depression scale (HAM-D17) and the basal levels and circadian rhythm of salivary cortisol. The study adopted them as indices because: salivary cortisol levels are high in patients with depression, their circadian rhythm related to salivary cortisol is often irregular, and these symptoms are alleviated as depression improves. **The mean HAM-D17 in all subjects taking the supplement was significantly improved after 12 weeks of taking the supplement**.
https://www.wellnessresources.com/news/omega-3-dha-and-phosphatidylserine-two-are-better-than-one Omega-3 DHA and Phosphatidylserine: Two Are Better Than One 2018
Omega 3 fish oil (DHA) and phosphatidylserine (PS) are two types of fat great for brain function, structure and health. They are essential components of cell membranes and support electrical function, mitochondrial activity, and receptor site activity in the brain. Both fats have separate duties, but when they are taken together, it becomes **"two are better than one" f**or cognitive function, healthy brain aging, and stress tolerance

Piperine (Black Pepper) **boost nutrient's absorption, antioxidant, antimicrobial, anti-inflammatory, gastro-protective, and antidepressant**

https://pubmed.ncbi.nlm.nih.gov/23768180/ Black pepper and health claims: a comprehensive treatise 2013
Black pepper (Piper Nigrum L.) is an important healthy food owing to its **antioxidant, antimicrobial potential and gastro-protective** modules. Black pepper, with piperine as an active ingredient, holds rich phytochemistry that also includes volatile oil, oleoresins, and alkaloids. More recently, cell-culture studies and animal modeling predicted the role of black pepper against number of maladies. The free-radical scavenging activity of black pepper and its active ingredients might be helpful in chemoprevention and controlling progression of tumor growth. Additionally, the key alkaloid components of Piper Nigrum, that is, **piperine assist in cognitive brain functioning, boost nutrient's absorption** and improve gastrointestinal functionality. In this comprehensive treatise, efforts are made to elucidate the **antioxidant, antimicrobial, anti-inflammatory, gastro-protective, and antidepressant activities of black peppe**r.
https://pubmed.ncbi.nlm.nih.gov/15231065/ Antioxidant efficacy of black pepper (Piper nigrum L.) and piperine in rats with high fat diet induced oxidative stress 2004
Significantly elevated levels of thiobarbituric acid reactive substances (TBARS), conjugated dienes (CD) and significantly lowered activities of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione-S-transferase (GST) and reduced glutathione (GSH) in the liver, heart, kidney, intestine and aorta were observed in rats fed the high fat diet as compared to the control rats. Simultaneous supplementation with black pepper or piperine lowered TBARS and CD levels and maintained SOD, CAT, GPx, GST, and **GSH levels to near those of control rats**. The data indicate that supplementation with black pepper or the active principle of black pepper, **piperine, can reduce high-fat diet induced oxidative stress to the cells**.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5785894/ Chronic diseases, inflammation, and spices: how are they linked? 2018
Piperine is the principal plant alkaloid isolated from black pepper (*Piper nigrum*) and long pepper (*Piper longum*). Piperine has several biological properties including analgesic, anti-convulsant, anti-tumor and anti-inflammatory activities [148]. Several studies have shown that piperine could attenuate the inflammatory response associated with chronic diseases such as AD, asthma, arthritis, chronic gastritis, endometritis, Parkinson's disease, etc.
The anti-inflammatory activity of piperine in these chronic diseases is achieved via downregulation of inflammatory pathways such as NF-κB, MAPK, AP-1, COX-2, NOS-2, IL-1β, TNF-α, PGE2, STAT3, etc. [148, 149, 151–154]
https://pubmed.ncbi.nlm.nih.gov/31207354/ Piperine attenuates cognitive impairment in an experimental mouse model of sporadic Alzheimer's disease 2019
Piperine, the **major alkaloid constituent of black pepper,** has been reported to possess a wide range of pharmacological effects on the central nervous system, including antidepressant, anticonvulsant and anti-ischemic activities. In the present study, we aimed to investigate the **therapeutic potential and neuroprotective mechanisms of piperine in an experimental mouse model of sporadic Alzheimer's disease (sAD)** induced by intracerebroventricular (ICV) infusion of streptozotocin (STZ). Our data revealed that the ICV-STZ-infused sAD mouse showed an increased

oxidative-nitrosative stress, an altered neurotransmission and an elevated neuroinflammation in hippocampus, as well as significant cognitive deficits. All these **alterations can be ameliorated by piperine in a dose-dependent manner. In summary, our findings predict a therapeutic potential of piperine against cognitive deficits in sAD mouse.** This effect might be due to its abilities to ameliorate oxidative-nitrosative stress, restore neurotransmission and reduce neuroinflammation.
https://pubmed.ncbi.nlm.nih.gov/20034530/ Piperine, the main alkaloid of Thai black pepper, protects against neurodegeneration and cognitive impairment in animal model of cognitive deficit like condition of Alzheimer's disease 2010
Recently, numerous medicinal plants possessing profound central nervous system effects and antioxidant activity have received much attention as food supplement to improve cognitive function against cognitive deficit condition including in Alzheimer's disease condition. Based on this information, the effect of piperine, a main active alkaloid in fruit of Piper nigrum, on memory performance and neurodegeneration in animal model of Alzheimer's disease have been investigated. The results showed that **piperine at all dosage range used in this study significantly improved memory impairment and neurodegeneration in hippocampus.** The possible underlying mechanisms might be partly associated with the decrease lipid peroxidation and acetylcholinesterase enzyme. Moreover, piperine also demonstrated the neurotrophic effect in hippocampus.
https://alzped.nia.nih.gov/intranasal-piperine-loaded Intranasal piperine-loaded chitosan nanoparticles as brain-targeted therapy in Alzheimer's disease: optimization, biological efficacy, and potential toxicity 2015
This work was the first to report additional mechanism of PIP in AD via **anti-apoptosis and anti-inflammatory effects**. To conclude, mucoadhesive CS-NPs were successfully tailored for effective, safe, and **non-invasive PIP delivery with 20-folds decrease in oral dose, opening a gate for a future with lower AD morbidity**.

Ptychopetalum olacoides **antioxidant, acetylcholinesterase inhibitory**

https://pubmed.ncbi.nlm.nih.gov/12895682/ Ptychopetalum olacoides, a traditional Amazonian "nerve tonic", possesses anticholinesterase activity 2003
The **cholinergic hypothesis of Alzheimer disease (AD)** has provided the rationale for the current pharmacotherapy of this disease, in an attempt to downgrade the cognitive decline caused by cholinergic deficits. Nevertheless, the **search for potent and long-acting acetylcholinesterase (AChE) inhibitors** that exert minimal side effects to AD patients is still an ongoing effort. Amazonian communities use traditional remedies prepared with Ptychopetalum olacoides (PO, Olacaceae) roots for treating various central nervous system conditions, including those associated with aging. The fact that PO ethanol extract (POEE) has been found to facilitate memory retrieval in the step down procedure in young and aged mice prompt us to evaluate its effects on AChE activity in memory relevant brain areas. POEE significantly inhibited AChE activity in vitro in a dose- and time-dependent manner in rat frontal cortex, hippocampus and striatum; **a significant inhibition was also found in these same brain areas of aged (14 months) mice after acute administration of POEE (100 mg/kg ip). We propose that such AChE inhibitory activity is a neurochemical correlate of a number of therapeutic properties traditionally claimed for P. olacoides, particularly those associated with cognition.**
https://pubmed.ncbi.nlm.nih.gov/15507336/ Memory retrieval improvement by Ptychopetalum olacoides in young and aging mice 2004
Consistently with its traditional use, the **data suggest that POEE facilitates memory retrieva**l. Although the antioxidant and acetylcholinesterase inhibitory properties previously described for this extract may be of relevance, the molecular mechanism(s) underlying the improvement in memory retrieval here reported merit further scrutiny.
https://pubmed.ncbi.nlm.nih.gov/18695930/ MK801- and scopolamine-induced amnesias are reversed by an Amazonian herbal locally used as a "brain tonic" 2009
This study complements previously reported promnesic properties of this plant extract and suggests that POEE may be further developed for **treating conditions associated with cognitive deficits, especially those linked with cholinergic malfunction.**
https://pubmed.ncbi.nlm.nih.gov/17433649/ Antioxidant activities of Ptychopetalum olacoides ("muirapuama") in mice brain 2007
Aging mice (14 months) were treated (i.p.) with saline, DMSO (20%) or POEE (100mg/kg body wt.), and the hippocampi, cerebral cortex, striata, hypothalamus and cerebellum dissected out 60 min later to measure antioxidant enzyme activities, free-radical production and damage to macromolecules. **POEE administration reduced free-radical production in the hypothalamus, lead to significant decrease in lipid peroxidation in the cerebral cortex, striatum and hypothalamus, as well as in the carbonyl content in cerebellum and striatum.** In terms of antioxidant enzymes, catalase activity was increased in the cortex, striatum, cerebellum and hippocampus, while glutathione peroxidase activity was increased in the hippocampus. This study **suggests that POEE contains compounds able to improve the cellular antioxidant network efficacy in the brain, ultimately reducing the damage caused by oxidative stress.**
https://pubmed.ncbi.nlm.nih.gov/19682881/ Anti-stress effects of the "tonic"Ptychopetalum olacoides (Marapuama) in mice 2010
POEE did not present anxiolytic effects, but was able to **prevent (p<0.01) the UCMS-induced anxiety** as assessed by the light/dark test (time spent in the lit area, POEE 100 and 300mg/kg 235.9+/-20.6s and 250.4+/-17.4s, respectively, compared to DMSO 104.7+/-24.4s). Likewise, although **POEE did not induce noticeable effects on glycemia,** it effectively (p<0.01) prevented the UCMS-induced hyperglycemia (POEE 100 and 300mg/kg 106.4+/-6.7mg/dl and 107.3+/-3.3mg/dl, respectively, compared to DMSO 134.6+/-5.9mg/dl). Additionally, POEE (50-200mg/kg i.p. and 800mg/kg p.o.) **significantly (p<0.01 and p<0.05, respectively) increased the time to hypoxia-induced convulsion** (by 38%, 51%, 59% and 27%, respectively for i.p. and p.o. treatments). The data indicate that POEE counteracts some of the effects brought about by chronic stress. This study combined with the identified **antioxidant and neuroprotective properties, as well as the claimed benefits associated with stressful periods suggest that Ptychopetalum olacoides (Marapuama) might possess adaptogen-like properties**
https://pubmed.ncbi.nlm.nih.gov/15302233/ Neuroprotective effects of Ptychopetalum olacoides Bentham (Olacaceae) on oxygen and glucose deprivation induced damage in rat hippocampal slices 2004
In comparison to OGD controls, slices incubated with POEE (0.6 microg/ml) during and after OGD exposure had **significantly increased cellular viability**. In addition, at this same concentration, POEE **prevented the increase of free radicals** content induced by OGD. **In view of the fact that respiratory chain inhibition and increased generation of free radicals are major consequences of the ischemic injury, this study suggests that Ptychopetalum olacoides contains useful neuroprotective compounds and, therefore, deserves further scrutiny.**

Polyphenol **(quercetin, grape seeds, Pomegranate, see olive oil) anti-oxidant**

Sources: Dark Chocolate(3448mg/100g),Strawberries(235mg),apple(136mb),Nuts(hazelnet 495mg),walnuts(28mg),almonds(187mg),pecans(493mg), red Onion(168mg)
Cloves(15188mg/100g), Dried Peppermint(11960mg/100g), star Anise(5460mg/100g), Cocoa Powder(3448mg/100g), Dried Sage and Rosemary, Blueberries(560-836mg/100g)
RDI: none assigned, recommend 500-1500mg/day
https://pubmed.ncbi.nlm.nih.gov/32023969/ Polyphenols in Alzheimer's Disease and in the Gut-Brain Axis 2020
Polyphenolic antioxidants, including dietary plant lignans, modulate the gut-brain axis, which involves transformation of these **polyphenolic compounds into physiologically active and neuroprotector compounds** (called human lignans) **through gut bacterial metabolism**. These gut bacterial metabolites exert their neuroprotective effects in various **neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD)** For example, **enterolactone and enterodiol, the therapeutically relevant polyphenols,** are formed as the **secondary gut bacterial metabolites of lignans**, the non-flavonoid polyphenolic compounds found in plant-based foods. These compounds are also **acetylcholinesterase inhibitors**, and thereby have potential applications as therapeutics in AD and other neurological diseases. Thus, gut bacterial metabolism of lignans and other dietary polyphenolic compounds results in the formation of neuroprotective polyphenols-some of which h**ave enhanced blood-brain barrier permeability.** It is hypothesized that gut bacterial metabolism-derived polyphenols, when combined with the nanoparticle-based blood-brain barrier (BBB)-targeted drug delivery, may prove to be effective therapeutics for various neurological disorders, including traumatic brain injury (TBI), AD, and PD.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6551378/ The protective effects of polyphenols on Alzheimer's disease: A systematic review 2019
Foods rich in polyphenols have been positively correlated to a reduced risk of several noncommunicable diseases, including Alzheimer's disease (AD). A total of 24 studies were included in this review. Twelve studies found a positive correlation with reduced cognitive decline. Five studies did not find any correlation and seven studies reported mixed results. Polyphenols are chemical compounds, a group of phytochemicals **found in several drinks such as green and black teas and red wine, and several foods such as fruits, vegetables, chocolate, olive oil, and plants** [16]. Some polyphenols are specific to one food group, such as isoflavones, which are specific to soya, whereas others, such as quercetin, are found in all plant products [16].
https://link.springer.com/article/10.1007/s11064-008-9696-7 Benefits from Dietary Polyphenols for Brain Aging and Alzheimer's Disease 2008
Food polyphenols can counteract these alterations in vitro and are therefore suggested to have potential anti-aging and brain-protective activities, as also indicated by the results of some epidemiological studies.
https://pubmed.ncbi.nlm.nih.gov/36076756/ Pomegranate (*Punica granatum* L.) Attenuates Neuroinflammation Involved in Neurodegenerative Diseases 2022
Food scientists have studied the many health benefits of polyphenols against pernicious human diseases. Evidence from scientific studies has shown that earlier healthy lifestyle changes, particularly in nutrition patterns, can reduce the burden of age-related diseases. In this context, a large number of plant-derived components belonging to the class of **polyphenols have been reported to possess neuroprotective benefits**. In this review, we examined studies on the effect of dietary polyphenols, notably from *Punica granatum* L., on neurodegenerative disease, including Alzheimer's disease, which is symptomatically characterized by impairment of cognitive functions. Based on preclinical and clinical trials, it appears that **pomegranate may prove valuable in treating neurodegenerative disorders, including Alzheimer's disease (AD) and Parkinson's disease (PD).** Therefore, due to the lack of information on human clinical trials, future in-depth studies, focusing on human beings, of several bioactive components of pomegranate's polyphenols and their synergic effects should be carried out to evaluate their curative treatment.
https://pubmed.ncbi.nlm.nih.gov/16945610/ Fruit and vegetable juices and Alzheimer's disease: the Kame Project 2006
Results: After adjustment for potential confounders, the **hazard ratio for probable Alzheimer's disease was 0.24 (95% confidence interval [CI], 0.09-0.61) comparing subjects who drank juices at least 3 times per week with those who drank less often than once per week with a hazard ratio of 0.84 (95% CI, 0.31-2.29) for those drinking juices 1 to 2 times per week** (P for trend < .01). This inverse association tended to be more pronounced among those with an apolipoprotein Eepsilon-4 allele and those who were not physically active. Conversely, no association was observed for dietary intake of vitamins E, C, or beta-carotene or tea consumption.
https://pubmed.ncbi.nlm.nih.gov/25312617/ **Dietary polyphenols for treatment of Alzheimer's disease**--future research and development 2014
Polyphenols are the most abundant components of our daily food, occupying the major portion of naturally occurring phytochemicals in plants. Currently, polyphenols have received a special attention from the scientific community against health risk because of their antioxidant capacity and the ability to scavenge the free radicals formed during the pathological process like cancer, cardiovascular diseases and neurodegenerative disorders. Alzheimer's disease, one of the common forms of dementia is an intricate, multifactorial mental illness which is characterized by age-dependent memory

loss ultimately leading to a steady decline of cognitive function. Extracellular amyloid beta deposition and intracellular tau hyperphosphorylation are the two main alterations occurring in the cells reported to cause neuronal dysfunction during AD. **Dietary intake of polyphenols is known to attenuate the progression of the disease by showing strong potential to tackle the alterations and reduce the risk of AD by reversing the cognitive deficits. A large number of polyphenolic compounds showing promising results against AD pathologies have been identified and described in the past decade.**

https://pubmed.ncbi.nlm.nih.gov/33629093/ Blueberry polyphenols alter gut microbiota & phenolic metabolism in rats 2021

Consuming polyphenol-rich fruits and vegetables, including blueberries, is **associated with beneficial health outcomes**. Interest in enhancing polyphenol intakes via dietary supplements has grown, though differences in fruit versus supplement matrix **on gut microbiota** and ultimate phenolic metabolism to bioactive metabolites are unknown. Gut microbial populations showed increased diversity at moderate doses but decreased diversity at high doses.

https://pubmed.ncbi.nlm.nih.gov/18598589/ Dietary reference intake (DRI) value for dietary polyphenols: are we heading in the right direction? 2008

A recent meta analysis shows promising actions of polyphenols from cocoa, soya and tea on flow **mediated dilation, blood pressure and LDL cholesterol**. Many epidemiological studies support the action of **polyphenols or polyphenol-rich foods on health**, but there are still many gaps in our knowledge. More adequately powered, randomised, placebo controlled human studies are needed on polyphenols. There is a large number of structurally different polyphenols which are relevant for health, and obtaining enough information to set a DRI for each of these will not be feasible in the foreseeable future.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9193594/ Dietary Polyphenols and the Risk of Alzheimer's Disease and Related Dementias Among Low-income Black and White Americans 2022

To examine the associations of dietary polyphenols and polyphenol-rich foods/beverages with the risk of Alzheimer's disease and related dementias (ADRD) in a multi-ethnic cohort of predominantly low-income Americans. Our findings indicate **beneficial associations of certain dietary polyphenols and polyphenol-rich tea for the prevention of ADRD among low-income Black Americans**.

https://pubmed.ncbi.nlm.nih.gov/30405413/#&gid=article-figures&pid=figure-1-uid-0

-quercetin has low Anti-AchE potency (ie has some natural ability) see Figure 1

https://link.springer.com/chapter/10.1007/978-981-16-4558-7_7 Therapeutic Potential of Polyphenols in Alzheimer's Therapy: Broad-Spectrum and Minimal Side Effects as Key Aspects 2022

Numerous studies have indicated that high consumption of fruits and vegetables rich in flavonoids and other polyphenols reduces the risk/incidence of age-related neurodegenerative disorders, highlighting the importance of these polyphenols as neuroprotective agents. Due to polyphenols' ability to influence and modulate multiple targets in the cascade of the pathogenesis of neurodegenerative diseases, they are considered a candidate with a promising result against neurodegeneration, halting the progression of the disease. There is now substantial evidence indicating that **oxidative damage to the brain is an early AD pathogenesis event**. Oxidative stress and damage to brain macromolecules are vital processes in neurodegenerative diseases. The **antioxidant properties of many polyphenols are purported to provide neuroprotection**. There are pieces of evidence that some of the **polyphenols can easily cross the blood-brain barrier (BBB**).

https://academic.oup.com/ajcn/article/79/5/727/4690182?login=false

Polyphenols in foods

	Source	By Serving
Hydroxybenzoic acids (2, 6)	Blackberry (100 g)	8–27
Protocatechuic acid	Raspberry (100 g)	6–10
Gallic acid	Black currant (100 g)	4–13
p-Hydroxybenzoic acid	Strawberry (200 g)	4–18
Hydroxycinnamic acids (2, 5–7)	Blueberry (100 g)	200–220
Caffeic acid	Kiwi (100 g)	60–100
Chlorogenic acid	Cherry (200 g)	36–230
Coumaric acid	Plum (200 g)	28–230
Ferulic acid	Aubergine (200 g)	120–132
Sinapic acid	Apple (200 g)	10–120
	Pear (200 g)	3–120
	Chicory (200 g)	40–100
	Artichoke (100 g)	45
	Potato (200 g)	20–38
	Corn flour (75 g)	23
	Flour: wheat, rice, oat (75 g)	5–7
	Cider (200 mL)	2–100
	Coffee (200 mL)	70–350
Anthocyanins (8–10)	Aubergine (200 g)	1500
Cyanidin	Blackberry (100 g)	100–400
Pelargonidin	Black currant (100 g)	130–400
Peonidin	Blueberry (100 g)	25–500
Delphinidin	Black grape (200 g)	60–1500
Malvidin	Cherry (200 g)	70–900
	Rhubarb (100 g)	200
	Strawberry (200 g)	30–150
	Red wine (100 mL)	20–35
	Plum (200 g)	4–50
	Red cabbage (200 g)	50
Flavonols (11–18)	Yellow onion (100 g)	35–120
Quercetin	Curly kale (200 g)	60–120
Kaempferol	Leek (200 g)	6–45
Myricetin	Cherry tomato (200 g)	3–40
	Broccoli (200 g)	8–20
	Blueberry (100 g)	3–16
	Black currant (100 g)	3–7
	Apricot (200 g)	5–10
	Apple (200 g)	4–8
	Beans, green or white (200 g)	2–10
	Black grape (200 g)	3–8
	Tomato (200 g)	0.4–3.0
	Black tea infusion (200 mL)	6–9
	Green tea infusion (200 mL)	4–7
	Red wine (100 mL)	0.2–3
Flavones (11–12, 14, 18)	Parsley (5 g)	1.2–9.2
Apigenin	Celery (200 g)	4–28
Luteolin	Capsicum pepper (100 g)	0.5–1
Flavanones (19–21)	Orange juice (200 mL)	40–140
Hesperetin	Grapefruit juice (200 mL)	20–130
Naringenin	Lemon juice (200 mL)	10–60
Eriodictyol		
Isoflavones (22–25)	Soy flour (75 g)	60–135
Daidzein	Soybeans, boiled (200 g)	40–180
Genistein	Miso (100 g)	25–90
Glycitein	Tofu (100 g)	8–70
	Tempeh (100 g)	43–53
	Soy milk (200 mL)	6–35
Monomeric flavanols (6, 17, 26, 27)	Chocolate (50 g)	23–30
Catechin	Beans (200 g)	70–110
Epicatechin	Apricot (200 g)	20–50

Cherry (200 g)	10−44
Grape (200 g)	6−35
Peach (200 g)	10−28
Blackberry (100 g)	13
Apple (200 g)	4−24
Green tea (200 mL)	20−160
Black tea (200 mL)	12−100
Red wine (100 mL)	8−30
Cider (200 mL)	8

Polysaccharides (special ones)

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3995358/ Polysaccharides from Medicinal Herbs As Potential Therapeutics for Aging and Age-Related Neurodegeneration 2014
For example, herbal **polysaccharides with considerable anti-oxidant and anti-inflammation capacities** have been shown to be beneficial in aging and age-related neurodegenerative diseases. A number of age-related neurodegenerative diseases, such as Alzheimer disease (AD) and Huntington disease (HD), are known to be linked with impaired proteostasis.[14] A set of quality control mechanisms, including the heat shock protein family, ubiquitin-proteasome system, and autophagy-lysosome system, are used by normal cells to maintain proteostasis and reduce proteotoxicity. As aging advances and stresses accumulate, however, proteostasis may be disrupted by excessive misfolded and aggregated proteins, leading to disequilibrium of cellular homeostasis and selective injury and death of neurons (Fig. 1). For example, overproduction and aggregation of amyloid-β peptide (Aβ), the main component of amyloid deposits in the brains of AD patients, can cause AD-like symptoms in animal models.[14] Therefore, **maintaining proteostasis, including prevention of protein misfolding and aggregation, as well as degradation of misfolded and aggregated proteins, may be an efficient way to reduce aggregation-associated neurotoxicity**. polysaccharides from ***Rubia cordifolia*** are found to reduce Aβ aggregates by activating proteasome activity.[15] the polysaccharide from ***Nerium indicum*****,** which is able to protect rat cortical neurons against Aβ cytotoxicity. In fact, anti-oxidant polysaccharides from **brown seaweeds** have been shown to ameliorate Aβ- and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced neuronal death and behavioral deficits in mice by increasing anti-oxidant enzyme activity and inhibiting lipid peroxidation.[18,19]
https://pubmed.ncbi.nlm.nih.gov/36088034/ Advances in polysaccharides of natural source of the anti-Alzheimer's disease effect and mechanism 2022
Alzheimer's disease (AD) is a complex neurodegenerative disorder. The pathology is characterized by the generation of amyloid plaques and neuronal fiber tangles in the brain. Although decades of research have been conducted, there is still a lack of effective treatments and countermeasures. Polysaccharide components of natural origin obtained by extraction and isolation possess a variety of pharmacological activities and medicinal values, and they are receiving increasing attention. **Polysaccharides have shown good promise in the field of AD prevention and treatment, and polysaccharides ameliorate AD in multiple ways by targeting different mechanisms with almost no toxic side effects.**
https://pubmed.ncbi.nlm.nih.gov/35902016/ Update on new trend and progress of the mechanism of polysaccharides in the intervention of Alzheimer's disease, based on the new understanding of relevant theories: A review 2022
Polysaccharides obtained from natural products can be used in the treatment of AD, which has attracted academic attention due to its advantages of multi-target, multi-channel, no or modest side effects. The TCM syndrome type of AD is mainly "qi and blood deficiency, kidney essence deficiency", and the medicine is mainly used to replenish qi and blood, kidney and bone marrow. Thus, there has been extensive and in-depth research on polysaccharides obtained from tonic Chinese herbal medicine in China

Sibiricum (Polygonatum sibiricum)

https://pubmed.ncbi.nlm.nih.gov/35661666/ A monomeric polysaccharide from Polygonatum sibiricum improves cognitive functions in a model of Alzheimer's disease by reshaping the gut microbiota 2022
Polygonatum sibiricum polysaccharides (PSPs) have the function of **nourishing the nerves and beneficial intelligence**, but the underlying mechanisms remain unclear. A 3-month course of PSP-1 improved the pathological behaviors related to memory and cognition, prevented synaptic loss, enhanced microglial phagocytosis of Aβ plaques, and decreased the concentrations of Aβ1-40 and Aβ1-42 in the brains of 5xFAD mice. Moreover, PSP-1 **reconstructed the gut microbiota composition**, including reducing the relative abundance of Helicobacter, and increasing Akkermansia muciniphila. The **gut barrier integrity** damage, the inflammatory responses, and the intestinal Aβ deposition were prevented by the PSP-1 treatment. The present study identified a **monomeric polysaccharide purified from PSPs** that significantly attenuates the cognitive deficits in 5xFAD mice, which could be partly explained by the reshaped gut microbiome.
https://pubmed.ncbi.nlm.nih.gov/33932516/ Polygonatum sibiricum polysaccharide prevents depression-like behaviors by reducing oxidative stress, inflammation, and cellular and synaptic damage 2021
Conclusion: These results indicate that **PSP prevents depression-like behaviors, and synaptic and neuronal damage probably by reducing ROS/HPA axis hyperfunction and the inflammatory response.**
https://pubmed.ncbi.nlm.nih.gov/36232521/ Use of Steaming Process to Improve Biochemical Activity of *Polygonatum sibiricum* Polysaccharides against D-Galactose-Induced Memory Impairment in Mice 2022
Polysaccharide from *Polygonatum sibiricum* (PSP) possesses **antioxidant, antiaging, and neuroprotective** activities. However, whether and how the steaming process influences the biological activities of PSP, especially against aging-related memory impairment, is not yet known. In this study, *Polygonatum sibiricum* rhizome was subjected to a "nine steaming and nine drying" process, then PSPs with different steaming times were abstracted. Additionally, the steamed PSPs increased anti-oxidative stress-related protein expression and decreased inflammation-related protein expression in D-gal-injured mice. Collectively, the **steaming process improves the effects of PSPs against D-gal-induced memory impairment in mice, likely by increasing the antioxidant activity of PSPs**.

Polysaccharide Krestin

https://pubmed.ncbi.nlm.nih.gov/34611829/ Polysaccharide Krestin Prevents Alzheimer's Disease-type Pathology and Cognitive Deficits by Enhancing Monocyte Amyloid-β Processing 2022
In the current study, flow cytometry and biochemical and behavioral techniques were applied to investigate the effects of polysaccharide krestin (PSK) on AD-related pathology in vitro and in vivo. We found that **PSK, widely used in therapy for various cancers, has the potential to enhance Aβ uptake** and intracellular processing by human monocytes in vitro. After administration of PSK by intraperitoneal injection, APP/PS1 mice **performed better in behavioral tests, along with reduced Aβ deposition, neuroinflammation, neuronal loss, and tau hyperphosphorylation**. These results suggest that PSK holds promise as a preventive agent for AD by strengthening the Aβ clearance by blood monocytes and alleviating AD-like pathology.

Angelica Polysaccharide

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6987749/ Angelica polysaccharide ameliorates memory impairment in Alzheimer's disease rat through activating BDNF/TrkB/CREB pathway 2020
This study aimed to investigate the **effect of Angelica sinensis polysaccharides (ASP) on Alzheimer's disease (AD)** and its underlying mechanisms. Pathological change of hippocampus CA1, CA3, and DG region was ameliorated by ASP. In addition, the effects of ASP were reversed by K252a (TrkB inhibitor). Our study demonstrated that **ASP could ameliorate memory impairment in AD rat through activating BDNF/TrkB/CREB pathway.**

Maitake Polysaccharide(Grifola frondosa)

https://pubs.rsc.org/en/content/articlehtml/2019/ra/c9ra08245j A Maitake (Grifola frondosa) polysaccharide ameliorates Alzheimer's disease-like pathology and cognitive impairments by enhancing microglial amyloid-β clearance 2019
Alzheimer's disease (AD) is characterized by the deposition of amyloid-β (Aβ) plaques, neuronal loss and neurofibrillary tangles. In addition, neuroinflammatory processes are thought to contribute to AD pathophysiology. **Maitake (Grifola frondosa), an edible/medicinal mushroom,** exhibits high nutritional value and contains a great amount of health-beneficial, bioactive compounds. It has been reported that **proteo-β-glucan, a polysaccharide derived from Maitake (PGM)**, possesses strong immunomodulatory activities. In the present study, the **results demonstrated that PGM could improve learning and memory impairment, attenuate neuron loss and histopathological abnormalities in APP/PS1 mice**. In addition, PGM treatment could activate microglia and astrocytes and promote microglial recruitment to the Aβ plaques. Also, PGM could enhance Aβ phagocytosis, and thereby alleviate Aβ burden and the pathological changes in the cortex and hippocampus in APP/PS1 mice. Moreover, PGM showed no significant effect on mice body weight. In conclusion, these findings indicated that administration of PGM could improve memory impairment via immunomodulatory action, and dietary supplementation with PGM may provide potential benefits on brain aging related memory dysfunction.

Polysaccharide of Schisandra Chinensis Fructus

https://neuro.unboundmedicine.com/medline/citation/30844489/Polysaccharide_of_Schisandra_Chinensis_Fructus_ameliorates_cognitive_decline_in_a_mouse_model_of_Alzheimer's_disease_
Polysaccharide of Schisandra Chinensis Fructus ameliorates cognitive decline in a mouse model of Alzheimer's disease.
2019
The purpose of our study is to investigate the effects of polysaccharides of Schisandra Chinensis Fructus (SCP) on animal model of Alzheimer's disease (AD). RESULTS
SCP could significantly improve the cognition and histopathological changes of AD mice, reduce the deposition of Aβ, downregulate the expression of pro-inflammatory cytokines and the activation of glial cells in the hippocampus. Further, SCP decreased nuclear displacement of NF-κB and MAPKs phosphorylation.
CONCLUSIONS: **SCP could improve the cognition of mice, and it may play an anti-AD role by activating the NF-κB/MAPK pathway to alleviate neuroinflammation.**

Polysaccharides of Danggui-Shaoyao-San

https://pubmed.ncbi.nlm.nih.gov/34776439/ Research Advances in the Treatment of Alzheimer's Disease with Polysaccharides of Danggui-Shaoyao-San 2022
Existing animal and clinical studies have found that **Danggui Shaoyao San (DSS), which has been used in gynecological diseases, is effective in the treatment of AD.**

Polysaccharides from Lycium barbarum

https://pubmed.ncbi.nlm.nih.gov/31715236/ Polysaccharides from Lycium barbarum ameliorate amyloid pathology and cognitive functions in APP/PS1 transgenic mice 2020
In this study, we will demonstrate that polysaccharides from L. barbarum (LBP1), a traditional natural compound, can reduce Aβ level and improve the cognitive functions in APP/PS1 transgenic mouse.

polysaccharide from Korean red ginseng

https://pubmed.ncbi.nlm.nih.gov/33422674/ Therapeutic effects of non-saponin fraction with rich polysaccharide from Korean red ginseng on aging and Alzheimer's disease 2021
Alzheimer's disease (AD) is an aging-related neurodegenerative disease that is characterized by cognitive deficits and the formation of amyloid plaques formed by the accumulation of amyloid-β (Aβ) peptides. Non-saponin fraction with rich polysaccharide (NFP) from red ginseng, the largest fraction of the components of red ginseng, perform many biological activities. Histological analysis indicated that **NFP significantly alleviated the accumulation of Aβ, neuroinflammation, neuronal loss, and mitochondrial dysfunction** in the subiculum of 5XFAD mouse model of AD. In addition, NFP treatment ameliorated mitochondrial deficits in Aβ-treated HT22 cells. Moreover, NFP treatment significantly increased the AHN and neuritogenesis of neural stem cells in both healthy and AD brains. Furthermore, NFP significantly increased cell proliferation in the HT22 cells. Finally, NFP administration significantly enhanced and restored the cognitive function of healthy and AD mice, respectively. Taken together, NFP treatment demonstrated changes in proteins involved in central nervous system organization/maintenance in aged brain and ameliorates AD pathology.

Potassium Potassium Chloride, Potassium Gluconate, Potassium Aspartate (NOT potassium iodine)

Source: leafy vegs, legumes, salmon(384mg), banana(358mg), potatoes(russet in skin)(550mg)
RDA: 4700mg/d (<2% of US adults meet this goal)
FDA has limited supplements to 99mg, so hard to get enough. Best to get from foods (leave potato peels on, cook whole)
https://ods.od.nih.gov/factsheets/Potassium-HealthProfessional/ Potassium
Potassium, the most abundant intracellular cation, is an essential nutrient that is naturally present in many foods and available as a dietary supplement.
Adequate Intake: 3400mg for male, 2600mg for female
In dietary supplements, **potassium is often present as potassium chloride, but many other forms—including potassium citrate, phosphate, aspartate, bicarbonate, and gluconate**—are also used [18]. The Supplement Facts panel on a dietary supplement label declares the amount of *elemental* potassium in the product, not the weight of the entire potassium-containing compound. Some dietary supplements contain **potassium iodide in microgram amounts, but this ingredient serves as a form of the mineral iodine, not potassium.**
Potassium-only supplements are also available, and most contain up to 99 mg potassium. First, the FDA has ruled that some oral drug products that **contain potassium chloride and provide more than 99 mg potassium are not safe because they have been associated with small-bowel lesions [19]**. A 2016 dose-response trial found that humans absorb about **94% of potassium gluconate in supplements, and this absorption rate is similar to that of potassium from potatoes [24].**
Many salt substitutes contain potassium chloride as a replacement for some or all of the sodium chloride in salt. The **potassium content of these products varies widely, from about 440 mg to 2,800 mg potassium per teaspoon [1]**
Higher potassium intakes have been associated with a **decreased risk of stroke and possibly other cardiovascular diseases** (CVDs) [16,49]. A meta-analysis of 11 prospective cohort studies in 247,510 adults found that a 1,640 mg per day higher potassium intake was associated with a significant 21% lower risk of stroke as well as nonsignificant lower risks of coronary heart disease and total CVD [39]. Similarly, the authors of a meta-analysis of 9 cohort studies reported a significant 24% lower risk of stroke with higher potassium intakes and a nonsignificant reduction in coronary heart disease and CVD risk [50].
https://pubmed.ncbi.nlm.nih.gov/27842602/ Rubidium and potassium levels are altered in Alzheimer's disease brain and blood but not in cerebrospinal fluid 2016
We found that both **potassium and rubidium levels were significantly decreased across all intracellular compartments in the Alzheimer's disease brain**. Our data provides evidence that contrasts the hypothesized disruption of the blood-brain barrier in Alzheimer's disease, with the systemic decrease in cortical potassium and rubidium levels suggesting influx of ions from the blood is minimal and that the observed changes are more likely indicative of an internal energy crisis within the brain. These findings may be the basis for potential diagnostic imaging studies using radioactive potassium and rubidium tracers.
https://pubmed.ncbi.nlm.nih.gov/26391254/ The increased potassium intake improves cognitive performance and attenuates histopathological markers in a model of Alzheimer's disease 2015
Alzheimer's disease (AD) is a neurodegenerative disorder characterized by hallmarks that include an accumulation of amyloid-β peptide (Aβ), inflammation, oxidative stress and synaptic dysfunction, which lead to a decrease in cognitive function. To date, the onset and progression of AD have been associated with pathologies such as hypertension and diabetes. Hypertension, a disease with a high incidence worldwide, is characterized by a chronic increase in blood pressure. Interestingly, this disease has a close relationship to the eating behavior of patients because high Na(+) intake is a significant risk factor for hypertension. In fact, a decrease in Na(+) consumption, along with an increase in K(+) intake, is a primary non-pharmacological approach to preventing hypertension. In the present work, we examined whether an increase in K(+) intake affects the expression of certain neuropathological markers or the cognitive performance of a murine model of AD. **We observed that an increase in K(+) intake leads to a change in the aggregation pattern of the Aβ peptide, a partial decrease in some epitopes of tau phosphorylation and improvement in the cognitive performance.** The recovery in cognitive performance was correlated with a significant improvement in the generation of long-term potentiation. We also observed a decrease in markers related to inflammation and oxidative stress such as glial fibrillary acidic protein (GFAP), interleukin 6 (IL-6) and 4-hydroxynonenal (4-HNE). Together, our **data support the idea that changes in diet, such as an increase in K(+) intake, may be important in the prevention of AD onset as a non-pharmacological therapy.**
https://pubmed.ncbi.nlm.nih.gov/31862274/ Potassium channels in the neuronal homeostasis and neurodegenerative pathways underlying Alzheimer's disease: An update 2019
With more than 80 subunits, potassium (K+) channels represent a group of ion channels showing high degree of diversity and ubiquity. They play important role in the control of membrane depolarization and cell excitability in several tissues, including the brain. Controlling the intracellular and extracellular K+ flow in cells, they also modulate the hormone and neurotransmitter release, apoptosis and cell proliferation. It is **therefore not surprising that an improper functioning of K+ channels in neurons has been associated with pathophysiology of a wide range of neurological disorders, especially Alzheimer's disease (AD).** This review aims to give a comprehensive overview of the basic properties and pathophysiological functions of the main classes of K+ channels in the context of disease processes, also discussing the progress, challenges and opportunities to develop drugs targeting these channels as potential pharmacological approach for AD treatment.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3444663/ Na+ and K+ ion imbalances in Alzheimer's disease 2012
Alzheimer's disease (AD) is associated with impaired glutamate clearance and **depressed Na+/K+ ATPase levels in AD brain** that might lead to a cellular ion imbalance. To test this hypothesis, [Na+] and [K+] were analyzed in postmortem brain samples of 12 normal and 16 AD individuals, and in cerebrospinal fluid (CSF) from AD patients and matched controls. **Statistically significant increases in [Na+] in frontal (25%) and parietal cortex (20%) and in cerebellar [K+] (15%) were observed in AD samples compared to controls.**
https://www.nature.com/articles/ncpneuro0186 **Potassium-sparing diuretics might reduce risk of Alzheimer's disease** 2005
Use of β-blockers and dihydropyridine calcium-channel blockers was associated with reduced incidence of AD in this study; non-dihydropyridine agents had no effect on AD risk. By far the greatest effect, however, was observed with the **use of potassium-sparing diuretics, which was associated with a 70% reduction in the risk of AD**. No association was found between other diuretic medications and AD risk. The protective effect of potassium-sparing diuretics might be related to their effect on potassium levels. Potassium-sparing diuretics cause an increase in plasma potassium levels, whereas other diuretics reduce plasma potassium concentration. Increased plasma potassium level has been associated with a reduced risk of dementia; low potassium levels are associated with oxidative stress, inflammation, platelet aggregation and vasoconstriction, all of which have been linked to the pathogenesis of AD.
https://pubmed.ncbi.nlm.nih.gov/22854410/ Sodium and potassium intakes among US adults: NHANES 2003-2008 2012
Overall, <2% of US adults and ~5% of US men consumed ≥4700 mg K/d (ie, met recommendations for potassium).
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(05)74899-6/fulltext Abnormal potassium-channel function in platelets in Alzheimer's disease 1999
Apamin is a potent bee venom toxin that blocks small calcium-activated potassium channels. This toxin is also the bee venom constituent responsible for the painful sensation that accompanies bee stings. The connection between pain deficiency and memory deterioration could be more than coincidental: apamin injection accelerated learning and memory acquisition in mice. **This connection implies that nociception and learning might share certain neuronal circuits, requiring correct function of similar potassium channels, which could be defective in Alzheimer's disease**.
https://pubmed.ncbi.nlm.nih.gov/31188425/ Apamin Improves Prefrontal Nicotinic Impairment in Mouse Model of Alzheimer's Disease 2020
We demonstrate that this impairment can be **remedied by apamin, a bee venom neurotoxin peptid**e that acts as a selective antagonist to the SK family of **calcium-sensitive potassium channels**.
https://pubmed.ncbi.nlm.nih.gov/18576999/ The effects of boiling and leaching on the content of potassium and other minerals in potatoes 2008
Individuals wishing to **maximize the mineral nutrition benefits of consuming potatoes should boil them whole or bake, roast, or microwave them.** Those who must reduce potassium uptake should boil small pieces before consuming them.
Salt Substitutes:
https://www.health.harvard.edu/heart-health/can-a-salt-substitute-cause-high-potassium-levels
A **quarter-teaspoon serving of one potassium chloride salt substitute contains about 800 milligrams (mg) of potassium,** or about one-sixth of the daily recommended intake for potassium, which is 4,700 mg.

Proanthocyanidins (see grape seed extract)

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4998082/ Effects of grape seed proanthocyanidin on Alzheimer's disease *in vitro* and *in vivo* 2016
Grape seed proanthocyanidin (GSPA) consists of catechin, epicatechin and epicatechin gallate, which are strong antioxidants that are beneficial to health and may attenuate or prevent Alzheimer's disease (AD). The findings from the *in vivo* experiments showed a significant enhancement in cognition and spatial memory ability, an improvement in the pathology of APP and tau protein and a decrease in PS-1 mRNA expression levels. Therefore, the results of the present study **indicated that GSPA may be a novel therapeutic strategy for the treatment of AD or may, at the very least, improve the quality of life of patients with AD.**
https://pubmed.ncbi.nlm.nih.gov/22496560/ Brain-targeted proanthocyanidin metabolites for Alzheimer's disease treatment 2012
While polyphenolic compounds have many health benefits, the potential development of polyphenols for the prevention/treatment of neurological disorders is largely hindered by their complexity as well as by limited knowledge regarding their bioavailability, metabolism, and bioactivity, especially in the brain. **We recently demonstrated that dietary supplementation with a specific grape-derived polyphenolic preparation (GP) significantly improves cognitive function in a mouse model of Alzheimer's disease (AD)**. GP is comprised of the proanthocyanidin (PAC) catechin and epicatechin in monomeric (Mo), oligomeric, and polymeric forms. **In this study, we report that following oral administration of the independent GP forms, only Mo is able to improve cognitive function and only Mo metabolites can selectively reach and accumulate in the brain at a concentration of ~400 nM.**

Pterostilbene polyphenol (more bioavailable than resveratrol) **both maybe heat sensitive**

Sources: Blueberries(52-99ng/gram), peanuts, red grapes (all very low levels?)
Supplement amount: 50-125mg twice daily (half life 75-104 minutes)
Side Effects: might feel hungrier, drug interaction serotinin?
https://pubmed.ncbi.nlm.nih.gov/29737568/ Pterostilbene **inhibits amyloid-β-induced neuroinflammation** in a microglia cell line by inactivating the NLRP3/caspase-1 inflammasome pathway 2018
Neuroinflammation has been known as an important pathogenetic contributor of Alzheimer's disease (AD). Pterostilbene is a natural compound which has neuroprotective activity. However, the effect of pterostilbene on amyloid-β (Aβ)-induced neuroinflammation has not been clarified. The aim of the present study was to investigate the effect of pterostilbene on Aβ-induced neuroinflammation in microglia. The results indicated that pterostilbene attenuated $A\beta_{1-42}$ -induced cytotoxicity of BV-2 cells. $A\beta_{1-42}$ induced NO production and iNOS mRNA and protein expression, while pterostilbene inhibited the induction.
https://pubmed.ncbi.nlm.nih.gov/21982274/ Low-dose pterostilbene, but not resveratrol, is a potent neuromodulator in aging and Alzheimer's disease 2012
Recent studies have implicated resveratrol and pterostilbene, a resveratrol derivative, in the protection against age-related diseases including Alzheimer's disease (AD). However, the mechanism for the favorable effects of resveratrol in the brain remains unclear and information about direct cross-comparisons between these analogs is rare. As such, the purpose of this study was to compare the effectiveness of diet-achievable supplementation of resveratrol to that of pterostilbene at improving functional deficits and AD pathology in the SAMP8 mouse, a model of accelerated aging that is increasingly being validated as a model of sporadic and age-related AD. Taken together our findings indicate that at equivalent and diet-achievable doses pterostilbene is a **more potent modulator of cognition and cellular stress than resveratrol,** likely driven by increased peroxisome proliferator-activated receptor alpha expression and increased lipophilicity due to substitution of hydroxy with methoxy group in pterostilbene.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6834512/ Pterostilbene attenuates amyloid-β induced neurotoxicity with regulating PDE4A-CREB-BDNF pathway
Amyloid-β (Aβ) is considered partially responsible for cognitive dysfunction in Alzheimer's disease (AD). **Resveratrol is known as an anti-neurotoxicity potential natural product, however low blood-brain-barrier (BBB) permissibility and low oral-bioavailability (OB) are the main limitations on its clinical potential.** In this study, we **illustrated that Pterostilbene (PTS), a kind of resveratrol analog which showed higher scores on BBB and OB, could overcome Aβ-induced neurotoxicity *in vitro* and *in vivo*. Resveratrol's positive effects on alleviating AD have been widely reported** [28]. In this study, we focused on a structural analog of Resveratrol, PTS, and its effects on APP/PS1 transgenic AD model *in vivo* and *in vitro*. With searching TCMSP database, **we found PTS was more druggable than Resveratrol according to its several druggable characters, such as BBB, DL, OB, and Caco-2 index.** Furthermore, we illustrated PDE4A was the essential target of PTS, which protected primary neuron cells against Aβ-induced cytotoxicity.
https://superfoodly.com/pterostilbene-supplement-benefits-longevity-miracle-or-hoax/ Pterostilbene Supplement Benefits: Longevity Miracle or Hoax
The pronunciation is terro-still-bean (the "p" is silent). It is a sirtuin activating compound as well as an antioxidant. It **can be found in blueberries, grapes, almonds, peanuts,** and other plant-based food sources. The bark of *Pterocarpus marsupium* (Indian kino tree) and some other non-food sources also contain trace amounts. **Chemically related to resveratrol**, it demonstrates many of the same health benefits and in some instances, **appears to offer even more profound results**.
Like resveratrol, the f**oods containing pterostilbene contain only miniscule amounts.** For example, how much pterostilbene there is in blueberries – which is one of the richest sources – has been detected as being between 99 ng to 520 ng per gram of fruit (the *Vaccinium ashei* species was measured) (1).
80% bioavailability versus 20% for resveratrol (4). That means it has 4x the rate of absorption. What is the half-life of pterostilbene? 105 minutes. Compare that to resveratrol, which is just 14 minutes (5). **Less oxidation from air , Less sensitive to light**
Just like alpha lipoic acid, pterostilbene has been **found to cross the blood brain barrier,** which means it might offer protective assistance for neurodegenerative diseases like Alzheimer's disease and cognitive decline from other oxidative stress contributors
https://pubmed.ncbi.nlm.nih.gov/29210129/ Effect of resveratrol and pterostilbene on aging and longevity
In this review, we discuss the relationship between resveratrol and pterostilbene and possible aging biomarker, including oxidative stress, inflammation, and high-calorie diets. Moreover, we also discuss the positive effect of resveratrol and pterostilbene on **lifespan, aged-related disease, and health maintenance**. Furthermore, we summarize a variety of important mechanisms modulated by resveratrol and pterostilbene possibly involved in attenuating age-associated disorders. Overall, we describe resveratrol and pterostilbene potential for **prevention or treatment of several age-related diseases by modulating age-related mechanisms**.
https://pubmed.ncbi.nlm.nih.gov/23431291/ Analysis of safety from a human clinical trial with pterostilbene
There were no statistically significant self-reported or major ADRs. Conclusion. Pterostilbene is generally safe for use in humans up to 250 mg/day.
https://pubmed.ncbi.nlm.nih.gov/35060152/ **Pterostilbene exert an anti-arthritic effect by attenuating inflammation, oxidative stress, and alteration of gut microbiota**
Pterostilbene significantly ($p < .001$) decreased the paw swelling, arthritic score, and increased the body weight. Besides **altered the antioxidant, inflammatory mediators, anti-collagen (C)II Ig, and inflammatory cytokines**. Furthermore, pterostilbene treatment helps to **restore the ecosystem of gut microbiota** in rats by reducing the relative abundance of Helicobacter, Desulfovibrio, Lachnospiraceae, and Mucispirillium. Based on the findings, we can say that pterostilbene has an **anti-arthritic effect via suppressing inflammatory responses** and **altering intestinal bacteria**. PRACTICAL APPLICATIONS: Arthritis is the painful disease and affected most of the people worldwide. In this experimental study, we estimated the anti-arthritic effect of pterostilbene against CFA-induced arthritis in rats. Pterostilbene noticeably suppressed the paw thickness, arthritic score, and organ index. Pterostilbene substantially altered the oxidative stress and inflammatory reaction. Pterostilbene considerably modulated the gut microbiota, suggesting the anti-arthritic effect.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3649683/ A Review of Pterostilbene Antioxidant Activity and Disease Modification
Multiple studies have demonstrated the antioxidant activity of pterostilbene in both *in vitro* and *in vivo* models illustrating both preventative and therapeutic benefits. The antioxidant activity of pterostilbene has been implicated in anticarcinogenesis, modulation of neurological disease, **anti-inflammation**, attenuation of vascular disease, and amelioration of diabetes. Pterostilbene (trans-3,5-dimethoxy-4-hydroxystilbene) is a naturally derived compound found primarily in blueberries and Pterocarpus marsupium (PM) heartwood [1, 2]. The amount of daily pterostilbene consumption varies according to dietary fruit intake, and it has been estimated that pterostilbene content **per blueberry varies from 99 ng to 520 ng/gram** depending on the type of berry ingested [3, 4]. Substantial evidence suggests that pterostilbene may have numerous preventive and therapeutic properties in a vast range of human diseases that include neurological, cardiovascular, metabolic, and hematologic disorders. Further benefits of pterostilbene have been reported in preclinical trials, in which pterostilbene was shown to be a potent anticancer agent in several malignancies [5]. Pterostilbene is **structurally similar to resveratrol**, a compound found in red wine that has **comparable antioxidant, anti-inflammatory, and anticarcinogenic properties**; however, pterostilbene exhibits **increased bioavailability** due to the presence of two methoxy groups which cause it to exhibit increased lipophilic and oral absorption (Figure 1) [6–10]. In animal studies, pterostilbene was shown to have 80% bioavailability compared to 20% for resveratrol making it potentially advantageous as a therapeutic agent [6]. The **multiple benefits of pterostilbene in the treatment and prevention of human disease have been attributed to its antioxidant, anti-inflammatory, and anticarcinogenic** properties leading to improved function of normal cells and inhibition of malignant cells [11, 12].
ARTHRISIS
https://pubmed.ncbi.nlm.nih.gov/35060152/ Pterostilbene exert an anti-arthritic effect by attenuating inflammation, oxidative stress, and alteration of gut microbiota
Pterostilbene is a revesterol analog with a long bioavailability and having **potent anti-inflammatory activity** in animal studies. In this study, we tried to scrutinize the anti-arthritic effect of pterostilbene against complete Freund's adjuvant (CFA)-induced arthritis model in rats. Pterostilbene significantly ($p < .001$) **decreased the paw swelling, arthritic score,** and increased the body weight. Besides altered the antioxidant, inflammatory mediators, anti-collagen (C)II Ig, and inflammatory cytokines. Furthermore, pterostilbene treatment helps to **restore the ecosystem of gut microbiota** in rats by reducing the relative abundance of Helicobacter, Desulfovibrio, Lachnospiraceae, and Mucispirillium. Based on the findings, we can say that pterostilbene has an anti-arthritic effect via suppressing inflammatory responses and altering intestinal bacteria. PRACTICAL APPLICATIONS: Arthritis is the painful disease and affected most of the people worldwide. In this experimental study, we estimated the anti-arthritic effect of pterostilbene against CFA-induced arthritis in rats. Pterostilbene noticeably suppressed the paw thickness, arthritic score, and organ index. Pterostilbene substantially altered the oxidative stress and inflammatory reaction. Pterostilbene considerably modulated the gut microbiota, suggesting the anti-arthritic effect.
https://pubmed.ncbi.nlm.nih.gov/24195064/ The effects of pterostilbene on neutrophil activity in experimental model of arthritis
These results indicate that the **promising effects of pterostilbene on reactive oxygen specie**s operate by different mechanisms in vitro and in the animal model of inflammation. In conclusion, the positive effects of pterostilbene in the model of arthritis may be attributed to regulation of neutrophil number.

Quercetin -anti-oxidant (also listed under various fruits and vegetables) TNF inhibitor

Sources: Red and Yellow Onions, Kale, Cherry Tomatoes, Broccoli, Blueberries, Apples, grapes, cherries, nuts(almonds,pistachios), green/yellow bell peppers
Supplement Levels: Typ 500-1000mg/day (take with **Vitamin C** to enhance bioavailability?) Maybe **LipoMicel brand**
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7023116/ Neuroprotective Effects of Quercetin in Alzheimer's Disease 2019
Studies suggested that **flavonoids are capable of crossing the blood–brain barrier (BBB)**, which makes them **potential agents in preventing neurodegenerative disorders**; however, different flavonoid subclasses differ in their ability to cross the BBB [20,21]. In the case of AD, their efficacy is attributed to the **reduction of Aβ toxicity and decreasing oxidative stress** [22,23].
Nevertheless, anti-AD effects of certain flavonoids, such as myricetin, rutin, fisetin, catechins, **quercetin**, kaempferol, and apigenin have been reported [24,25,26,27].
Quercetin is one of the most potent antioxidants of plant origin and is one of the predominant flavonoids found more commonly in edible plants [28]. It belongs to the flavonols class of flavonoids, representing a major class of polyphenols. The dietary intake of total flavonoids is estimated to be 200–350 mg/day, and the **intake of quercetin is 10–16 mg/day**. Several flavonoids have anti-inflammatory activity, among which flavanones such as naringenin have weak activity, while **flavonols including quercetin, kaempferol, and myricetin have strong anti-inflammatory activity.** families rich in quercetin are Compositae, Passiflorae, Rhamnaceae, and Solanaceae [49]. **Onions, asparagus, red leaf lettuce, apples, capers, and berries contain relatively high concentrations of quercetin** [29,50 in vitro studies have confirmed that the **esters-based precursors of quercetin increase the bioavailability of quercetin** [46]
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5214562/?report=reader . Overviews of Biological Importance of Quercetin: A Bioactive Flavonoid
Quercetin, a plant pigment is a potent antioxidant flavonoid and more specifically a flavonol, found mostly in onions, grapes, berries, cherries, broccoli, and citrus fruits. It is a **versatile antioxidant** known to possess protective abilities against tissue injury induced by various drug toxicities.
The plant such as Curcuma domestica valeton, Cuscuta reflexa, Daucus carota, Emblica officinalis, Foeniculum vulgare, Glycyrrhiza glabra, Mangifera indica, Momordica charantia, Ocimum sanctum, Psoralea corylifolia, Santalum album, Solanum nigrum, Swertia chirayita, and Withania somnifera are known for its antioxidant activity and these plants showed significant biological activities against disease such as diabetes, hypercholesterolemia, and inflammatory disorders.[2,3]
Quercetin is one of the important bioflavonoids present in more than twenty plants material [Table 1] and which is known for its **anti-inflammatory, antihypertensive, vasodilator effects, antiobesity, antihypercholesterolemic and antiatherosclerotic activities**.[4,5
It is one of the most abundant dietary flavonoids found in fruits (mainly citrus), green leafy vegetables as well as many seeds, buckwheat, nuts, flowers, barks, broccoli, olive oil, apples, onions, green tea, red grapes, red wine, dark cherries, and berries such as blueberries and cranberries. The highest concentrations of flavonols were found in **vegetables such as onions and broccoli, fruits such as apples, cherries, and berries, and drinks such as tea and red wine.**
The name quercetin (3,3',4',5,7-pentahydroxyflavone) [Figure 1] comes from the Latin word "Quercetum" which means Oak Forest, belongs to the class called flavonols that cannot be produced in the human body.[14] It is yellow color and is
poorly soluble in hot water, quite soluble in alcohol and lipids and is insoluble in cold water. Quercetin is said to be one of the most widely used bioflavonoids for the treatment of metabolic and inflammatory disorders
In a study done by Greek cardiologists on thirty men who already had coronary heart disease (CHD) on the consumption of **red grape polyphenol extract rich in quercetin caused an increase in flow-mediated dilation of major arteries, a potent indicator of improved endothelial health**.[28]
Flavonoid-rich plant or food supplement improves the cognition functions and protects vulnerable neurons by enhancing existing neuronal function or by stimulating neuronal regeneration.[40]
https://pubmed.ncbi.nlm.nih.gov/25666032/ The flavonoid quercetin ameliorates Alzheimer's disease pathology and protects cognitive and emotional function in aged triple transgenic Alzheimer's disease model mice 2015
In this study, we evaluated the **neuroprotective effect of quercetin** (25 mg/kg) administration via i.p. injection every 48 h for 3 months on aged (21-24 months old) triple transgenic AD model (3xTg-AD) mice. These results were supported by a **significant reduction in the paired helical filament (PHF), β-amyloid (βA) 1-40 and βA 1-42 levels** and a decrease in BACE1-mediated cleavage of APP (into CTFβ). Additionally, **quercetin induced improved performance on learning and spatial memory tasks** and greater risk assessment behavior based on the elevated plus maze test. Together, these findings suggest that **quercetin reverses histological hallmarks of AD and protects cognitive and emotional function in aged 3xTg-AD mice.**
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8617296/ Mechanism of quercetin therapeutic targets for Alzheimer disease and type 2 diabetes mellitus 2021
Quercetin has demonstrated antioxidant, anti-inflammatory, hypoglycemic, and hypolipidemic activities, suggesting therapeutic potential against type 2 diabetes mellitus (T2DM) and Alzheimer's disease (AD).
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5934583/ Quercetin enrich diet during the early-middle not middle-late stage of alzheimer's disease ameliorates cognitive dysfunction 2018
The aim of this study was to evaluate the protective effects of dietary flavonoid quercetin against Alzheimer's disease (AD) and detect the explicit administration of quercetin in early-middle or middle-late stage of AD pathology could play the effect as well as its mechanism of action. In this study, APP/PS1 mice were used to investigate cognitive impairment and related pathologies. The results showed that **quercetin enrich diet could play an ameliorated pathology development of AD** in APP/PS1 mice. And then we next determined administration of quercetin in early-middle and middle-late stage of AD pathology, which exerted that only quercetin enrich diet during the early-middle stage of AD pathological development period ameliorates cognitive dysfunction and the protection effect was mainly related to increased Aβ clearance and reduced astrogliosis. These findings suggest a possible new protective role for dietary flavonoids on AD. This new role might expand the preventive and/or therapeutic use of AD in conditions.
https://www.sciencedirect.com/science/article/abs/pii/S0955286308000806 Protective effect of quercetin in primary neurons against Aβ(1–42): relevance to Alzheimer's disease 2009
Quercetin, a flavonoid found in various foodstuffs, has **antioxidant properties and increases glutathione (GSH) levels** and antioxidant enzyme function. Considerable attention has been focused on increasing the intracellular GSH levels in many diseases, including Alzheimer's disease (AD). Amyloid beta-peptide [Aβ(1–42)], elevated in AD brain, is associated with oxidative stress and neurotoxicity. We aimed to investigate the protective effects of quercetin on Aβ(1–42)-induced oxidative cell toxicity in cultured neurons in the present study.
https://pubmed.ncbi.nlm.nih.gov/27710596/ The Effect of Quercetin on Inflammatory Factors and Clinical Symptoms in Women with Rheumatoid Arthritis: A Double-Blind, Randomized Controlled Trial 2016
Quercetin supplementation for 8 weeks significantly reduced EMS, morning pain, and after-activity pain ($p < 0.05$). DAS-28 and HAQ scores decreased in the quercetin group compared to placebo and the number of patients with active disease significantly decreased in the quercetin group. **Plasma hs-TNFα level was significantly reduced** in the quercetin group compared to placebo ($p < 0.05$).
https://pubmed.ncbi.nlm.nih.gov/26904161/ Mechanisms of Neuroprotection by Quercetin: Counteracting Oxidative Stress and More 2016
Increasing interest has recently focused on determining whether several natural compounds, collectively referred to as nutraceuticals, **may exert neuroprotective actions in the developing, adult, and aging nervous system. Quercetin, a polyphenol widely present in nature, has received the most attention in this regard.** Several studies in vitro, in experimental animals and in humans, have provided supportive evidence for neuroprotective effects of quercetin, either against neurotoxic chemicals or in various models of neuronal injury and neurodegenerative diseases. The exact mechanisms of such protective effects remain elusive, though many hypotheses have been formulated. In addition to a possible direct antioxidant effect, quercetin may also act by stimulating cellular defenses against oxidative stress.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5785894/ Chronic diseases, inflammation, and spices: how are they linked? 2018
Quercetin is a dietary flavonoid obtained from onions. The anti-cancer, anti-inflammatory, and anti-oxidant properties of this phytochemical are demonstrated by numerous studies. Quercetin is effective against various chronic diseases including arthritis, breast cancer, dermatitis, diabetes, IBD, hepatitis, psoriasis, etc. due to its ability to inhibit the dysregulated inflammatory pathways involved in these chronic diseases (Table 2) [138–144]. The anti-inflammatory properties of quercetin is attributed to its ability to downregulate NF-κB and MAPK pathways and enhance PI3K/Akt and Nrf2 pathways [145–147] (Table 2)

Bioavialability

https://pubmed.ncbi.nlm.nih.gov/28377278/ Factors modulating bioavailability of quercetin-related flavonoids and the consequences of their vascular function 2017
Current intervention studies imply that intake of **quercetin-rich onion improves vascular health**. Onion may be superior to quercetin supplement from the viewpoint of quercetin bioavailability, probably because the food matrix enhances the intestinal absorption of quercetin. **α-Glucosylation increases its bioavailability** by elevating the accessibility to the absorptive cells. Prenylation may enhance bioaccumulation at the target site by increasing the cellular uptake. However, these chemical modifications do not guarantee health benefits to the vascular system. Dietary quercetin is exclusively present as their conjugated form in the blood stream.
https://pubmed.ncbi.nlm.nih.gov/23514412/ Bioavailability of quercetin: problems and promises 2013
Quercetin (QC) is a typical plant flavonoid, possesses diverse pharmacologic effects including antiinflammatory, antioxidant, anti-cancer, anti-anaphylaxis effects and against aging. However, the application of QC in pharmaceutical field is limited due to its **poor solubility, low bioavailability, poor permeability and instability**. To improve the bioavailability of QC, numerous approaches have been undertaken, involving the use of promising drug delivery systems such as inclusion complexes**, liposomes, nanoparticles or micelles, which appear to provide higher solubility and bioavailability**. Enhanced bioavailability of QC in the near future is likely to bring this product to the forefront of therapeutic agents for treatment of human disease.
https://pubmed.ncbi.nlm.nih.gov/23717772/ Quercetin and vitamin C supplementation: effects on lipid profile and muscle damage in male athletes 2013
Quercetin, which is considered as a health-promoting antioxidant, belongs to the broad flavonoids group. **Numerous experimental studies have proved that quercetin and vitamin C provide anti-inflammatory and antioxidant properties**.
https://jnhpresearch.com/index.php/jnhpr/article/view/17 Quercetin LipoMicel—A Novel Delivery System to Enhance Bioavailability of Quercetin 2021
Results: Oral **absorption of quercetin was significantly enhanced with the LipoMicel delivery system** compared to free quercetin. Improvements in *in vitro* gastric stability and intestinal solubility were observed with LipoMicel, leading to significantly higher blood concentration and enhanced duration of a stable concentration of quercetin in the body. Compared to free quercetin, 8- and 9-fold increases in AUC and Cmax were attained with the LipoMicel delivery system, and 10-fold higher quercetin plasma concentrations detected at 12 hours after administration.

https://www.evergreennutrition.com/product/p-450-1378/ **Micelle Technology**
The unique antioxidants in quercetin support blood vessel health. Our unique patent-pending technology creates a liquid micelle matrix that **disperses the quercetin into tiny micro-droplets**, resulting in a superior delivery system for enhanced absorption. The dosage for the Natural Factors' Quercetin LipoMicel Matrix™ is 250 to 500 mg per day. Each soft-gel capsule contains 250 mg of quercetin within the LipoMicel Matrix™. Preliminary absorption data indicate a 5 to 10-fold greater absorption for this advanced form over regular quercetin. This indicates that each capsule of Quercetin LipoMicel Matrix™ would have a **bioequivalence of 1,250 to 2,500 to regular quercetin powder**. If two capsules are taken daily that bioequivalence increases to 2,500 to 5,000 mg of regular quercetin.

Resveratrol (red wine polyphenol) (see pterostilbene as improved option)

https://pubmed.ncbi.nlm.nih.gov/32520230/ Resveratrol in Alzheimer's disease: a review of pathophysiology and therapeutic potential
Resveratrol demonstrates **beneficial and protective effects in AD models** and seems to provide a promising therapeutic alternative.
https://pubchem.ncbi.nlm.nih.gov/compound/resveratrol Resveratrol is a phytoalexin derived from grapes and other food products with antioxidant and potential chemopreventive activities. Resveratrol is a plant polyphenol **found in high concentrations in red grapes** that has been proposed as a treatment for hyperlipidemia and to prevent fatty liver, diabetes, atherosclerosis and aging. Resveratrol use has not been associated with serum enzyme elevations or with clinically apparent liver injury.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6164842/ Resveratrol: A Double-Edged Sword in Health Benefits
Resveratrol (3,5,4′-trihydroxy-trans-stilbene) belongs to polyphenols' stilbenoids group, possessing two phenol rings linked to each other by an ethylene bridge. This natural polyphenol has been detected in more than **70 plant species**, especially in grapes' skin and seeds, and was found in discrete amounts in red wines and various human foods. Resveratrol also exhibit antitumor activity, and is considered a potential candidate for prevention and treatment of several types of cancer. Indeed, resveratrol anticancer properties have been confirmed by many in vitro and in vivo studies, which shows that resveratrol is able to inhibit all carcinogenesis stages (e.g., initiation, promotion and progression). Even more, other bioactive effects, namely as **anti-inflammatory**, anticarcinogenic, cardioprotective, vasorelaxant, phytoestrogenic and neuroprotective have also been reported. Nonetheless, resveratrol application is still being a major challenge for pharmaceutical industry, **due to its poor solubility and bioavailability**, as well as adverse effects. However, some studies have documented that it may behave as a pro-oxidizing agent [112]; thus, paradoxically, it may also have implication in pathology of several diseases. It was documented that **resveratrol behaved as an antioxidant during dark span and as a pro-oxidant during light span**, possibly reflecting the putative changing ratio between pro- and antioxidant activities in various organs during 24-h cycle. Atherosclerotic lesions staining in control and resveratrol-treated groups revealed that resveratrol-treated rabbits had significantly more aortic surface area covered by atherosclerotic lesions. Therefore, resveratrol promoted atherosclerotic development, rather than protect against it. Resveratrol has been reported to both reduce cell growth and induce apoptosis in normal cells, when administered at high doses. Additionally, resveratrol consumption at m**odest doses result in a life span increase in 1-year old mice**. However, when mice consumed **larger resveratrol doses (1800 mg/kg), animals were shown to die within 3–4 months** [148]
https://pubmed.ncbi.nlm.nih.gov/28815614/ Resveratrol for Alzheimer's disease
Resveratrol is a potent activator of SIRT1, and thus may mimic caloric restriction to prevent diseases of aging. We conducted a randomized, double-blind, placebo-controlled, phase II trial of resveratrol for individuals with mild-to-moderate AD. **Resveratrol (1) is detectable in cerebrospinal fluid (at low nanomolar levels), (2) is safe and well tolerated, (3) alters AD biomarker trajectories, (4) preserves blood-brain barrier integrity, and (5) modulates the CNS immune response.**
https://pubmed.ncbi.nlm.nih.gov/16766037/ Resveratrol--a boon for treating Alzheimer's disease?
Resveratrol, a **red wine polyphenol**, is known to protect against cardiovascular diseases and cancers, as well as to **promote antiaging effects** in numerous organisms. It also modulates **pathomechanisms of debilitating neurological disorders, such as strokes, ischemia, and Huntington's disease**. The role of **resveratrol in Alzheimer's disease is still unclear**, although some recent studies on red wine bioactive compounds suggest that **resveratrol modulates multiple mechanisms of Alzheimer's disease pathology**. Emerging literature indicates that mechanisms of aging and Alzheimer's disease are intricately linked and that these mechanisms can be modulated by both calorie restriction regimens and calorie restriction mimetics, the prime mediator of which is the SIRT1 protein, a human homologue of yeast silent information regulator (Sir)-2, and a member of NAD+-dependent histone deacetylases. Calorie restriction regimens and calorie restriction-mimetics trigger sirtuins in a wide variety of organisms, ranging from bacteria to mouse. In a mouse model of Huntington's disease, resveratrol-induced SIRT1 was found to protect neurons against ployQ toxicity and in Wallerian degeneration slow mice, **resveratrol was found to protect the degeneration of neurons from axotomy, suggesting that resveratrol may possess therapeutic value to neuronal degeneration.**

https://pubmed.ncbi.nlm.nih.gov/29168580/ Resveratrol, pterostilbene, and dementia
Resveratrol is a natural phytoestrogen with **neuroprotective properties**. Polyphenolic compounds including resveratrol exert in vitro **antioxidant, anti-inflammatory, and antiamyloid effects**. Resveratrol and its derivative pterostilbene are **able to cross the blood-brain barrier** and to influence brain activity. In comparison to resveratrol, pterostilbene appears to be more effective in combatting brain changes associated with aging.
The findings of **available intervention trials of resveratrol in individuals with mild cognitive impairment or AD do not provide evidence of neuroprotective or therapeutic effects.** Future clinical trials should be conducted with long-term exposure to preparations of resveratrol and pterostilbene with high bioavailability

Rhodiola rosea

https://pubmed.ncbi.nlm.nih.gov/27059687/ Rhodiola rosea L. and Alzheimer's Disease: From Farm to Pharmacy
hodiola rosea L. (**roseroot**) is a common member of the family Crassulaceae, known as one of the most important **popular medicinal plants in the northern region of Europe**. The roots of R. rosea possess a wide range of pharmacological activities such as a**ntioxidant, antiinflammatory, anticancer, cardioprotective, and neuroprotective effects** that are because of the presence of different phytochemicals such as **phenols and flavonoids**. In addition, the presence of salidroside, rosavins, and p-tyrosol are responsible for its beneficial effects for the treatment of on depression, fatigue, and cognitive dysfunction. **A plethora of studies report that R. rosea has potent neuroprotective effects through the suppression of oxidative stress, neuroinflammation, and excitotoxicity in brain tissues and antagonism of oncogenic p21-activated kinase.** However, to our knowledge, no review articles have been published addressing the neuroprotective effects of R. rosea. Therefore, the present article aims at critically reviewing the available literature on the beneficial effects of R. rosea on as a therapeutic strategy for the treatment of Alzheimer's disease and other neurodegenerative diseases where oxidative stress plays a major role in disease development and progression.
https://pubmed.ncbi.nlm.nih.gov/26967223/ **Salidroside**, a Bioactive Compound of Rhodiola Rosea, Ameliorates Memory and Emotional Behavior in Adult Mice
Rhodiola Rosea (R. Rosea) is a plant used in traditional popular medicine to **enhance cognition and physical performance**. R. Rosea medicinal properties have been related to its capability to act as an adaptogen, i.e., a substance able to increase the organism's resistance to a variety of chemical, biological, and physical stressors in a non-specific way. These adaptogen properties have been **mainly attributed to the glycoside salidroside**, one of the bioactive compounds present in the standardized extracts of R. Rosea. Here, we aimed to investigate whether a **single dose of salidroside is able to affect memory and emotional behavior in wild type adult mice**. We performed fear conditioning to assess cued and contextual memory, elevated plus maze and open field to evaluate anxiety, and tail suspension test to evaluate depression. Our results showed that a single i.p. administration of **salidroside was able to enhance fear memory and exerted an anxiolytic and antidepressant effect.** These data confirmed the adaptogenic effect of R. Rosea bioactive compounds in animal models and suggest that salidroside might represent an interesting pharmacological tool to ameliorate cognition and counteract mood disorders.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3652169/ Anti-Inflammatory and Neuroprotective Effects of Constituents Isolated from *Rhodiola rosea*
To determine the biological activity of *Rhodiola rosea*, the protein expression of iNOS and proinflammatory cytokines was measured after the activation of murine microglial BV2 cells by LPS under the exposure of constituents of *Rhodiola rosea*: crude extract, rosin, rosarin, and salidroside (each 1–50 μg/mL). The L-glutamate-induced neurotoxicity was suppressed by the treatment with rosin but not by rosarin. The level of phosphorylated MAPK, pJNK, and pp38 was increased by L-glutamate treatment but decreased by the treatment with rosin and salidroside. **These results indicate that *Rhodiola rosea* may have therapeutic potential for the treatment of inflammation and neurodegenerative disease.** *R. rosea* root contains about 28 compounds, of which salidroside (rhodioloside), rosavins, and p-tyrosol are thought to have the most critical therapeutic activity [4]. *R. rosea* may play a role in the amelioration of neurodegenerative diseases, **such as Alzheimer's disease (AD), via its anti-inflammatory and neuroprotective properties**.

Rosemary (*Rosmarinus officinalis* [family Lamiaceae])-Rosmarinic Acid(see link with copper)

- Rosmarinic acid is a compound concentrated in certain plants, including herbs and spices like rosemary and oregano
-Note oil useful for aromatherapy
https://pubmed.ncbi.nlm.nih.gov/35052628/ Potential Therapeutic Use of the Rosemary Diterpene Carnosic Acid for Alzheimer's Disease, Parkinson's Disease, and Long-COVID through NRF2 Activation to Counteract the NLRP3 Inflammasome

Rosemary (*Rosmarinus officinalis* [family Lamiaceae]), an herb of economic and gustatory repute, is employed in traditional medicines in many countries. Rosemary contains **carnosic acid (CA) and carnosol (CS)**, abietane-type phenolic diterpenes, which account for most of its biological and pharmacological actions, although claims have also been made for contributions of another constituent, rosmarinic acid. This review focuses on the potential **applications of CA and CS for Alzheimer's disease (AD)**, Parkinson's disease (PD), and coronavirus disease 2019 (COVID-19), in part via inhibition of the NLRP3 inflammasome. **CA exerts antioxidant, anti-inflammatory, and neuroprotective effects via phase 2 enzyme induction** initiated by activation of the KEAP1/NRF2 transcriptional pathway, which in turn attenuates NLRP3 activation. In addition, we propose that CA-related compounds may serve as therapeutics against the brain-related after-effects of SARS-CoV-2 infection, termed "long-COVID." Because CA has been shown to not only act systemically but also to **penetrate the blood-brain barrier a**nd reach the brain parenchyma to exert neuroprotective effects, we discuss the evidence that CA or rosemary extracts containing CA may represent an effective countermeasure against both acute and chronic pathological events initiated by SARS-CoV-2 infection as well as other chronic **neurodegenerative diseases including AD** and PD.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7491497/ Therapeutic effects of rosemary (*Rosmarinus officinalis* L.) and its active constituents on nervous system disorders

Rosemary has **significant antimicrobial, anti-inflammatory, anti-oxidant, anti-apoptotic, anti-tumorigenic, antinociceptive, and neuroprotective properties**. Furthermore, it shows important clinical **effects on mood, learning, memory, pain, anxiety, and sleep.** The aim of the current work is to review the potential neuropharmacological effects of different rosemary extracts and its active constituents on nervous system disorders, their relevant mechanisms and its preclinical application to recall the therapeutic potential of this herb and more directions of future research projects. Recently, noticeable scientific interest is focused on the beneficial therapeutic properties of different kinds of rosemary extracts and its main constituents, **such as carnosic acid, carnosol, rosmarinic acid**, etc. A large number of studies either on animal models or cultured cells indicate the wide range medicinal properties of rosemary and its compounds such as **anti-inflammatory (8, 9), anti-oxidant (10), antinociceptive (11), neuroprotective (12), antidepressant, anti-hysteric, ameliorative of memory and mental fatigue**. Rosemary has also been classified as **"generally safe" or GRA**S (CFR182.10; 182.20) by the FDA in America. The neuronal dysfunction observed in disorders associated with aging such as Alzheimer's disease is mainly thought to be from oxidative stress. Free radicals are responsible for oxidative stress and aging (37). Aging and related diseases reveal when endogenous anti-oxidants are not able to counter free radicals damage to cells and cellular molecules (38). So, plant extracts with anti-oxidant ingredients might be a great help. In this regard a study by Farr *et al*. 2016, investigated the effects of **rosemary extract contained 60% or 10% carnosic acid and spearmint extract contained 5% rosmarinic acid, anti-oxidant-based components of rosemary for 90 days, on memory and learning in mice and their results showed the positive effects of these ingredients on memory improvement in a mouse model** (39). Song and colleagues, 2016, also confirmed the effect of rosemary extract containing **20% carnosic acid on the improvement of cognitive deficits in rats** and it might be mediated by **anti-oxidative (decreased ROS and increased superoxide dismutase (SOD)) and anti-inflammatory** (reduced protein level of TNF-α, IL-6, and IL-1β in hippocampus) properties of rosemary (42). The **inhalation of rosemary oil in 144 healthy volunteers induced subjective effects on mood as well as objective effects on cognitive performance (43). In another study, the aroma of rosemary oil improved performance in exam students by enhancing free radical scavenging activity and decreasing cortisol levels (44). In a study by Pengelly *et al*. 2012, rosemary powder (750 mg), the dose nearest to the normal culinary consumption, showed positive influences on the speed of memory, the time taken to effectively regain information from both episodic and working memory, on 28 older adults (mean age, 75 years) which is a useful predictor of cognitive function during aging (45).** These results point to the value of further studies on the effects of different doses of rosemary on memory and cognition over the longer period of time. Rasoolijazi and colleagues, 2015, evaluated the effect of rosemary extract on memory and anti-oxidant status of the hippocampus in middle-aged rats. They reported that prescription of rosemary extract (50,100 and 200 mg/kg/day, containing 40% carnosic acid, o.p.) for 12 weeks in middle-aged **rats increased spatial memory** and the activity of SOD and chloramphenicol acetyltransferase (CAT) anti-oxidant enzymes (49). In order to check the possible effects of stimulation through the sense of smell on cognitive function, another team applied a**romatherapy treatment on Alzheimer patients and proposed that aromatherapy might improve cognitive function,** especially in Alzheimer patients (61).

https://pubmed.ncbi.nlm.nih.gov/20377818/ Effect of aromatherapy on patients with Alzheimer's disease 2010

Aromatherapy consisted of the use of **rosemary** and lemon essential oils in the morning, and lavender and orange in the evening. All p**atients showed significant improvement** in personal orientation related to cognitive function on both the GBSS-J and TDAS after therapy. In particular, patients with AD showed significant improvement in total TDAS scores. In conclusion, we found **aromatherapy an efficacious non-pharmacological therapy for dementia**. Aromatherapy may have some potential for improving cognitive function, especially in AD patients.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6165352/ Antioxidant and Antimicrobial Properties of Rosemary (*Rosmarinus officinalis,* L.): A Review

Several studies have reported that rosemary extracts show biological bioactivities such as hepatoprotective, antifungal, insecticide, **antioxidant and antibacterial.** When a new rosemary extract is tested, the most important aspect to take into account is the method of extraction and the sort of solvent used, as this will affect the antioxidant properties. Considering the methods used, in general, the yield of rosemary extract indicated by various authors varies between 2% and 26% based on the raw material used. Among the most effective antioxidant constituents of rosemary, the cyclic diterpene diphenols, **carnosolic acid and carnosol** have been identified. Because **rosemary is a cheap, available, and a non-toxic herb, these considerations warrant the introduction of rosemary extracts or essential oils, with high phenolic compound contents, into the food industry**.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8772720/ Potential Therapeutic Use of the Rosemary Diterpene Carnosic Acid for Alzheimer's Disease, Parkinson's Disease, and Long-COVID through NRF2 Activation to Counteract the NLRP3 Inflammasome

Rosemary contains **carnosic acid (CA) and carnosol (CS)**, abietane-type phenolic diterpenes, which account for most of its biological and pharmacological actions, although claims have also been made for contributions of another constituent, **rosmarinic acid**.

Carnosic acid (CA), a diterpene found in the herb rosemary, is a safe pro-electrophilic drug (PED) that activates the KEAP1/NRF2 transcriptional pathway, leading to the **sustained induction of phase 2 antioxidant and anti-inflammatory enzymes**. CA exerts **neuroprotective and anti-inflammatory effects and has been proposed to be a potential therapeutic against chronic neurodegenerative disorders, such as AD and PD**, and acute and chronic effects of infections such as SARS-CoV-2.

https://www.nature.com/articles/s41598-019-45168-1 Rosmarinic acid suppresses Alzheimer's disease development by reducing amyloid β aggregation by increasing monoamine secretion

A new mechanism is revealed by which a polyphenol, **rosmarinic acid (RA), suppresses amyloid β (Aβ) accumulation in mice**. Here we examined the brains of mice (Alzheimer's disease model) using DNA microarray analysis and revealed that the dopamine (DA)-signaling pathway was enhanced in the group fed RA versus controls. In conclusion, **RA-initiated monoamine increase in the brain may beneficially act against AD**.

https://pubmed.ncbi.nlm.nih.gov/36034857/ *Rosmarinus officinalis* and Methylphenidate Exposure Improves Cognition and Depression and Regulates Anxiety-Like Behavior in $AlCl_3$-Induced Mouse Model of Alzheimer's Disease 2022

Rosmarinus officinalis, a perennial herb, has been potentially known to have **antioxidant and anti-inflammatory properties**. The present study investigated the potential effects of MPH and ***R. officinalis* in comparison with the standard drug, Donepezil,** on cognition, anxiety, and depression in the $AlCl_3$-induced mouse model of AD. The animals were divided into eight groups (n = 8, each). The results revealed that the **MPH- and *R. officinalis*-treated groups significantly improved memory impairment, whereas *R. officinalis* substantially reduced depression and anxiety as compared with other treatment groups**. MPH treatment induced an antidepressant effect and increased anxiety-like behavior. Moreover, the $AlCl_3$ exposure led to the formation of amyloid beta (Aβ) plaques in mice hippocampus; however, none of the tested drugs caused a significant reduction in amyloid burden at the selected doses. The present study suggested the **potential of *R. officinalis* to improve memory as well as neuropsychiatric symptoms in AD**. Although *R. officinalis* improved cognitive abilities, it did not reduce the amyloid plaque burden, which indicates that the memory-enhancing effects of *R. officinalis* are due to some alternate mechanism that needs to be explored further.

https://www.liebertpub.com/doi/full/10.1089/jmf.2011.0005 Short-Term Study on the Effects of Rosemary on Cognitive Function in an Elderly Population 2012

Rosemary (*Rosmarinus officinalis* L.) has traditional **reputations that justify investigation for a potential role in reducing widespread cognitive decline in the elderly**. A randomized, placebo-controlled, double-blinded, repeated-measures crossover study was conducted to investigate possible acute effects of dried rosemary leaf powder on cognitive performance. Twenty-eight older adults (mean age, 75 years) were tested using the Cognitive Drug Research computerized assessment system 1, 2.5, 4, and 6 hours following a placebo and four different doses of rosemary. Doses were counterbalanced, and there was a 7-day washout between visits. There was a biphasic dose-dependent effect in measures of speed of memory: **the lowest dose (750 mg) of rosemary had a statistically significant beneficial** effect compared with placebo (*P*=.01), **whereas the highest dose (6,000 mg) had a significant impairing effect** (*P*<.01). There were significant deleterious effects on other measures of cognitive performance, although these were less consistent. Speed of memory is a potentially useful predictor of cognitive function during aging. **The positive effect of the dose nearest normal culinary consumption points to the value of further work on effects of low doses over the longer term.**

https://pubmed.ncbi.nlm.nih.gov/24301255/ Rosmarinic acid prevents lipid peroxidation and increase in acetylcholinesterase activity in brain of streptozotocin-induced diabetic rats 2014

We investigated the efficacy of **rosmarinic acid (RA) in preventing lipid peroxidation and increased activity of acetylcholinesterase (AChE)** in the brain of streptozotocin-induced diabetic rats. The results demonstrated that the treatment with RA (10 mg/kg) significantly reduced the level of lipid peroxidation in hippocampus (28%), cortex (38%) and striatum (47%) of diabetic rats when compared with the control. In addition, it was found that hyperglycaemia caused significant increased in the activity of AChE in hippocampus (58%), cortex (46%) and striatum (30%) in comparison with the control. On the other hand, the treatment with RA reversed this effect to the level of control after 3 weeks. In conclusion, the present findings showed that treatment with **RA prevents the lipid peroxidation and consequently the increase in AChE activity** in diabetic rats, demonstrating that this compound can modulate cholinergic neurotransmission and prevent damage oxidative in brain in the diabetic state. Thus, we can suggest that RA could be a promising compound in the complementary therapy in diabetes.

https://www.tandfonline.com/doi/full/10.3109/14756366.2015.1135914 Rosmarinic acid inhibits some metabolic enzymes including glutathione *S*-transferase, lactoperoxidase, acetylcholinesterase, butyrylcholinesterase and carbonic anhydrase isoenzymes 2015

In the present study, the inhibition effects of rosmarinic acid on tumour-associated carbonic anhydrase IX and XII isoenzymes, **AChE**, BChE, LPO and GST enzymes were evaluated. Rosmarinic acid inhibited these enzymes with K_is in the range between micromolar to picomolar. The **best inhibitory effect of rosmarinic acid was observed against both AChE** and BChE.

Rutin polyphenol(quercetin-3-O-rutinoside) anti-inflammatory and antioxidant

-suspect Quercetin is better option

Supplement amount: 50-500mg with meal

https://pubmed.ncbi.nlm.nih.gov/26898570/ Rutin as a Natural Therapy for Alzheimer's Disease: Insights into its Mechanisms of Action 2016

Rutin (quercetin-3-O-rutinoside) is a multifunctional natural flavonoid glycoside with profound effects on the various cellular functions under pathological conditions. Due to the ability of rutin and/or its metabolites to **cross the blood brain barrier**, it has also been shown to **modify the cognitive and various behavioral symptoms of neurodegenerative diseases.** In this review, its therapeutic potential for Alzheimer's disease (AD) is evaluated through appraisal of current literatures relevant to the various cellular and molecular targets of the disease. Among the most relevant mechanisms involved are **effect on amyloid beta (Aβ)** processing, aggregation and action; alteration of the oxidant-antioxidant balance associated with neuronal cell loss; **removing the inflammatory component of neurodegeneration**, etc. The effect of rutin resulting from its physicochemical features related to effects like metal chelation and bioavailability are also discussed.
https://pubmed.ncbi.nlm.nih.gov/30820451/ Sodium rutin ameliorates Alzheimer's disease-like pathology by enhancing microglial amyloid-β clearance 2019
he accumulation of **aggregated amyloid-β (Aβ) in the brain** is the first critical step in the pathogenesis of Alzheimer's disease (AD), which also includes synaptic impairment, neuroinflammation, neuronal loss, and eventual cognitive defects. Emerging evidence suggests that impairment of Aβ phagocytosis and clearance is a common phenotype in late-onset AD. Rutin (quercetin-3-rutinoside) has long been investigated as a natural flavonoid with different biological functions in some pathological circumstances. **Sodium rutin (NaR), could promote Aβ clearance by increasing microglial by increasing the expression levels of phagocytosis-related receptors in microglia.** Moreover, NaR promotes a metabolic switch from anaerobic glycolysis to mitochondrial OXPHOS (oxidative phosphorylation), which could provide microglia with sufficient energy (ATP) for Aβ clearance. Thus, **NaR administration could attenuate neuroinflammation and enhance mitochondrial OXPHOS and microglia-mediated Aβ clearance, ameliorating synaptic plasticity impairment and eventually reversing spatial learning and memory deficits.** Our findings suggest that NaR is a potential therapeutic agent for AD.
https://pubmed.ncbi.nlm.nih.gov/24512768/ Rutin improves spatial memory in Alzheimer's disease transgenic mice by reducing Aβ oligomer level and attenuating oxidative stress and neuroinflammation 2014
Results demonstrated that orally administered rutin significantly attenuated memory deficits in AD transgenic mice, decreased oligomeric Aβ level, increased super oxide dismutase (SOD) activity and glutathione (GSH)/glutathione disulfide (GSSG) ratio, reduced GSSG and malondialdehyde (MDA) levels, downregulated microgliosis and astrocytosis, and decreased interleukin (IL)-1β and IL-6 levels in the brain. These results indicated that **rutin is a promising agent for AD treatment because of its antioxidant, anti-inflammatory, and reducing Aβ oligomer activities**.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8196535/ Rutin prevents tau pathology and neuroinflammation in a mouse model of Alzheimer's disease 2021
In combination with the previously reported therapeutic effects of rutin on Aβ pathology, **rutin is a promising drug candidate for AD treatment based its combinatorial targeting of tau and Aβ.**
https://pubmed.ncbi.nlm.nih.gov/16981462/ Comparative study on effects of rutin and quercetin on metabolism in osteoblast cells 2006
Results: Quercetin showed significant stimulatory effects on proliferation and mineralization in ROB cells, so it could promote bone formation. However, rutin could not imporve stimulation of bone formation because it increased proliferation and inhibited differentation and had no remarkable influence on ROB cells in vitro.

Saffon (*Crocus Sativus* L.) [Carotenoid: Crocin(polychroite), red powder made from saffron] (anti-AChE)

Supplement: 30mg/day (15mg twice daily) (Amazon $0.63/15mg)
https://pubmed.ncbi.nlm.nih.gov/33441068/ *Crocus Sativus* L. (Saffron) in Alzheimer's Disease Treatment: Bioactive Effects on Cognitive Impairment
Crocus sativus L. (saffron) appears to own **neuroprotective effects on cognitive impairment in patients with Alzheimer's disease (AD**). A total of 1477 studies published until November 2020 were identified during an initial phase, of which 24 met the inclusion criteria and were selected for this review. Seventeen in vitro and in vivo preclinical studies have described the efficacy of saffron on cognitive impairment in animal models of AD, highlighting that **crocin appears to be able to regulate glutamate levels, reduce oxidative stress, and modulate Aβ and tau protein aggregation.** Only four clinical studies have indicated that the effects of saffron on cognitive impairment were not different from those produced by donepezil and memantine and that it had a better safety profile.
https://pubmed.ncbi.nlm.nih.gov/20831681/ Saffron in the treatment of patients with mild to moderate Alzheimer's disease: a 16-week, randomized and placebo-controlled trial
Forty-six patients with probable AD were screened for a 16-week, double-blind study of parallel groups of patients with mild to moderate AD. Patients were randomly assigned to receive capsule saffron 30 mg/day (**15 mg twice per day**) (Group A) or capsule placebo (two capsules per day) for a 16-week study. **Results: After 16 weeks, saffron produced a significantly better outcome on cognitive function than placebo** (ADAS-cog: F=4·12, d.f.=1, P=0·04; CDR: F=4·12, d.f.=1, P=0·04).
https://pubmed.ncbi.nlm.nih.gov/25163440/ **Comparing the efficacy and safety of Crocus sativus L. with memantine** in patients with moderate to severe Alzheimer's disease: a double-blind randomized clinical trial
In this randomized double-blind parallel-group study, 68 patients with moderate to severe AD (Mini-Mental State Examination score of 8-14) received **memantine (20 mg/day) or saffron extract (30 mg/day) capsules for 12 months**. Participants were evaluated every month by Severe Cognitive Impairment Rating Scale (SCIRS) and Functional Assessment Staging (FAST) in addition to recording the probable adverse events. Results: **Both treatment groups showed similar outcomes** as demonstrated by insignificant effect for time × treatment interaction on SCIRS scores [F(2.95, 194.78) = 2.25, p = 0.08]. There was no significant difference between the two groups in the scores changes from baseline to the endpoint on SCIRS (p = 0.38) and FAST (p = 0.87). The frequency of adverse events was not significantly different between the two groups as well.
Conclusions: In addition to its favorable safety profile, 1-year administration of saffron extract capsules showed to be comparable with memantine in reducing cognitive decline in patients with moderate to severe AD. Confirmatory studies with larger sample sizes and longer follow-up periods are warranted.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4599112/ The effects of *Crocus sativus* (saffron) and its constituents on nervous system: A review
Saffron has been suggested to be effective in the treatment of a wide range of disorders including coronary artery diseases, hypertension, stomach disorders, dysmenorrhea and **learning and memory impairments**. In addition, different studies have indicated that saffron has **anti-inflammatory, anti-atherosclerotic, antigenotoxic and cytotoxic activities.** Administration of *C. sativus* and its constituents **increased glutamate and dopamine levels in the brain** in a dose-dependent manner. Our literature review showed that *C. sativus* and its components can be considered as promising agents in the treatment of nervous system disorders. **Crocin belongs to a group of natural carotenoid c**ommercially obtained from the dried stigma of *C. sativus*. It has a deep red color, forms crystals with a melting point of 186 ^{0}C and is **easily soluble in water**. Crocin is responsible for the color of saffron. **Crocins, accounting for almost 6–16% of saffron dry weight** (Gregory et al., 2005 ▶), are hydrophilic chemicals. α –crocin (crocin 1) is a carotenoid which comprises the majority of crocins found in saffron. It could be so **easily dissolved in water that is used as color additive** (Melnyk et al., 2010 ▶). Administration of **saffron 30 mg/day (15 mg twice daily) was found to be as effective as donepezil for treatment of mild-to-moderate AD in the subjects of 55 years and older** (Akhondzadeh et al., 2010a ▶). In addition, the frequency of saffron extract side effects was similar to those of donepezil except for vomiting, which occurred more frequently in the donepezil group (Akhondzadeh et al., 2010a ▶). In another study, 4**6 patients with mild-to-moderate AD were treated by saffron for 16 weeks. The results showed that the cognitive functions in saffron-treated group were significantly better than placebo** (Akhondzadeh et al. 2010b ▶).
https://www.researchgate.net/publication/309452537_Vitamin_E_Turmeric_and_Saffron_in_Treatment_of_Alzheimer's_Disease Vitamin E, Turmeric and Saffron in Treatment of Alzheimer's Disease
The paper provides a literature review on a few ongoing possible antioxidant therapy treatments for the disease. The paper highlights use of vitamin E, turmeric and saffron for an alternative antioxidant therapy approach. Clinical studies report their therapeutic abilities as protective agents for nerve cells against free radical damage, moderating acetylcholinesterase (AChE) activity and reducing neurodegeneration, which are found as key factors in Alzheimer's.
https://www.researchgate.net/publication/364735707_Studying_saffron_nanopowder_Crocus_Sativus_L_on_the_temporal_memory_of_rats_suffering_Parkinson's_disease Studying saffron nanopowder (Crocus Sativus L.) on the temporal memory of rats suffering Parkinson's disease
Pretreatment o**f saffron nano powder 5 and 10 nanograms for 5 days) reduced spatial memory significantly improved in parkinsonian rats (P>0.05). Saffron nanopowder is able to bring parameters related to spatial memory such as platform finding time in parkinsonian rats closer to the control group**.
https://pubmed.ncbi.nlm.nih.gov/31534969/ Crocin Improves Cognitive Behavior in Rats with Alzheimer's Disease by Regulating Endoplasmic Reticulum Stress and Apoptosis
A total of 48 healthy male SD rats were randomly divided into **control group, AD model group, resveratrol group, and crocin group, with 12 rats per group**. AD model was established by injecting A$\beta_{25\text{-}35}$ to the lateral ventricle of rats, and thereafter the rats were administrated with resveratrol (40 mg/kg), crocin (40 mg/kg), or PBS daily for 14 days. The learning and memory abilities of AD rats were significantly decreased, which was **significantly rescued by resveratrol and crocin.** The apoptotic cell number of Hippo and PFC neurons in AD model group was significantly higher than that in control group (P<0.01), while **resveratrol and crocin significantly decreased the apoptotic cell number in AD group** (P<0.01). Compared with the control group, the expression of Bcl2 in PFC and hippo of AD model group was significantly decreased (P<0.01), while those of Bax, Caspase3, GRP78, and CHOP were significantly increased (P<0.01). **Resveratrol and crocin could significantly reverse the expression of these proteins in AD rats** (P<0.05).
https://pubmed.ncbi.nlm.nih.gov/30569175/ Investigation of the neuroprotective effects of crocin via antioxidant activities in HT22 cells and in mice with Alzheimer's disease
In mice with AD induced by d-galactose and aluminum trichloride, **crocin substantially improved the cognition and memory abilities of the mice** as measured by their coordination of movement in an open field test, and reduced their escape time in the Morris water maze test compared with untreated mice. Biochemical analysis confirmed that crocin was able to reduce the Aβ1-42 content in the mouse brains, **increase the levels of glutathione peroxidase**, superoxide dismutase, acetylcholine and choline acetyltransferase, and reduce the levels of ROS and acetylcholinesterase in the serum, cerebral cortex and hypothalamus compared with untreated mice. Immunohistochemical analysis demonstrated that crocin reduced Aβ1-42 deposition in the hippocampus of the brains of treated mice compared with untreated mice. I**n conclusion, crocin demonstrates good prospects in the treatment of AD through the oxidative stress-associated apoptosis signaling pathway.**
https://pubmed.ncbi.nlm.nih.gov/34010562/ Evolving Role of Natural Products from Traditional Medicinal Herbs in the Treatment of Alzheimer's Disease 2019
Saffron is a crimson-colored spice that is widely cultivated in Iran, India, and Greece. In addition to its usage in the textile and cosmetic industries, saffron is also recommended for its medicinal properties [65,66]. The major component of saffron is safranal, a carboxaldehyde. In vitro and in vivo studies show that the phytochemicals present in saffron possess antioxidant, anti-inflammatory, and anti-amyloidogenic properties [64,65,66]. To assess the efficacy of saffron in the treatment of mild to moderate AD, researchers enrolled forty-six patients that were randomly assigned to receive **saffron 30 mg/day** or placebo. After sixteen weeks, **saffron produced a significantly better outcome on cognitive performance** (ADAS-cog and CDR scores) than placebo. The double-blind, placebo-controlled study suggested that **saffron was safe and effective in mild to moderate AD** [133].
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6201143/

daily intake of *Crocus sativus* L. (Iridaceae) dried extract **(30 mg/day) significantly improved cognitive capacity comparable to that observed in donepezil-treated patients** (Akhondzadeh et al., 2010).

https://pubmed.ncbi.nlm.nih.gov/19838862/ A 22-week, multicenter, randomized, double-blind controlled trial of Crocus sativus in the treatment of mild-to-moderate Alzheimer's disease 2009

Rationale: There is increasing evidence to suggest the possible efficacy of Crocus sativus (saffron) in the management of Alzheimer's disease (AD).

Objective: The purpose of the present investigation was to assess the efficacy of C. sativus in the treatment of patients with mild-to-moderate AD.

Methods: Fifty-four Persian-speaking adults 55 years of age or older who were living in the community were eligible to participate in a 22-week, double-blind study of parallel groups of patients with AD. The main efficacy measures were the change in the Alzheimer's Disease Assessment Scale-cognitive subscale and Clinical Dementia Rating Scale-Sums of Boxes scores compared with baseline. Adverse events (AEs) were systematically recorded. Participants were randomly assigned to receive a **capsule saffron 30 mg/day (15 mg twice per day)** or donepezil 10 mg/day (5 mg twice per day).

Results: **Saffron at this dose was found to be effective similar to donepezil in the treatment of mild-to-moderate AD after 22 weeks.** The frequency of AEs was similar between saffron extract and donepezil groups with the exception of vomiting, which occurred significantly more frequently in the donepezil group.

Conclusion: This phase II study provides preliminary evidence of a possible therapeutic effect of saffron extract in the treatment of patients with mild-to-moderate Alzheimer's disease. This trial is registered with the Iranian Clinical Trials Registry (IRCT138711051556N1).

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6941716/pdf/pnfs-24-363.pdf A Review of Potential Efficacy of Saffron (*Crocus sativus* L.) in Cognitive Dysfunction and Seizures 2019

To investigate the protective effects of saffron tea in a model of aflatoxin B1-induced neurotoxicity, Balb-c mice received saffron infusion (90 mg styles/200 mL, ad libitum access, 2 weeks) and were exposed to aflatoxin B1 (0.6 mg/kg/d, i.p., 4 days). **Saffron tea prevented cognitive defects** indicated using step-through passive avoidance tasks. **Improvements in memory retention were accompanied by restoring oxidative damage biomarkers including glutathion and lipid peroxidation** as well as **modulating the activities of acetylcholinesterase (AChE)** and monoamine oxidase (MAO) isoforms in the whole brain and cerebellum (Linardaki et al., 2017).

Loss of cholinergic neurons due to A ✓ and tau formation correlates with cognitive deficits (Hampel et al., 2018). In vitro enzymatic and molecular docking studies revealed that the inhibitory action of saffron extract and its **constituents (crocetin, dimethylcrocetin, and safranal) on acetylcholinesterase increases synaptic acetylcholine level**s (Geromichalos et al., 2012).

https://pubmed.ncbi.nlm.nih.gov/22655699/ Saffron as a source of **novel acetylcholinesterase inhibitors**: molecular docking and in vitro enzymatic studies 2012

Inhibitors of acetylcholine breakdown by acetylcholinesterase (AChE) constitute the main therapeutic modality for Alzheimer's disease. In the search for natural products with **inhibitory action on AChE**, this study investigated the activity of saffron extract and its constituents by in vitro enzymatic and molecular docking studies. Saffron has been used in traditional medicine against Alzheimer's disease. Saffron extract showed moderate AChE inhibitory activity (up to 30%), but IC(50) values of crocetin, dimethylcrocetin, and safranal were 96.33, 107.1, and 21.09 μM, respectively. Kinetic analysis showed mixed-type inhibition, which was verified by in silico docking studies. Safranal interacts only with the **binding site of the AChE,** but crocetin and dimethylcrocetin bind simultaneously to the catalytic and peripheral anionic sites. These results reinforce previous findings about the beneficial action of saffron against Alzheimer's disease and may be of value for the development of novel therapeutic agents based on carotenoid-based dual binding inhibitors.

https://pubmed.ncbi.nlm.nih.gov/23168242/ Investigation of the neuroprotective action of saffron (Crocus sativus L.) in aluminum-exposed adult mice through behavioral and neurobiochemical assessment 2013

Brain Al was determined by atomic absorption spectrometry, while, for the first time, crocetin, the main active metabolite of saffron, was determined in brain after intraperitoneal saffron administration by HPLC. Al intake caused memory impairment, **significant decrease of AChE** and BuChE activity, activation of brain MAO isoforms but inhibition of cerebellar MAO-B, **significant elevation of brain MDA and significant reduction of GSH content**. Although saffron extract co-administration **had no effect on cognitive performance of mice**, **it reversed significantly the Al-induced changes in MAO activity and the levels of MDA and GSH. AChE activity was further significantly decreased in cerebral tissues of Al+saffron group**. The biochemical changes support the neuroprotective potential of saffron under toxicity.

Salvia officinalis extract (Sage) (Salvia officinalis L. and Salvia lavandulaefolia L.)(anti-AchE) (also improves mood)

Supplement dosage: 300-600mg dried sage leaf (Amazon 453g sage leaf powder = $44.37) (also available in oil 2ml 3 times day)

https://scholar.google.com/scholar_lookup?journal=J+Clin+Pharm+Ther.&title=Salvia+officinalis+extract+in+the+treatment+of+patients+with+mild+to+moderate+Alzheimer%E2%80%99s+disease:+a+double+blind,+randomized+and+placebo-controlled+trial&author=S+Akhondzadeh&author=M+Noroozian&author=M+Mohammadi&author=S+Ohadinia&author=AH+Jamshidi&volume=28&issue=1&publication_year=2003&pages=53-59&pmid=12605619&doi=10.1046/j.1365-2710.2003.00463.x&

Salvia officinalis extract in the treatment of patients with mild to moderate Alzheimer's disease: a double blind, randomized and placebo-controlled trial

S. officinalis extract produced a **significant better outcome on cognitive functions than placebo** (ADAS-cog: F ¼4Æ77, d.f. ¼1, P ¼0Æ03) (CDR-SB: F ¼10Æ84, d.f. ¼1, P < 0Æ003). There were no significant differences in the two groups in terms of observed sideeffects except agitation that appears to be more frequent in the placebo group (P ¼0Æ09).

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5634728/ Pharmacological properties of Salvia officinalis and its components

Present review highlights the up-to-date information on the pharmacological findings that have been frequently reported for S. officinalis. These findings include anticancer, **anti-inflammatory,** antinociceptive, antioxidant, antimicrobial, antimutagenic, **antidementia**, hypoglycemic, and hypolipidemic effects.

Clinical trials confirm the results of animal studies and demonstrated that S. officinalis **enhances cognitive performance both in healthy participants and patients with cognitive impairment or dementia**.

https://onlinelibrary.wiley.com/doi/abs/10.1046/j.1365-2710.2003.00463.x Salvia officinalis extract in the treatment of patients with mild to moderate Alzheimer's disease: a double blind, randomized and placebo-controlled trial

Results: At 4 months, S. officinalis extract **produced a significant better outcome on cognitive functions than placebo** (ADAS-cog: F = 4·77, d.f. = 1, P = 0·03) (CDR-SB: F = 10·84, d.f. = 1, P < 0·003).

https://phcogj.com/article/1073 Evaluation of Traditional Herb Extract Salvia officinalis in Treatment of Alzheimers Disease

The elevated level of enzymes and decreased level of tissue antioxidant markers were observed in treatment comparative to piracetam treatment group. While 300 mg/kg extract significantly reduced the elevated levels of the enzymes and also significantly **increased the tissue antioxidant levels**, while **decreased the glutathione levels when compared with the control**. Conclusion: The histopathological study confirmed the recovery. The **herbal extract (150 and 300 mg/kg) has shown effectiveness against Alzheimer's disease.**

https://pubmed.ncbi.nlm.nih.gov/24836739/ Systematic review of clinical trials assessing pharmacological properties of Salvia species on memory, cognitive impairment and Alzheimer's disease

Six studies investigated on the effects of S. officinalis and S. lavandaeluaefolia on cognitive performance in healthy subjects. The two remaining were carried out to study the effects of sage on Azheimer's disease. **Our review shows that S. officinalis and S. lavandulaefolia exert beneficial effects by enhancing cognitive performance both in healthy subjects and patients with dementia or cognitive impairment and is safe for this indication.**

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7353372/ Chronic Supplementation with a Mix of Salvia officinalis and Salvia lavandulaefolia Improves Morris Water Maze Learning in Normal Adult C57Bl/6J Mice

Results: All Salvia groups had a significant effect on Y-maze markers on day 1 of administration. **Only the mix of two Salvia species (Cognivia™) demonstrated significant improvements in Morris water maze markers** at the end of administration.

https://www.alzheimersorganization.org/sage-and-alzheimers Better known by its common name, sage, Salvia Officinalis has several benefits for mental health. Salvia Officinalis has been shown to **reduce inflammation and act as an anti-oxidant.** Inflammation and oxidants are both believed to be significant contributors to the damage seen in Alzheimer's disease. **Salvia Officinalis inhibits cholinesterase. Cholinesterase is a harmful enzyme that contributes to the brain damage seen in Alzheimer's disease**. Several prescription medicines used to treat Alzheimer's(**donepezil/Aricept & rivastigmine/Exelon) are "cholinesterase inhibitors"** and work in a similar fashion to Salvia Officinalis, attempting to inhibit cholinesterase.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6201143/

A clinical trial with *Salvia officinalis* L. administered to patients with mild to moderate AD for a 16-weeks period led to improved cognitive performance (Perry et al., 2003). Of importance, *S. officinalis* also attenuated cognitive impairment in patients suffering from moderate to severe AD when used for up to 1 year. However, authors recognized that long-term efficacy, safety and administration strategy still require further investigation (Tune, 2001). *Salvia* spp. are particularly rich in terpenes, whose anti-AChE capacity has been assessed through enough pre-clinical tests, but are awaiting clinical trials (Rollinger et al., 2004; Kennedy and Scholey, 2006). On the other hand, a 22-weeks randomized, double-blind, multicenter trial, including 54 individuals suffering from mild-to-moderate AD, showed that daily intake of *Crocus sativus* L. (Iridaceae) dried extract (30 mg/day) significantly improved cognitive capacity comparable to that observed in donepezil-treated patients (Akhondzadeh et al., 2010).

https://pubmed.ncbi.nlm.nih.gov/16205785/ Effects of cholinesterase inhibiting sage (Salvia officinalis) on mood, anxiety and performance on a psychological stressor battery 2006

Salvia officinalis (sage) has previously been shown both to possess in vitro **cholinesterase inhibiting properties,** and to enhance mnemonic performance and improve mood in healthy young participants. In this double-blind, placebo-controlled, crossover study, 30 healthy participants attended the laboratory on three separate days, 7 days apart, receiving a different treatment in counterbalanced order on each occasion (**placebo, 300, 600 mg dried sage lea**f). On each day mood was assessed predose and at 1 and 4 h postdose. Each mood assessment comprised completion of Bond-Lader mood scales and the State Trait Anxiety Inventory (STAI) before and after 20 min performance of the Defined Intensity Stress Simulator (DISS) computerized multitasking battery. In a concomitant investigation, an extract of the sage leaf exhibited dose-dependent, in vitro **inhibition of acetylcholinesterase** and, to a greater extent, butyrylcholinesterase. **Both doses of sage led to improved ratings of mood in the absence of the stressor (that is, in pre-DISS mood scores) postdose, with the lower dose reducing anxiety and the higher dose increasing 'alertness', 'calmness' and 'contentedness' on the Bond-Lader mood scales.** The reduced anxiety effect following the lower dose was, however, abolished by performing the DISS, with the same dose also being associated with a reduction of alertness during performance. Task performance on the DISS battery was improved for the higher dose at both postdose sessions, but reduced for the lower dose at the later testing session. The **results confirm previous observations of the cholinesterase inhibiting properties of S. officinalis, and improved mood and cognitive performance following the administration of single doses to healthy young participants.**

https://pubmed.ncbi.nlm.nih.gov/15639154/ Positive modulation of mood and cognitive performance following administration of acute doses of Salvia lavandulaefolia essential oil to healthy young volunteers 2005
Members of the Sage family, such as Salvia officinalis and Salvia lavandulaefolia, have a **long history of use as memory-enhancing agents coupled with cholinergic properties** that may potentially be relevant to the amelioration of the cognitive deficits associated with Alzheimer's disease. The current study utilised a placebo-controlled, double-blind, balanced, crossover design in order to comprehensively assess any mood and cognition modulation by S. lavandulaefolia. Twenty-four participants received single doses of placebo, 25 microl and 50 microl of a standardised essential oil of S. lavandulaefolia in an order dictated by a Latin square. The results showed that administration of S. lavandulaefolia resulted in a **consistent improvement** for both the 25- and 50-microl dose on the 'Speed of Memory' factor. There was also an improvement on the 'Secondary Memory' factor for the 25-microl dose. **Mood was consistently enhanced**, with increases in self-rated 'alertness', 'calmness' and 'contentedness' following the 50-microl dose and elevated 'calmness' following 25 microl. These results represent further evidence that **Salvia is capable of acute modulation of mood and cognition in healthy young adults.** The data also suggest that previous reports of memory enhancement by Salvia may be due to more efficient retrieval of target material.
https://pubmed.ncbi.nlm.nih.gov/24413832/ Acetylcholinesterase inhibitory, antioxidant and phytochemical properties of selected medicinal plants of the Lamiaceae family 2014
The present study aimed to evaluate **acetylcholinesterase (AChE) inhibitory and antioxidant activities** of Lamiaceae medicinal plants growing wild in Croatia. Using Ellman's colorimetric assay all tested ethanolic extracts and their hydroxycinnamic acid constituents demonstrated in vitro AChE inhibitory properties in a dose dependent manner. The extracts of Mentha x piperita, M. longifolia, **Salvia officinalis**, Satureja montana, Teucrium arduini, T. chamaedrys, T. montanum, T. polium and Thymus vulgaris at **1 mg/mL showed strong inhibitory activity against AChE.** The antioxidant potential of the investigated Lamiaceae species was assessed by DPPH• scavenging activity and total antioxidant capacity assays, in comparison with hydroxycinnamic acids and trolox. The extracts differed greatly in their total hydroxycinnamic derivatives content, determined spectrophotometrically. **Rosmarinic acid** was found to be the predominant constituent in most of the investigated medicinal plants (by RP-HPLC) and had a **substantial influence on their AChE inhibitory and antioxidant properties,** with the exception of Teucrium species. These findings indicate that Lamiaceae species are a **rich source of various natural AChE inhibitors and antioxidants that could be useful in the prevention and treatment of Alzheimer's** and other related diseases.

SAMe (S-adenosyl-L-methionine) ademetionine in Europe

https://pubmed.ncbi.nlm.nih.gov/3350998/ S-adenosyl-L-methionine in the treatment of Alzheimer's disease 1988
To test these possibilities, we administered S-adenosyl-L-methionine (SAMe), an agent shown to increase membrane fluidity in animals, to patients with AD. Treatment with SAMe led to marked increases in membrane fluidity. However, it produced neither improvement nor worsening of symptoms. The results imply that **while SAMe may be useful for other conditions associated with altered membrane fluidity (such as normal aging), changing membrane fluidity per se is not likely to lead to marked changes in symptoms in AD.**
https://pubmed.ncbi.nlm.nih.gov/20595412/ S-adenosyl methionine **(SAMe) augmentation of serotonin reuptake** inhibitors for antidepressant nonresponders with major depressive disorder: a double-blind, randomized clinical trial 2010
Participants were 73 serotonin reuptake inhibitor (SRI) nonresponders with major depressive disorder enrolled in a 6-week, double-blind, randomized trial of adjunctive oral SAMe (target dose: 800 mg/twice daily). Patients continued to receive their SRI treatment at a stable dose throughout the 6-week trial. These preliminary results suggest that SAMe can be an effective, well-tolerated, and safe adjunctive treatment strategy for SRI nonresponders with major depressive disorder and warrant replication.
https://www.healthcentral.com/article/my-experience-taking-same-sadenosyllmethionine
"...a compound produced by our bodies from methionine. Methionine is an amino acid found in protein-rich foods. How does SAM-e work? With additional help from vitamin B-12 and folic acid, SAM-e relinquishes a methyl group from its composition to surrounding tissues and organs. Through this action, SAM-e helps with the maintenance of cell membranes, removal of toxic substances from the body, and the production of mood-enhancing neurotransmitters."
So it is recommended that you t**ake B-12 and folic acid to help facilitate the effects of SAMe**.

Serotonin **Precursors: 5-HTP, Tryptophan(band in 1989 due to batch)**

https://pubmed.ncbi.nlm.nih.gov/21870888/ Role of serotonin in Alzheimer's disease: a new therapeutic target? 2011
Mounting evidence accumulated over the past few years indicates that the neurotransmitter serotonin plays a significant role in cognition. As a drug target, **serotonin receptors have received notable attention** due in particular to the role of several serotonin-receptor subclasses in cognition and memory. The intimate anatomical and neurochemical association of the serotonergic system with brain areas that regulate memory and learning has directed current drug discovery programmes to focus on this system as a major therapeutic drug target.
https://pubmed.ncbi.nlm.nih.gov/30351155/ [Nutrition strategies that improve cognitive function
Low levels of serotonin have been linked to decreased learning, reasoning and memory.
https://pubmed.ncbi.nlm.nih.gov/35955097/ Chronic-Exposure Low-Frequency Magnetic Fields (Magnetotherapy and Magnetic Stimulation) Influence Serum Serotonin Concentrations in Patients with Low Back Pain-Clinical Observation Study 2022
Conclusions: **Magnetotherapy and magnetic stimulation, acting in a similar way, increase the concentration of serotonin**. Weak magnetic fields work similarly to the stronger ones used in TMS. It is possible to use them in the treatment of mental disorders or other diseases with low serotonin concentrations.
https://www.hopkinsmedicine.org/news/media/releases/brain_scan_study_adds_to_evidence_that_lower_brain_serotonin_levels_are_linked_to_dementia 2017
In a study looking at brain scans of people with mild loss of thought and memory ability, Johns Hopkins researchers report evidence of **lower levels of the serotonin** transporter — a natural brain chemical that regulates mood, sleep and appetite
https://www.sciencedirect.com/science/article/abs/pii/S0969996117301109?via%3Dihub Molecular imaging of serotonin degeneration in mild cognitive impairment 2017
Lower serotonin transporter binding is observed in mild cognitive impairment versus controls in cortical, limbic, sensory and motor regions.
https://www.sciencedirect.com/science/article/pii/S0301008220300551 Tryptophan metabolites modify brain Aβ peptide degradation: A role in Alzheimer's disease? 2020
Highlights
Brain Aβ peptide degradation and clearance are controlled by neprilysin.
Tryptophan metabolites modulate several metalloproteinases including neprilysin.
Tryptophan metabolites 5-HIAA or KYNA induce brain or neuronal neprilysin expression.
5-HIAA reduces brain Aβ peptides and improves memory deficits in a mouse model of AD.
KYNA induces neprilysin to prevent or counteract Aβ peptide-induced neurotoxicity.

Sesame Seed (Sesamin and sesamolin) -antioxidant **(compared with resveratrol)**

https://pubmed.ncbi.nlm.nih.gov/30118882/ Sesamin and sesamolin reduce amyloid-β toxicity in a transgenic Caenorhabditis elegans 2018
Alzheimer's disease (AD) is a devastating neurodegenerative disease characterized by β-amyloid (Aβ) plaques in the brain. At the present, there is no approved drug with a proven disease-modifying effect. Sesame seed (Sesame indicum) has long been known as a healthy food in Southeast Asian countries. **Sesame lignans obtained from sesame seed possess antioxidant property** that exhibit a variety of beneficial effects in various models. The objective of this study was to investigate the protective effects of sesame lignans including sesamin, sesamolin, and sesamol against Aβ toxicity in Caenorhabditis elegans (C. elegans) model of Aβ toxicity and to address whether these sesame lignans have a positive effect on lifespan extension. A transgenic C. elegans expressing human Aβ was used to investigate protective effects of sesame lignans against Aβ toxicity. **Sesamin and sesamolin significantly alleviated Aβ-induced paralysis.** The real-time PCR revealed that both sesamin and sesamolin did not affect the expression of Aβ transgene. However, we found that only **sesamin inhibited Aβ oligomerization**. These findings demonstrated that, among three sesame lignans tested, sesamin protected against Aβ toxicity by reducing toxic Aβ oligomers. **Sesamin and sesamolin also significantly improved Aβ-induced defect** in chemotaxis behavior and reversed the defect to normal. Moreover, sesamin prolonged median and mean lifespan of the wild type worm. On the other hand, sesamolin and sesamol failed to extend lifespan. These results offer valuable evidence for the future use of sesamin in the development of agents for the treatment of AD. It is also worth investigating the structure-activity relationship of lignan-related structures and their anti-Aβ toxicity activities in the future.

https://pubmed.ncbi.nlm.nih.gov/25472416/ The relationship of antioxidant components and antioxidant activity of sesame seed oil 2015
Although **sesame seed oil contains high levels of unsaturated fatty acids** and even a small amount of free fatty acids in its unrefined flavored form, it shows markedly greater stability than other dietary vegetable oils. The good stability of sesame seed oil against autoxidation has been ascribed not only to its **inherent lignans and tocopherols** but also to browning reaction products generated when sesame seeds are roasted. Also, there is a strong synergistic effect among these components. The lignans in sesame seed oil can be categorized into two types, i.e. inherent lignans (sesamin, sesamolin) and lignans mainly formed during the oil production process (sesamol, sesamolinol, etc.). The most abundant tocopherol in sesame seed oil is **γ-tocopherol.** This article reviews the antioxidant activities of lignans and tocopherols as well as the browning reaction and its products in sesame seed and/or its oil. It is concluded that the composition and structure of browning reaction products and their impacts on sesame ingredients need to be further studied to better explain the remaining mysteries of sesame oil.
https://wwww.unboundmedicine.com/medline/citation/30118882/Sesamin_and_sesamolin_reduce_amyloid_%CE%B2_toxicity_in_a_transgenic_Caenorhabditis_elegans_

Alzheimer's disease (AD) is a devastating neurodegenerative disease characterized by β-amyloid (Aβ) plaques in the brain. At the present, there is no approved drug with a proven disease-modifying effect. **Sesame seed (Sesame indicum) has long been known as a healthy food in Southeast Asian countries. Sesame lignans obtained from sesame seed possess antioxidant property that exhibit a variety of beneficial effects in various models.** These findings demonstrated that, among three sesame lignans tested, **sesamin protected against Aβ toxicity by reducing toxic Aβ oligomers. Sesamin and sesamolin also significantly improved Aβ-induced defect in chemotaxis behavior and reversed the defect to normal**. Moreover, sesamin prolonged median and mean lifespan of the wild type worm.
https://pubmed.ncbi.nlm.nih.gov/30929586/ Sesamin and sesamol attenuate H_2O_2-induced oxidative stress on human neuronal cells via the SIRT1-SIRT3-FOXO3a signaling pathway 2021
An imbalance of free radicals and antioxidant defense systems in physiological processes can result in protein/DNA damage, inflammation, and cellular apoptosis leading to neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD). **Sesamin and sesamol, compounds derived from sesame seeds and oil, have been reported to exert various pharmacological effects, especially antioxidant activity. Conclusion: The findings suggest that sesamin and sesamol are compounds that potentially protect neuronal cells against oxidative stress similar to that of the resveratrol, the reference compound.**

Shankhpushpi, Convolvulus pluricaulis (Cp), Acetylcholinesterase (AChE) inhibitor, anti-inflammatory, anti-oxidant

https://pubmed.ncbi.nlm.nih.gov/36225186/ Protective Mechanisms of Nootropic Herb Shankhpushpi (*Convolvulus pluricaulis*) against Dementia: Network Pharmacology and Computational Approach 2022
The findings indicate that scopoletin, kaempferol, **quercetin**, 4-hydroxycinnamic acid, and ayapanin are the main active constituents of CP which might **account for its memory enhancement and neuroprotective effects** and that target proteins such as PTGS1, PTGS2, NOS3, PPARG, ACHE, MAOA, MAOB, INSR, HMOX1, and TRKB could be druggable targets against dementia.
https://pubmed.ncbi.nlm.nih.gov/35878793/ Role of Shankhpushpi (Convolvulus pluricaulis) in neurological disorders: An umbrella review covering evidence from ethnopharmacology to clinical studies 2022
The crude herb and its metabolites have exhibited a wide range of in vitro and in vivo neuropharmacological effects, **including memory enhancement**, anxiolytic, tranquilizing, anti-depressant, anti-stress, **neurodegenerative, anti-inflammatory, anti-oxidant,** analgesic, sedative, anti-convulsant, and **Alzheimer's disease-reversing effects**.

https://pubmed.ncbi.nlm.nih.gov/34010562/ Evolving Role of Natural Products from Traditional Medicinal Herbs in the Treatment of Alzheimer's Disease 2019
Shankhpushpi, or Convolvulus pluricaulis (Cp), is used for **nerve regeneration and for improvement of memory** [68,70,91,136]. The major chemical components include triterpenoids, flavonol glycosides, anthocyanins, and steroids, which are responsible for Cp's nootropic and memory-enhancing properties [67,68,69,137].
https://pubmed.ncbi.nlm.nih.gov/35212831/ Novel insights on acetylcholinesterase inhibition by Convolvulus pluricaulis, scopolamine and their combination in zebrafish 2022
Acetylcholinesterase (AChE) inhibitors increase the retention of acetylcholine (ACh) in synapses. Although they alleviate cognitive deficits in Alzheimer's disease, their limited benefits warrant investigations of plant extracts with similar properties. We studied the anti-AChE activity of Convolvulus pluricaulis (CP) in a zebrafish model of cognitive impairment induced by scopolamine (SCOP). This suggested the ability of CP to mediate both competitive and non-competitive modes of inhibition. Surprisingly, SCOP showed AChE inhibition in larvae, possibly mediated via the choline-binding sites. CP + SCOP induced a concentration-dependent increase in AChE inhibition and ACh depletion. Abnormal motor responses were observed with ISOX, CP, ISOX + SCOP, and CP + SCOP, indicative of undesirable effects on the peripheral cholinergic system. Our study proposes the examination of CP, SCOP, and CP + SCOP as **potential AChE inhibitors for their ability to modulate cognitive deficits**.
https://pubmed.ncbi.nlm.nih.gov/35878793/ Role of Shankhpushpi (Convolvulus pluricaulis) in neurological disorders: An umbrella review covering evidence from ethnopharmacology to clinical studies 2022
The crude herb and its metabolites have exhibited a wide range of in vitro and in vivo neuropharmacological effects, including **memory enhancement, anxiolytic, tranquilizing, anti-depressant, anti-stress, neurodegenerative, anti-inflammatory, anti-oxidant, analgesic, sedative, anti-convulsant, and Alzheimer's disease-reversing effects.** Network pharmacology results indicate that compounds from C. pluricaulis interact with various proteins, neuro synapses, signaling pathways, and serotonergic synapse which plays a crucial role in neurotransmission, Alzheimer's disease, long-term depression, addictions to alcohol, cognitive disorders, psychological conditions, and increasing serotonin concentration in synapses.
https://pubmed.ncbi.nlm.nih.gov/32194410/ Phytochemical Profile, Pharmacological Attributes and Medicinal Properties of *Convolvulus prostratus* - A Cognitive Enhancer Herb for the Management of Neurodegenerative Etiologies 2020
This medicinal herb has been reported to contain many bioactive phytoconstituents, such as, alkaloid (convolamine), flavonoid (kaempferol) and phenolics (scopoletin, β-sitosterol and ceryl alcohol), that have been ascribed to the observed medicinal properties. Several research teams across the globe have highlighted the neuro-pharmacological profile of *C. prostratus*, wherein, the **neuroprotective, nootropic and neuro-modulatory roles** have been described. Besides, role of *C. prostratus* extracts in neurodegeneration has been well demonstrated. Despite of such elaborative preclinical pharmacological profile, detailed clinical investigations and mechanistic mode-of-action studies of this important herb are yet to be executed. The present review is attempted to showcase the phytochemical profile, pharmacological attributes and medicinal information of *C. prostratus*; with comprehensive research gap analysis. It is hoped that the scientific update on the ethnomedicinal aspects of this herb would thrive research propagation and development of the CNS phytopharmaceuticals, originated from *C. prostratus*.
https://pubmed.ncbi.nlm.nih.gov/29051039/ Convolvulus pluricaulis (Shankhapushpi) ameliorates human microtubule-associated protein tau (hMAPτ) induced neurotoxicity in Alzheimer's disease Drosophila model 2019
We studied the **neuroprotective effects of C. pluricaulis extract (aqueous) against human microtubule-associated protein tau (hMAPτ) i**nduced neurotoxicity in **Alzheimer's disease** (AD) Drosophila model. We analysed the lifespan, locomotor activity, τ protein level, reactive oxygen species (ROS), lipid peroxidation (LPO), catalase (CAT), superoxide dismutase (SOD) and **acetylcholinesterase (AChE)** activities in 10^{th}, 20^{th} and 30^{th} days old control (wild type), τ control tauopathy Drosophila reared on C. pluricaulis supplemented with regular food or regular standard food. C. pluricaulis significantly offsets hMAPτ induced early death and extends the lifespan and diminishes the level of τ protein in tauopathy Drosophila. C. pluricaulis also enhances the antioxidant enzyme activities and **ameliorates the τ-induced oxidative stress and restore the depleted AChE activity in the fly model. This study provides the first evidence that supplementation of C. pluricaulis along with the regular standard food ameliorate the neurotoxic effect of hMAPτ in AD Drosophila model and also reveals that it is a potent neuroprotective agent.**
https://pubmed.ncbi.nlm.nih.gov/19505562/ Neuroprotective role of Convolvulus pluricaulis on aluminium induced neurotoxicity in rat brain 2009
The potential of CPE to inhibit aluminium induced toxicity was compared with rivastigmine tartrate (1mg/kg), which was taken as standard. The potential of the extract to prevent aluminium-induced neurotoxicity was also reflected at the microscopic level, indicative of its neuroprotective effects.
Conclusion: Convolvulus pluricaulis possesses neuroprotective potential, thus validating its use in alleviating toxic effects of aluminium.

Shilajit (main ingredient fulvic acid)

https://pubmed.ncbi.nlm.nih.gov/22482077/ Shilajit: a natural phytocomplex with potential procognitive activity 2012
Shilajit is a natural substance found mainly in the Himalayas, formed for centuries by the gradual decomposition of certain plants by the action of microorganisms. It is a potent and very safe dietary supplement, restoring the energetic balance and potentially able to prevent several diseases. Recent investigations point to an interesting medical application toward the control of cognitive disorders associated with **aging, and cognitive stimulation**. Thus, **fulvic acid,** the main active principle, **blocks tau self-aggregation**, opening an avenue toward the study of Alzheimer's therapy. In essence, this is a nutraceutical product of demonstrated benefits for human health. Considering the expected impact of shilajit usage in the medical field, especially in the neurological sciences, more investigations at the basic biological level as well as clinical trials are necessary, in order to understand how organic molecules of shilajit and particularly fulvic acid, one of the active principles, and oligoelements act at both the molecular and cellular levels and in the whole organism
https://pubmed.ncbi.nlm.nih.gov/23131823/ Can nutraceuticals prevent Alzheimer's disease? Potential therapeutic role of a formulation containing shilajit and complex B vitamins 2012
We analyze the status of biological studies and present data of a clinical trial developed in patients with mild AD. **Studies suggest that shilajit and its active principle fulvic acid, as well as a formula of shilajit with B complex vitamins, emerge as novel nutraceutical with potential uses against this brain disorder.**
https://pubmed.ncbi.nlm.nih.gov/21785188/ Fulvic acid inhibits aggregation and promotes disassembly of tau fibrils associated with Alzheimer's disease 2011
Alzheimer's disease is a neurodegenerative disorder involving extracellular plaques (amyloid-β) and intracellular tangles of tau protein. Recently, **tangle formation has been identified as a major event involved in the neurodegenerative process**, due to the conversion of either soluble peptides or oligomers into insoluble filaments. At present, the current therapeutic strategies are aimed at natural phytocomplexes and polyphenolics compounds **able to either inhibit the formation of tau filaments or disaggregate them**. However, only a few polyphenolic molecules have emerged to prevent tau aggregation, and natural drugs targeting tau have not been approved yet. Fulvic acid, a humic substance, has several nutraceutical properties with potential activity to protect cognitive impairment. In this work **we provide evidence to show that the aggregation process of tau protein, forming paired helical filaments (PHFs) in vitro, is inhibited by fulvic acid** affecting the length of fibrils and their morphology. In addition, we investigated whether fulvic acid is capable of disassembling preformed PHFs. We show that the fulvic acid is an active compound against preformed fibrils affecting the whole structure by diminishing length of PHFs and probably acting at the hydrophobic level, as we observed by atomic force techniques. Thus, fulvic acid is likely to provide new insights in the development of potential treatments for Alzheimer's disease using natural products.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6151376/ Therapeutic Potential of Fulvic Acid in Chronic Inflammatory Diseases and Diabetes 2018
Several studies indicate that FvA can act as an anti-inflammatory by reducing the release of proinflammatory mediators from cells. First, Junek et al. show that FvA at 200 μg/mL **can reduce tumour necrosis factor alpha (TNF-α) expression** after exposure to the endotoxin Lipopolysaccharide (LPS) in differentiated human monocytes (U937) [14].

Slibinin – Milk Thistle **(combine with curcumin)**

Carduus marianum, Holy thistle, Lady's thistle, Mary thistle, Marian thistle, Silibinin, *Silybum marianum,* Silymarin

Supplement: 300-900mg/day

https://www.herbalgram.org/resources/expanded-commission-e/milk-thistle-fruit/

http://www.silibinin.org/milk-thistle.php Milk Thistle

Milk thistle is a popular herbal supplement that has been used for a couple of thousand of years now. It is used mainly to **treat liver conditions** naturally since early times. In fact, the earliest record of this plant being used for medicinal purposes dates back to the 4th century B.C. as evidenced by the writings of Theophrastus, a famous Greek philosopher during his time. This herbal supplement is derived from the flowering plant belonging to the genus Silybum Adans. and the daisy family Asteraceae. It is also known in a variety of names including silymarin, St. Mary thistle, Marian thistle, Holy thistle, Lady's thistle and Mediterranean thistle. This plant is common in North Africa and Asia Minor and in the southern parts of Europe and Russia.

https://pubmed.ncbi.nlm.nih.gov/23492971/ "Silymarin", a promising pharmacological agent for treatment of diseases 2011

In animal studies, silymarin has been reported to be nontoxic and symptom free with the **maximum oral doses of 2500 and 5000 mg/kg**.

Conclusion Silymarin possess wide range of in vitro and in vivo mechanisms, such as **antioxidant, anti- inflammatory, dose dependent anti-apoptotic** and modifying cell transporters. Hence, it can be used as a promising medication in complementary medicine.

https://pubmed.ncbi.nlm.nih.gov/36077922/ **Silymarin Modulates Microbiota in the Gut** to Improve the Health of Sow from Late Gestation to Lactation 2022

Inflammatory responses reduce milk production in lactating sows. Silymarin may modulate inflammatory reactions. Here, we aimed to verify whether dietary silymarin supplementation could alleviate inflammatory responses in lactating sows through microbiota change in the gut. We also investigated how silymarin impacts inflammatory response in lactating sows. Dietary silymarin supplementation tended to decrease (p = 0.06) somatic cell count in the colostrum of sows. Dietary silymarin supplementation reduced the gut bacterial community and the richness of the gut microbial community (p < 0.01) using 16S rRNA gene sequencing. It is suggested that **dietary silymarin supplementation in late gestation until lactation has anti-inflammatory effects in lactation sow, which could be associated with the modulation of gut microbiota.**

https://www.researchgate.net/publication/364965231_A_review_of_therapeutic_potentials_of_milk_thistle_Silybum_marianum_L_and_its_main_constituent_silymarin_on_cancer_and_their_related_patents 2022

Milk thistle and silymarin have been used as **complementary treatments for cancers such as skin, prostate, and colorectal cancers, as well as hepatoprotective agents**. Silymarin exerts a chemopreventive effect on reactivating cell death pathways by modulation of the antiapoptotic proteins and synergizing with agonists of death domain receptors. Based on the results of these patents, silymarin could be beneficial to oncology patients, especially for the treatment of the side effects of anticancer chemotherapeutics.

https://cancerchoices.org/therapy/milk-thistle/ - lots of good information and references

Silibinin, one of the flavonoids in milk thistle, has **demonstrated antioxidant and anti-inflammatory effects**.

Milk thistle may **prevent or treat liver dysfunction** in patients undergoing anticancer therapy.10 Silymarin has reduced liver toxicity associated with methotrexate (MTX) chemotherapy in children with acute lymphoblastic leukemia (ALL).11

It also would be safe to combine milk thistle as a standardized extract in supplement form (typically **300-900mg** is used daily to deal with elevated liver enzymes) because milk thistle does not appear to affect any CYP pathways. Milk thistle is a safe herb that supports liver cell regeneration. It is likely safe concurrent with chemotherapy

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6155865/ Silymarin/Silybin and Chronic Liver Disease: A Marriage of Many Years 2017

Silymarin is the extract of *Silybum marianum*, or milk thistle, and its major active compound is silybin, which has a **remarkable biological effect**. It is used in different **liver disorders**, particularly chronic liver diseases, cirrhosis and hepatocellular carcinoma, because of its **antioxidant, anti-inflammatory and antifibrotic power.** Indeed, the anti-oxidant and anti-inflammatory effect of silymarin is oriented towards the reduction of virus-related liver damages through inflammatory cascade softening and immune system modulation.

https://pubmed.ncbi.nlm.nih.gov/10586080/ Silymarin suppresses TNF-induced activation of NF-kappa B, c-Jun N-terminal kinase, and apoptosis 1995

Silymarin blocked TNF-induced activation of NF-kappa B in a dose- and time-dependent manner. **Silymarin also inhibited the TNF-induced activation** of mitogen-activated protein kinase kinase and c-Jun N-terminal kinase and abrogated TNF-induced cytotoxicity and caspase activation. Silymarin suppressed the TNF-induced production of reactive oxygen intermediates and lipid peroxidation. Overall, the inhibition of activation of NF-kappa B and the kinases may provide in part the molecular basis for the anticarcinogenic and anti-inflammatory effects of silymarin, and its effects on caspases may explain its role in cytoprotection.

Alzheimer's

https://pubmed.ncbi.nlm.nih.gov/21185897/ Silibinin: a novel inhibitor of Aβ aggregation 2011

Alzheimer's disease (AD) is characterized by the abnormal aggregation of amyloid β peptide (Aβ) into extracellular fibrillar deposits known as amyloid plaque. Inhibition of Aβ aggregation is therefore viewed as a potential method to halt or slow the progression of AD. It is reported that silibinin (silybin), a flavonoid derived from the herb milk thistle (Silybum marianum), attenuates cognitive deficits induced by Aβ25-35 peptide and methamphetamine. However, it remains unclear whether silibinin interacts with Aβ peptide directly and decreases Aβ peptide-induced neurotoxicity. In the present study, we identified, through employing a ThT assay and electron microscopic imaging that silibinin also appears to act as a novel inhibitor of Aβ aggregation and this effect showed dose-dependency. We also show that silibinin prevented SH-SY5Y cells from injuries caused by Aβ(1-42)-induced oxidative stress by decreasing H(2)O(2) production in Aβ(1-42)-stressed neurons. Taken together, these results indicate that silibinin may be a novel therapeutic agent for the treatment of AD.

https://nutritionandhealing.com/2017/05/17/milk-thistle-reduces-alzheimers-memory-loss/

The study out of China found that the plant compound silibinin — a flavonoid derived from milk thistle — **can suppress many of the abnormal brain processes** associated with Alzheimer's and even REVERSE memory loss. We still have a lot to learn about what causes Alzheimer's, but we do know that the disease is linked to the formation of brain "plaques" and "tangles" made of excess proteins called beta amyloid. In the study, rats were injected with beta amyloid to mimic Alzheimer's. But after they were given **silibinin, the rats improved significantly on memory tests like running through a maze and recognizing objects.**

https://www.alzdiscovery.org/uploads/cognitive_vitality_media/Silymarin-Cognitive-Vitality-For-Researchers.pdf Silymarin (Milk thistle) 2020

Some evidence suggests that silymarin may be effective for liver diseases or metabolic conditions. However, evidence is weak for Alzheimer's disease, and many supplements have high levels of mycotoxins.

200-600mg/day, 6 hour half life

https://pubmed.ncbi.nlm.nih.gov/10325444/ Aminotransferase levels and silymarin in de novo tacrine-treated patients with Alzheimer's disease **1999 (old and focus on tacrine efficacy)**

Silymarin is a well-known hepatoprotective agent. Tacrine, the first drug marketed for Alzheimer's disease (AD), induces an elevation of serum liver transaminase prohibiting an effective dosage in many patients. This 12-week randomised, double-blind, placebo-controlled study was undertaken to evaluate the ability of silymarin to antagonise or prevent the hepatotoxic effects of tacrine and to analyse its action on tacrine efficacy and tolerability. **Findings:** 222 patients were recruited and received silymarin and tacrine (110 patients) or placebo and tacrine (112 patients). 28 patients dropped out; 217 were included in the intent-to-treat analysis. **No statistical difference** was observed between the two groups for serum ALAT (p = 0.39). Fewer patients had ALAT levels >5 ULN in the silymarin group (-33.3%). Side effects and notably gastrointestinal disorders were much less frequent in the silymarin group. **Cognitive performance remained unchanged in both groups**.

https://pubmed.ncbi.nlm.nih.gov/28735062/ Silibinin ameliorates anxiety/depression-like behaviors in amyloid β-treated rats by upregulating BDNF/TrkB pathway and attenuating autophagy in hippocampus 2017

Depression is one of the most frequent psychiatric disorders of Alzheimer's disease (AD). Depression and anxiety are associated with increased risk of developing AD. Silibinin, a flavonoid derived from milk thistle (Silybum marianum), has been used as a hepato-protectant in the clinical treatment of liver diseases. In this study, the effect of silibinin on Aβ-induced anxiety/depression-like behaviors in rats was investigated. Silibinin significantly attenuated anxiety/depression-like behaviors caused by Aβ1-42-treatment as shown in tail suspension test (TST), elevated plus maze (EPM) and forced swimming tests (FST). Moreover, silibinin was able to attenuate the neuronal damage in the hippocampus of Aβ1-42-injected rats. Silibinin-treatment up-regulated the function through BDNF/TrkB pathway and attenuated autophagy in the hippocampus. **Our study provides a new insight into the protective effects of silibinin in the treatment of anxiety/depression.**

https://pubmed.ncbi.nlm.nih.gov/28004303/ Silibinin ameliorates $A\beta_{25-35}$-induced memory deficits in rats by modulating autophagy and attenuating neuroinflammation as well as oxidative stress 2017

Alzheimer's disease (AD) is a progressive, neurodegenerative disease. **Accumulating evidence suggests that inflammatory response, oxidative stress and autophagy are involved in amyloid β (Aβ)-induced memory deficits.** Silibinin (silybin), a flavonoid derived from the herb milk thistle, is well known for its hepatoprotective activities. In this study, we investigated the neuroprotective effect of silibinin on $A\beta_{25-35}$-injected rats. **Results demonstrated that silibinin significantly attenuated $A\beta_{25-35}$-induced memory deficits in Morris water maze** and novel object-recognition tests. Silibinin exerted anxiolytic effect in $A\beta_{25-35}$-injected rats as determined in elevated plus maze test. **Silibinin attenuated the inflammatory responses, increased glutathione (GSH) levels** and decreased malondialdehyde (MDA) levels, and upregulated autophagy levels in the $A\beta_{25-35}$-injected rats. In conclusion, **silibinin is a potential candidate for AD treatment because of its anti-inflammatory, antioxidant and autophagy regulating activities.**

https://www.sciencedirect.com/science/article/pii/S0278691509003664 Effect of silymarin on biochemical parameters of oxidative stress in aged and young rat brain 2009

Rats were treated with SM at doses of 200 and 400 mg/kg/day (SM200 and SM400). The LPO analyzed through FOX was increased in the hippocampus of aged animals treated with SM400, but in the cortex of young and aged, the highest dose of SM decreased LPO analyzed through TBARS. Both doses have seemed most effective in the reduction of oxidized proteins in aged brain. These results suggest that SM may contribute to the prevention of aged-related and pathological degenerative processes in the brain.

https://www.sciencedirect.com/science/article/abs/pii/S0944711306000419 Protective effect of silymarin on oxidative stress in rat brain 2007

Male albino Wistar rats were treated with SM (200 mg/kg/die orally) for three days, or with APAP single oral administration (3 g/kg) or with SM (200 mg/kg/die orally) for 3 days and APAP single oral administration (3 g/kg) at third day. Successively the following parameters were measured: reduced and oxidized glutathione (GSH and GSSG), ascorbic acid (AA), enzymatic activity variations of superoxide dismutase (SOD) and malondialdehyde levels (MDA).

Our results showed a **significant decrease of GSH levels**, AA levels and SOD activity and an increase of MDA and GSSG levels after APAP administration. After SM administration GSH and AA significantly increase and SOD activity was significantly enhanced. In the SM+APAP group, GSH values significantly increase and the others parameters remained unchanged respect to control values. These results **suggest that SM may to protect the SNC by oxidative damage for its ability to prevent lipid peroxidation and replenishing the GSH levels.**
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9372765/pdf/25789430-2022-micropub.biology.000617.pdf Curcumin, but not its degradation products, in combination with silibinin is primarily responsible for the inhibition of colon cancer cell proliferation 2022
In the present study we showed that the curcumin degradation products in combination with silibinin did not inhibit cell growth compared to the curcumin plus silibinin combination. Our result supports our previous study that **curcumin and silibinin in combination inhibit cell growth significantly** (Montgomery et al. 2016). Among the curcumin degraded products, either singly or in combination with silibinin, none of them showed significant inhibition of cell growth compared to control.
We have published data showing that a combination of curcumin and silymarin (CS), elicited synergistically enhanced anticancer activity in vitro (Montgomery et al. 2016). In the present study, we showed it is curcumin but not the curcumin degradation products that elicit the combination anticancer effects with silibinin. Our future studies will be focused on the mechanism by which curcumin plus silibinin causes the anticancer effects using in vitro and in vivo systems

St John's Wort (Hypericum perforatum)

https://pubmed.ncbi.nlm.nih.gov/24156265/ Reduced Alzheimer's disease pathology by St. John's Wort treatment is independent of hyperforin and facilitated by ABCC1 and microglia activation in mice 2013
These data (i) support the significant beneficial **potential of SJW extracts on AD proteopathy**, and (ii) demonstrate for the first time that **hyperforin concentration does not necessarily correlate with their therapeutic effects**. Hence, by activating ABC transporters, specific extracts of **SJW may be used to treat AD and other diseases involving peptide accumulation and cognition impairment. We propose that the anti-depressant and anti-dementia effects of these hyperforin-reduced phytoextracts could be combined for treatment of the elderly, with a concomitant reduction in deleterious hyperforin-related side effects.**

https://pubmed.ncbi.nlm.nih.gov/19657198/ St. John's wort - an overview 2009
Hypericum extracts have consistently shown activity in pharmacological models related to antidepressant effects. Randomized clinical trials show that Hypericum extracts are more effective than placebo and similarly **effective as standard antidepressants while having better tolerability in the acute treatment of major depressive episodes**. The most important risk associated with Hypericum extracts are interactions with other drugs. Therefore, **physicians need to be informed whether their patients take St. John's wort products**. If the risk of interactions is adequately taken into account, high quality Hypericum extracts are an effective and safe tool in the hand of qualified health profession-als in primary care.
https://wwww.unboundmedicine.com/medline/citation/23701205/St__John's_Wort_reduces_beta_amyloid_accumulation_in_a_double_transgenic_Alzheimer's_disease_mouse_model_role_of_P_glycoprotein_ 2014
Mice receiving St. John's Wort extract showed (i) **significant reductions of parenchymal beta-amyloid 1-40 and 1-42 accumulation**; and (ii) moderate, but statistically significant increases in cerebrovascular P-glycoprotein expression. Thus, the induction of cerebrovascular P-glycoprotein may be a **novel therapeutic strategy to protect the brain from beta-amyloid accumulation, and thereby impede the progression of Alzheimer's disease.**

Sugar – Glycemic Index

https://pubmed.ncbi.nlm.nih.gov/30351155/ [Nutrition strategies that improve cognitive function
Cognitive capacity can be influenced by components of the diet. **Low glycemic index foods seem to improve attention, memory and functional capacity**, while those rich in simple sugars are associated with difficulty in concentration and attention. The brain needs a continuous supply of amino acids for the synthesis of neurotransmitters, especially serotonin and catecholamines.
https://pubmed.ncbi.nlm.nih.gov/27933449/ Clearing the fog: a review of the effects of dietary omega-3 fatty acids and added sugars on chemotherapy-induced cognitive deficits
We propose that a diet rich in long-chain, marine-derived omega-3 fatty acids and **low in added sugars may be an ideal pattern for preventing or alleviating neuroinflammation** and oxidative stress, thereby protecting neurons from the toxic effects of chemotherapy.
https://pubmed.ncbi.nlm.nih.gov/27116240/ Nutrient intake, nutritional status, and cognitive function with aging
With respect to nutrients, there is evidence to support the critical role of several B vitamins in particular, but also of vitamin D, antioxidant vitamins (including vitamin E), and omega-3 fatty acids, which are preferentially taken up by brain tissue. On the other hand, high intakes of nutrients that contribute to hypertension, atherosclerosis, and **poor glycemic control may have negative effects on cognition** through these conditions. Collectively, the evidence suggests that considerable slowing and reduction of cognitive decline may be achieved by following a healthy dietary pattern, which limits intake of added sugars, while maximizing intakes of fish, fruits, vegetables, nuts, and seeds.

Sulforaphane **isothiocyanate (sulphur containing compounds) present in cruciferous fruits in inactive form Glucoraphanin**

Food Sources: Broccoli(raw), Brussels Sprouts, Cabbage, Cauliflower, Kale, Watercress, Turnips, Radish
-Supplement from amazon 70mg worth in Broccole Sprout extract 1000mg (optimal dose unknown)
-Sulforaphane is sometimes also called sulforafan, or 1-Isothiocyanato-4-(methylsulfinyl) butane.
https://www.verywellhealth.com/sulforaphane-5083128 What Is Sulforaphane?
Sulforaphane in **cruciferous vegetables occurs in a stored, inactive form as glucoraphanin**. Glucoraphanin is converted to sulforaphane's active form by the enzyme myrosinase. This activation is triggered by chopping or chewing but can also be produced in the gut by certain bacteria.1
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5785894/ Chronic diseases, inflammation, and spices: how are they linked? 2018
Sulforaphane is an isothiocyanate (sulphur containing compounds) distributed amongst cruciferous vegetables including mustard. Studies have shown that sulphoraphane possesses anti-cancer and cardioprotective activities [155]. It elicits protection against cardiovascular diseases via activation of Nrf2 [155]. Studies also reported that sulforaphane represents a promising agent for treatment of chronic diseases such as AD, bladder cancer, colorectal cancer, diabetes, and lung cancer [156–158] (Table 2). Another study has also suggested that sulforaphane **inhibit pro-inflammatory signaling through inhibition of NF-κB pathway** [159]
https://pubmed.ncbi.nlm.nih.gov/26827637/ Sulforaphane exerts its anti-inflammatory effect against amyloid-β peptide via STAT-1 dephosphorylation and activation of Nrf2/HO-1 cascade in human THP-1 macrophages 2016
The anti-inflammatory effect of sulforaphane on Aβ1-42-induced IL-1β production was diminished by small interfering RNA-mediated knockdown of Nrf2 or HO-1. Moreover, sulforaphane significantly attenuated the levels of microRNA-146a, which is selectively upregulated in the temporal cortex and hippocampus of AD brains. The aforementioned effects of sulforaphane were replicated by the tyrosine kinase inhibitor, herbimycin A, and Nrf2 activator. These results indicate that signal transducer and activator of transcription-1 dephosphorylation, HO-1 and its upstream effector, Nrf2, play a pivotal role in triggering an anti-inflammatory signaling cascade of sulforaphane that results in **decreases of IL-1β release a**nd microRNA-146a production in Aβ1-42-stimulated human microglia-like cells. These findings **suggest that the phytochemical sulforaphane has a potential application in AD therapeutics.**
https://pubmed.ncbi.nlm.nih.gov/33805772/ Pre-Clinical Neuroprotective Evidences and Plausible Mechanisms of Sulforaphane in Alzheimer's Disease 2021
Sulforaphane, a potent dietary bioactive agent obtainable from cruciferous vegetables, has been extensively studied for its effects in disease prevention and therapy. **Sulforaphane potently induces transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2)-**mediated expression of **detoxification, anti-oxidation,** and immune system-modulating enzymes, and possibly acts as an anti-carcinogenic agent. The increase in pre-clinical evidences consistently suggests that sulforaphane has a multi-faceted neuroprotective effect on AD pathophysiology. The **anti-AD-like evidence of sulforaphane seen in cells and animals indicates the need to pursue sulforaphane research for relevant biomarkers in AD pre-symptomatic populations.**
https://pubmed.ncbi.nlm.nih.gov/29382536/ Epigenetic modification of Nrf2 by sulforaphane increases the antioxidative and anti-inflammatory capacity in a cellular model of Alzheimer's disease 2018
Sulforaphane was **reported to exert neuroprotective effects via upregulating expression of nuclear factor erythroid 2-related factor 2 (Nrf2) and has received increasing attention as an alternative candidate for treatment of Alzheimer's disease (AD).** However, the mechanism to account for Nrf2 upregulation by sulforaphane in AD remains unknown. Herein, we found that sulforaphane upregulated Nrf2 expression and promoted Nrf2 nuclear translocation via decreasing DNA methylation levels of the Nrf2 promoter in mouse neuroblastoma N2a cells stably expressing human Swedish mutant amyloid precursor protein (N2a/APPswe cells), a cellular model of AD. Furthermore, sulforaphane (1.25 and 2.5 μM) decreased the levels of amyloid β 1-40 ($A\beta_{1-40}$) (21.7% and 33.4% decrease for intracellular $A\beta_{1-40}$; 22.0% and 30.2% decrease in culture medium), $A\beta_{1-42}$ (26.4% and 42.9% decrease for intracellular $A\beta_{1-42}$; 25.8% and 43.8% decrease in culture medium), reactive oxygen species (15.0% and 28.5% decrease), and malondialdehyde (MDA) (34.4% and 39.2% decrease) and increased superoxide dismutase (SOD) (60.0% and 89.3% increase) activity in N2a/APPswe cells. Sulforaphane also decreased the levels of pro-inflammatory cytokines interleukin 1β (IL-1β) (16.5% and 33.6% decrease) and IL-6 (15.6% and 26.1% decrease) and reduced phosphorylated nuclear factor-κB (NF-κB) p65 (19.2% and 32.2% decrease), cyclooxygenase-2 (COX-2) (20.5% and 28.6% decrease), and iNOS protein (40.2% and 54.7% decrease) expression levels in N2a/APPswe cells. Our study suggested that **sulforaphane upregulated the expression of Nrf2 and promoted the nuclear translocation of Nrf2 by decreasing DNA demethylation levels of the Nrf2 promoter, thus leading to antioxidative and anti-inflammatory effects in a cellular model of AD.**
https://pubmed.ncbi.nlm.nih.gov/30941620/ Sulforaphane - role in aging and neurodegeneration 2019
In the last several years, numerous molecules derived from plants and vegetables have been tested for their **antioxidant, anti-inflammatory, and anti-aging properties**. One of them is sulforaphane (SFN), an isothiocyanate present in cruciferous vegetables. SFN activates the antioxidant and anti-inflammatory responses by inducing Nrf2 pathway and inhibiting NF-κB. It also has an epigenetic

effect by inhibiting HDAC and DNA methyltransferases and modifies mitochondrial dynamics. Moreover, **SFN preserves proteome homeostasis** (proteostasis) by activating the proteasome, which has been shown to **lead to increased cellular lifespan and prevent neurodegeneration**. In this review, we describe some of the molecular and physical characteristics of SFN, its mechanisms of action, and the effects that SFN treatment induces in order to discuss its relevance as a **"miraculous" drug to prevent aging and neurodegeneration.**
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5410605/ Beneficial Effects of Sulforaphane Treatment in Alzheimer's Disease May Be Mediated through Reduced HDAC1/3 and Increased P75NTR Expression 2017
We found that **sulforaphane ameliorated behavioral cognitive impairments and attenuated brain Aβ burden in Alzheimer's disease model mice**. In conclusion, this study demonstrates that sulforaphane can ameliorate neurobehavioral deficits and reduce the Aβ burden in Alzheimer's disease model mice, and the mechanism underlying these effects may be associated with up-regulation of p75 neurotrophin receptor mediated, apparently at least in part, via reducing the expression of histone deacetylase1 and 3.
https://www.thermofisher.com/blog/proteomics/alzheimers-disease-sulforaphane-inhibits-peptide-aggregation/ Alzheimer's Disease: Sulforaphane Inhibits Peptide Aggregation 2015
Two distinctive features of Alzheimer's disease are neurofibrillary tangles and amyloid plaques. As the disease develops, soluble amyloid beta 1-40 peptides (Aβ) begin to aggregate in the brain, inducing toxicity via an as-yet-undetermined mechanism. Researchers have previously observed that **several naturally occurring molecules can inhibit Aβ toxicity.**
One compound with the potential to do this is sulforaphane (SFN), an isothiocyanate found in cruciferous vegetables that boasts anticancer, antidiabetic, antioxidant and antimicrobial properties. Recent studies have revealed that SFN plays neuropreventive roles in several conditions, including Alzheimer's disease, stroke, traumatic brain injury and Parkinson's disease.
https://pubmed.ncbi.nlm.nih.gov/29614663/ Sulforaphane Inhibits the Generation of Amyloid-β Oligomer and Promotes Spatial Learning and Memory in Alzheimer's Disease (PS1V97L) Transgenic Mice 2018
Pretreating cultured cortical neurons with sulforaphane also protected against neuronal injury caused by Aβ oligomers in vitro. These findings suggest that **sulforaphane may be a potential compound that can inhibit Aβ oligomer production in AD.**
https://pubmed.ncbi.nlm.nih.gov/33207780/ Efficacy of Sulforaphane in Neurodegenerative Diseases 2020
Sulforaphane (SFN) is a phytocompound belonging to the isothiocyanate family. Although it was also found in seeds and mature plants, SFN is mainly present in sprouts of **many cruciferous vegetables, including cabbage, broccoli, cauliflower, and Brussels sprouts**. SFN is produced by the conversion of glucoraphanin through the enzyme myrosinase, which leads to the formation of this isothiocyanate. SFN is especially characterized by antioxidant, anti-inflammatory, and anti-apoptotic properties, and for this reason, it aroused the interest of researchers. The aim of this review is to summarize the experimental studies present on Pubmed that report the efficacy of SFN in the **treatment of neurodegenerative disease, including Alzheimer's disease (AD)**, Parkinson's disease (PD), and multiple sclerosis (MS). Therefore, thanks to its beneficial effects, **SFN could be useful as a supplement to counteracting neurodegenerative diseases.**
https://pubmed.ncbi.nlm.nih.gov/29714053/ Sulforaphane Upregulates the Heat Shock Protein Co-Chaperone CHIP and Clears Amyloid-β and Tau in a Mouse Model of Alzheimer's Disease 2018
Conclusion: These results demonstrate that **sulforaphane treatment upregulates CHIP and has the potential to decrease the accumulation of Aβ and tau in patients with AD.**

Sweeteners, Artificial

https://pubmed.ncbi.nlm.nih.gov/28428346/ Sugar- and Artificially Sweetened Beverages and the Risks of Incident Stroke and Dementia: A Prospective Cohort Study 2017
We studied 2888 participants. When comparing daily cumulative intake to 0 per week (reference), **the hazard ratios were 2.96** (95% confidence interval, 1.26-6.97) for ischemic stroke and 2.89 (95% confidence interval, 1.18-7.07) for Alzheimer's disease. Sugar-sweetened beverages were not associated with stroke or dementia.
Conclusions: Artificially sweetened soft drink consumption was associated with a higher risk of stroke and dementia.
https://www.theguardian.com/society/2017/apr/21/link-dementia-stroke-diet-drinks-artificial-sweeteners-study Should link between dementia and artificial sweeteners be taken with a pinch of salt?
It's a shocking conclusion. But the **first reason to pause is that the study found no such risk in people who drank standard sugary lemonades and colas.**
When it came to dementia, **the link with diet drinks that researchers saw disappeared once they took some elements of the health of the people in the study into account**. "When the researchers accounted for other risk factors for Alzheimer's, such as risk genes, diabetes, heart disease, cholesterol levels and weight, this significant association was lost, suggesting that these drinks are not the whole story," said Dr Rosa Sancho, head of research at Alzheimer's Research UK. The researchers point to it themselves: "We are unable to determine whether artificially sweetened soft drink intake increased the risk of incident dementia through diabetes mellitus **or whether people with diabetes mellitus were simply more likely to consume diet beverages,**" they write. But they call for more research and others will support them in that.
https://naturalon.com/dangerous-link-found-between-aspartame-and-alzheimers/view-all/ Dangerous Link Found Between **Aspartame** and Alzheimer's
Even recently, studies have been confirming a long held suspicion that artificial sweeteners are behind the development of Alzheimer's disease. The main mechanism of harm seems to be methanol toxicity, a frequently ignored problem associated with aspartame. A recently published, two part article states what many researchers have been saying for years; that methanol acts very differently in animals than in humans.
Mice that were fed methanol showed partial Alzheimer's symptoms, while rhesus monkeys that were fed a methanol solution of 3 percent developed persistent pathological changes that related to the development of Alzheimer's. This article expands this investigation to the non-human primate, in this case, rhesus macaque, that showed that the feeding of methanol led to a persistent memory decline in the monkeys that continued longer than the 6 month study.
https://www.homehelpershomecare.com/kankakee/community-blog/2018/april/how-alternative-sweeteners-can-help-alzheimer-s/ How Alternative Sweeteners Can Help Alzheimer's
t is now known that sugar has a serious impact on Alzheimer's Disease, so if you know or care for someone who has Alzheimer's or dementia, now is the time to help them cut sugar out of their diet because their overall health depends on it!
https://www.researchgate.net/publication/334680310_Artificial_Sweeteners_-_Aspartame_Worth_the_Risk/link/5d39c0b2299bf1995b4a7575/download
Artificial sweeteners: Worth the risk, aspartam and alzheimer's disease 2018
When an artificial sweetener containing aspartame is ingested, **aspartame gets metabolized into three metabolites of phenylalanine, aspartic acid and methanol. These metabolites have adverse effects and the ability to degenerate the neurons on the hippocampal area of the brain.** The neurodegenration, especially in hippocampal area leads to memory losses, cognitive impairment and eventually to AD and dementia.

Taurine(Amino Acid, regulates calcium)

Sources: Scallops (827mg), Salmon(94mg), Tilapia(972mg), Octopus(335mg), Turkey(306mg), Chicken(170mg), Seaweed(1300mg), Beef(40mg), Pork(48mg), energy drink(750mg)
Amazon Taurine Powder $0.15/serving of 2.5g (mix in juice drink)
Supplement: <3000mg/day
https://pubmed.ncbi.nlm.nih.gov/15003996/#:~:text=Taurine%20prevents%20the%20neurotoxicity%20of%20beta-amyloid%20and%20glutamate,implications%20for%20Alzheimer%27s%20disease%20and%20other%20neurological%20disorders Taurine prevents the neurotoxicity of beta-amyloid and glutamate receptor agonists: activation of GABA receptors and possible implications for Alzheimer's disease and other neurological disorders. 2004
We show that **taurine, a beta-amino acid** found at high concentrations in the brain, **protects chick retinal neurons in culture against the neurotoxicity** of Abeta and glutamate receptor agonists. The protective effect of taurine is not mediated by interaction with glutamate receptors, as demonstrated by binding studies using radiolabeled glutamate receptor ligands. The neuroprotective action of taurine is blocked by picrotoxin, an antagonist of GABA(A) receptors. GABA and the GABA(A) receptor agonists phenobarbital and melatonin also protect neurons against Abeta-induced neurotoxicity. These results suggest that activation of GABA receptors decreases neuronal vulnerability to excitotoxic damage and that pharmacological manipulation of the excitatory and inhibitory neurotransmitter tonus may protect neurons against a variety of insults. **GABAergic transmission may represent a promising target for the treatment of AD** and other neurological disorders in which excitotoxicity plays a relevant role.
https://pubmed.ncbi.nlm.nih.gov/35334949/ Taurine Supplementation as a Neuroprotective Strategy upon Brain Dysfunction in Metabolic Syndrome and Diabetes 2022
Given the possible **cytoprotective actions of taurine**, such cerebral accumulation of taurine might constitute a compensatory mechanism that attempts to prevent neurodegeneration. The present article provides an overview of brain taurine homeostasis and reviews the mechanisms by which taurine can afford neuroprotection in individuals with obesity and diabetes. We conclude that further research is needed for understanding taurine homeostasis in metabolic disorders with an impact on brain function.
https://pubmed.ncbi.nlm.nih.gov/35866158/ Taurine and Astrocytes: A Homeostatic and Neuroprotective Relationship. 2022
endogenous mechanisms for taurine production in neural cells, an exogenous supply of taurine is required to meet physiological needs. **Taurine is required for optimal postnatal brain development**; however, its brain concentration decreases with age. Synthesis of taurine in the central nervous system (CNS) occurs predominantly in astrocytes. A metabolic coupling between astrocytes and neurons has been reported, in which astrocytes provide neurons with hypotaurine as a substrate for taurine production. Taurine has **antioxidative, osmoregulatory, and anti-inflammatory functions, among other cytoprotective properties**. Astrocytes release taurine as a gliotransmitter, promoting both extracellular and intracellular effects in neurons.
https://pubmed.ncbi.nlm.nih.gov/11746381/ Role of **taurine in regulation of intracellular calcium level** and neuroprotective function in cultured neurons. 2001
Here we propose that the primary underlying mechanism of the neuroprotective function of taurine is due to its action i**n preventing or reducing glutamate-induced elevation of intracellular free calcium, [Ca(2+)]**
https://pubmed.ncbi.nlm.nih.gov/15757628/ Mode of action of taurine as a neuroprotector. 2005
Previously, it has been shown that taurine exerts its **protective function against glutamate-induced neuronal excitotoxicity** through its action in **reducing glutamate-induced elevation of intracellular free calcium, [Ca2+]i.** Here, we report the mechanism underlying the effect of taurine in reducing [Ca2+]i.
https://pubmed.ncbi.nlm.nih.gov/19239147/ Mechanism of neuroprotective function of taurine. 2009

Taurine has potent protective function against glutamate-induced neuronal injury presumably through its function in **regulation of intracellular free calcium level, [Ca2+]**i. In this communication, we report that taurine exerts its protective function through one or more of the following mechanisms: 1. Inhibition of glutamate-induced calcium influx through L-, N- and P/Q-type voltage-gated calcium channels and NMDA receptor calcium channel;
https://pubmed.ncbi.nlm.nih.gov/23968934/ Mechanisms underlying taurine protection **against glutamate-induced neurotoxicity**. 2013
Taurine appears to exert potent protections against glutamate (Glu)-induced injury to neurons, but the underlying molecular mechanisms are not fully understood.
https://pubmed.ncbi.nlm.nih.gov/32516961/ Expedition into Taurine Biology: Structural Insights and Therapeutic Perspective of Taurine in Neurodegenerative Diseases 2020
Together, taurine enacts protection in NDs by **causing misfolded proteins to refold,** so as to regain their stability and functionality.
https://pubmed.ncbi.nlm.nih.gov/32968166/ Evaluation of the neuroprotective effect of taurine in Alzheimer's disease using functional molecular imaging 2020
Our results reveal that although taurine treatment did not completely recover the glutamate system, it significantly increased metabolic glutamate receptor type 5 brain uptake. Therefore, **taurine has therapeutic potential against AD.**
https://pubmed.ncbi.nlm.nih.gov/28849459/ Taurine Directly Binds to Oligomeric Amyloid-β and Recovers Cognitive Deficits in Alzheimer Model Mice 2017
Alzheimer's disease (AD) is the most common cause of dementia leading to severe cognitive decline. During the progression of AD, amyloid-β (Aβ) monomers aggregate into neurotoxic soluble oligomeric Aβ that causes cognitive impairments. Our previous study indicates that oral supplementation of taurine at 1000 mg/kg/day significantly ameliorates hippocampal-dependent cognitive deficits in APP/PS1 transgenic AD mouse model. However, Aβ plaques and oligomeric Aβ levels are not affected after administration of taurine and the oral dosage of taurine was relatively high. Thus, in this study, we focused on direct correlation between taurine and oligomeric Aβ, causing memory deficits in a lower oral dosage of taurine, 250 mg/kg/day. We induced AD-like cognitive impairments to adult normal mice and orally administered taurine via drinking water for 10 days. We confirmed that taurine administration improved cognitive deficits in oligomeric Aβ-infusion mice in Y-maze and passive avoidance tests without activity alteration of mice. In addition, we found that taurine directly bound to oligomeric Aβ in surface plasmon resonance analyses. **Our results propose that taurine can ameliorate cognitive impairment by directly binding to oligomeric Aβ in oral administration of 250 mg/kg/day for 10 days.**
https://pubmed.ncbi.nlm.nih.gov/35954180/ Versatile Triad Alliance: Bile Acid, Taurine and Microbiota. 2022
Taurine is the most abundant free amino acid in the body, and is **mainly derived from the diet, but can also be produced endogenously from cysteine**. It plays multiple essential roles in the body, including development, energy production, osmoregulation, **prevention of oxidative stress, and inflammation**. Taurine is also crucial as a molecule used to conjugate bile acids (BAs). In the gastrointestinal tract, BAs deconjugation by enteric bacteria results in high levels of unconjugated BAs and free taurine. Depending on conjugation status and other bacterial modifications, BAs constitute a pool of related but highly diverse molecules, each with different properties concerning solubility and toxicity, capacity to activate or inhibit receptors of BAs, and direct and indirect impact on microbiota and the host, whereas free **taurine has a largely protective impact on the host, serves as a source of energy for microbiota,** regulates bacterial colonization and defends from pathogens. Several **remarkable examples of the interaction between taurine and gut microbiota** have recently been described. This review will introduce the necessary background information and lay out the latest discoveries in the interaction of the co-reliant triad of BAs, taurine, and microbiota.
https://pubmed.ncbi.nlm.nih.gov/31468402/ Effects of Dietary Taurine Supplementation on Blood and Urine Taurine Concentrations in the Elderly Women with Dementia. 2019
After 4 weeks, the taurine concentrations in serum and urine of dietary taurine supplemented group were 218.0 ± 15.6 μM and 6502.6 ± 380.6 μM, which were significantly higher compared to control group. Dietary taurine supplemented group showed positive changes in the score on language and execute performance. **So taurine supplementation can provide beneficial effects to the elderly and the elderly with dementia.**
https://pubmed.ncbi.nlm.nih.gov/31468412/ The Development of Taurine Supplementary Menus for the Prevention of Dementia and Their Positive Effect on the Cognitive Function in the Elderly with Dementia. 2019
. In particular, in the case of TG, a **significant increase was observed in the score for 'Judgment and abstract thinking'** ($p < 0.05$). An increased tendency was also observed for scores of 'Place orientation' ($p = 0.071$) and 'Ability to execute' ($p = 0.054$), although statistically not significant. In the case of TLG, score of **f 'Place orientation' and 'Judgment and abstract thinking' was significantly increased** ($p < 0.05$). These results show that **dietary taurine supplementation has positive effects on the cognitive function** (MMSE-DS) of elderly women with dementia. Therefore, it is necessary to include dietary taurine supplementation for the treatment and prevention of dementia. In addition, it is necessary to develop and supply a variety of menus containing taurine.
https://pubmed.ncbi.nlm.nih.gov/28849444/ Past Taurine Intake Has a Positive Effect on Present Cognitive Function in the Elderly 2017
The average taurine index of the elderly with dementia (104.7 points) was significantly lower than average taurine index of the normal elderly (123.7 points) ($p < 0.01$). There were **positive correlations between total taurine index and total score of cognitive function in all the elderly subjects** ($p < 0.05$). In particular, as taurine index was higher, there were significantly higher scores of cognitive function such as 'time orientation' and 'judgement and abstract thinking' ($p < 0.01$). In conclusion, these results suggest that past taurine intake may have a positive effect on present cognitive function in the elderly.
https://pubmed.ncbi.nlm.nih.gov/28849443/ Comparison of Urinary Excretion of Taurine Between Elderly with Dementia and Normal Elderly. 2017
However, **urinary excretion of taurine in the elderly with dementia was significantly higher than the normal elderly** (41.2%, $P < 0.05$).
https://pubmed.ncbi.nlm.nih.gov/31468411/ Taurine-Related Nutritional Knowledge Has a Positive Effect on Intake of Taurine and Cognitive Function in the Elderly 2019
These results suggest that nutritional education of the elderly about taurine is needed, and it is **strongly recommended that the elderly frequently consume taurine-containing foods and supplements to prevent dementia.**
https://pubmed.ncbi.nlm.nih.gov/31468404/ Food Preference of the Elderly for the Development of Taurine-Containing Elderly-Friendly Foods 2019
Among the taurine-containing foods, whip-arm octopus, manila clam, dried anchovy, flatfish, pollack, laver, green laver, sea tangle, seaweed, cod, croaker, and cutlassfish were the preferred foods of most subjects. Elderly females preferred significantly more squid, octopus, eel, mudfish, and sea cucumber than that of elderly males ($p < 0.05$). Elderly males preferred and consumed significantly more taurine-supplement than did elderly females ($p < 0.05$). These results will be used as baseline data for development of a customized TEF for Korean elderly.
https://pubmed.ncbi.nlm.nih.gov/35882813/ The Effects of Dietary Taurine-Containing Jelly Supplementation on Cognitive Function and Memory Ability of the Elderly with Subjective Cognitive Decline 2022
The jelly used in the study contained **3 g of taurine** and was reprocessed in the soft state like pudding considering the safe intake and preference and provided for 4 weeks. The score for subjective memory showed significant difference 4 weeks after supplementation (3.0 points) than before supplementation (2.6 points) ($p < 0.05$). Especially, it increased significantly only in the female elderly ($p < 0.01$). These results show that dietary taurine-containing jelly supplementation has **positive effects on the memory ability of the elderly with subjective cognitive decline.** Therefore, it is s**uggested to supplement products for the elderly, such as pudding or jelly, with dietary taurine to improve memory ability and cognitive function of the elderly.**
https://pubmed.ncbi.nlm.nih.gov/30006901/ The Effects of Oral Taurine on Resting Blood Pressure in Humans: a Meta-Analysis. 2018
results translated to mean **~ 3 mmHg reductions in both SBP (range = 0-15 mmHg) and DBP** (range = 0-7 mmHg) following a range of doses (1 to 6 g/day) and supplementation periods (1 day to 12 weeks), with no adverse events reported.

Tomatoes

https://pubmed.ncbi.nlm.nih.gov/33577362/ A narrative review on the potential of tomato and lycopene for the prevention of Alzheimer's disease and other dementias. 2022
Oxidative stress is a major factor in aging and is implicated in the pathogenesis of tumors, diabetes mellitus, cardiovascular and neurodegenerative diseases, including Alzheimer Disease (AD). **Bioactive constituents of tomato as polyphenols and carotenoids, among which lycopene (LYC)** are effective in reducing markers of oxidative stress, and appear to have a protective modulator role on the pathogenetic mechanisms, cognitive symptoms and behavioral manifestations of these diseases in cell cultures and animal models. Limited evidence from human intervention trials suggests that increasing tomato intake, besides improving CV markers, enhances cognitive performances.
https://pubmed.ncbi.nlm.nih.gov/35205105/ Tomatoes: An Extensive Review of the Associated Health Impacts of Tomatoes and Factors That Can Affect Their Cultivation 2022
The review then details some of the health benefits associated with tomato consumption, including anticancer properties, cardiovascular and **neurodegenerative diseases** and skin health. This review also discusses the impact **tomatoes can have on the gut microbiome** and associated health benefits, including reducing the risk of inflammatory bowel diseases. Other health benefits of eating tomatoes are also discussed in relation to effects on diabetes, the immune response, exercise recovery, and fertility. Finally, this review also addresses the negative effects that can occur as a result of overconsumption of tomato products and lycopene supplements.

Tryptophan (band in 1989 by FDA) see 5-HTP and serotonin

tryptophan —> 5-HTP —> serotonin https://www.healthyplace.com/depression/articles/5-htp-serotonin-connection

Vitamin A

https://gizmodo.com/are-vitamin-supplements-killing-our-gut-bacteria-1795299961 Are Vitamin Supplements Killing Our Gut Bacteria?
Most surprisingly, **less vitamin A meant more of one bacterium, called *Bacteroides vulgatus,*** and vice versa.

https://pubmed.ncbi.nlm.nih.gov/22221326/ Vitamin A and Alzheimer's disease
Plasma or cerebrospinal fluid concentrations of **vitamin A and β-carotene have been reported to be lower in AD patients**, and these vitamins have been clinically **shown to slow the progression of dementia**. Vitamin A (retinol, retinal and retinoic acid) and β-carotene have been shown in in vitro studies to inhibit the formation, extension and destabilizing effects of β-amyloid fibrils.
https://pubmed.ncbi.nlm.nih.gov/15080368/ Vitamin A supplementation and risk of skeletal fracture
Effects of toxic amounts of vitamin A include skeletal effects; from acute toxic exposure to chronic high-dose intake of vitamin A, these effects have led experts to speculate that long-term consumption of diets high in vitamin A (retinol) **stimulates bone resorption and inhibits bone formation**, and may contribute to osteoporosis and hip fractures.
https://awakeningfromalzheimers.com/your-brain-needs-vitamin-a-but-not-too-much/ Your Brain Needs Vitamin A – But Not Too Much!
A study conducted by Canadian and Chinese scientists found that having just slightly less vitamin A than you need significantly increases your risk of Alzheimer's disease. In this study, the researchers found that folks with the lowest vitamin A levels experienced the most drastic decline in their memories as they aged.
Research shows that **too much vitamin A can**:

- Cause the immune system to malfunction and make you more vulnerable to illness by "downregulating" the activity of some immune cells.3
- Impair the function of mitochondria (the cells' "batteries") and disrupt their production of cellular energy.4
- Help cancerous tumors grow bigger by enabling them to generate a bigger supply of blood vessels. (Cancer tumors grow their own network of blood vessels in a process called angiogenesis.)5

The **best way to get vitamin A is to eat plenty of fruits and vegetables that are rich in carotenoids** – plant pigments that the body makes into vitamin A. The foods richest in carotenoids include carrots, sweet potatoes, pumpkin, spinach, cantaloupe, apricots and mangoes.

Vitamin B

Nicotinamide Riboside [alternate form of Vitamin B3] (TNF inhibitor??)

https://wearefeel.com/blogs/learn/best-form-of-b3-niacin-vs-nicotinamide#:~:text=Nicotinamide%2C%20also%20known%20as%20niacinamide%2C%20is%20an%20amide,vitamin%20B3%20supplements%20contain%20either%20nicotinamide%20or%20niacin .
What forms of vitamin B3 are there?
In supplements, vitamin B3 generally comes in the following forms:
niacin, nicotinamide, nicotinamide riboside
The difference?
Most people associate vitamin B3 with niacin, but nicotinic acid isn't actually the form natural vitamin B takes within your body. Whether it's under the guise of niacin, nicotinamide, or nicotinamide amide, your body inevitably converts the vitamin B you take in supplements into nicotinamide adenine dinucleotide (NAD). The way that your body converts dietary vitamin B into NAD makes all the difference.
Nicotinamide, also known as niacinamide, is an amide of nicotinic acid, which is commonly known as niacin. **Nicotinamide riboside (NR), on the other hand, is a chemically altered form of nicotinamide that has unique attributes.** NR has limited applications, however, so most vitamin B3 supplements contain either nicotinamide or niacin.
Takeaways:
Niacin is an oxidated form of nicotine that the body can convert into NAD
Nicotinamide is an amide of niacin that is more similar to NAD and has fewer side effects
Nicotinamide riboside is a synthetic form of nicotinamide that has different attributes
Why is vitamin B3 in nicotinamide form better?
Nicotinamide is more similar to NAD than niacin, which may explain why this type of vitamin B3 has such a minimal side effect profile. While pellagra, which is the medical term for vitamin B3 deficiency, is rare, treatment of this condition with niacin causes unexplained skin flushing. This flushing doesn't appear to be harmful, but it is concerning when it occurs. Nicotinamide does not cause any skin flushing, but like other forms of vitamin B3, it can be harmful at high doses.

https://pubmed.ncbi.nlm.nih.gov/32486488/ Nicotinamide Riboside-The Current State of Research and Therapeutic Uses. 2020
Nicotinamide riboside (NR) has recently become one of the most studied nicotinamide adenine dinucleotide (NAD+) precursors, due to its numerous potential health benefits mediated via elevated NAD+ content in the body. NAD+ is an essential coenzyme that plays important roles in various metabolic pathways and increasing its overall content has been confirmed as a valuable strategy for treating a wide variety of pathophysiological conditions. Accumulating evidence on NRs' health benefits has validated its efficiency across numerous animal and human studies for the treatment of a number of cardiovascular, neurodegenerative, and metabolic disorders.
https://pubmed.ncbi.nlm.nih.gov/34694148/ Modulation of cGAS-STING Pathway by Nicotinamide Riboside in Alzheimer's Disease. 2021
Numerous studies demonstrate a **global decrease in nicotinamide adenine dinucleotide (NAD+) with aging**. This decline is associated with the development of several of the hallmarks of aging such as reduced mitophagy and neuroinflammation, processes thought to play a significant role in the progression of Alzheimer's disease (AD). Augmentation of NAD+ by **oral administration of a precursor, nicotinamide riboside (NR), reduces senescence of affected cells, attenuates DNA damage and neuroinflammation i**n the transgenic APP/PS1 murine model of AD. Inflammation mediated by microglial cells plays an important role in progression of AD and other neurodegenerative diseases. The cytoplasmic DNA sensor, cyclic GMP-AMP synthase (cGAS) and downstream stimulator of interferon genes (STING), generates an interferon signature characteristic of senescence and inflammaging in the brain of AD mice. Elevated cGAS-STING observed in the AD mouse brains and human AD fibroblasts was normalized by NR. This intervention also increased mitophagy with improved cognition and behavior in the APP/PS1 mice. These studies suggest that modulation of the cGAS-STING pathway may benefit AD patients and possibly other disorders characterized by compromised mitophagy and excessive neuroinflammation.
https://pubmed.ncbi.nlm.nih.gov/32925178/ Can nicotinamide riboside protect against cognitive impairment? 2020
Oral supplementation with nicotinamide riboside can inhibit the accumulation of pathological hallmarks of Alzheimer's disease and improve learning and memory in various murine models for dementia. Nicotinamide riboside can also reduce DNA damage, neuroinflammation, apoptosis, and improved hippocampal synaptic plasticity in diabetic mice, and another Alzheimer's disease mouse model. The cognitive benefits of nicotinamide riboside in Alzheimer's disease models may be modulated in part by upregulation of proliferator-activated-γ coactivator 1α-mediated β-secretase 1(BACE-1) ubiquitination and degradation, **preventing Aβ production in the brain**. Nicotinamide riboside also **maintained blood-brain barrier integrity** and **maintained the gut microbiota** in a mouse model for cerebral small vessel disease and alcohol-induced depression, respectively. Oral nicotinamide riboside has been shown to be **bioavailable and well tolerated** in humans with limited adverse effects compared to other NAD+ precursors.
Summary: Oral nicotinamide riboside may represent a promising stratagem to **improve cognitive decline during 'normal' ageing, Alzheimer's disease** and other diseases. Results from recent clinical trials are needed to enumerate the preclinical benefits in humans
https://pubmed.ncbi.nlm.nih.gov/23312803/ Nicotinamide riboside restores cognition through an upregulation of proliferator-activated receptor-γ coactivator 1α regulated β-secretase 1 degradation and mitochondrial gene expression in Alzheimer's mouse models. 2013
Nicotinamide adenine dinucleotide (NAD)(+), a coenzyme involved in redox activities in the mitochondrial electron transport chain, has been identified as a key regulator of the **lifespan-extending effects,** and the activation of NAD(+) expression has been **linked with a decrease in beta-amyloid (Aβ) toxicity in Alzheimer's disease**
(AD). Nicotinamide riboside (NR) is a NAD(+) precursor, it promotes peroxisome proliferator-activated receptor-γ coactivator 1 (PGC)-1α expression in the brain. Evidence has shown that PGC-1α is a crucial regulator of Aβ generation because it affects β-secretase (BACE1) degradation. In this study we tested the hypothesis that NR treatment in an AD mouse model could attenuate Aβ toxicity through the activation of PGC-1α-mediated BACE1 degradation. Using the Tg2576 AD mouse model, using in vivo behavioral analyses, biochemistry assays, small hairpin RNA (shRNA) gene silencing and electrophysiological recording, we found (1) dietary treatment of Tg2576 mice with 250 mg/kg/day of N**R for 3 months significantly attenuates cognitive deterioration** in Tg2576 mice and coincides with an increase in the steady-state levels of NAD(+) in the cerebral cortex; (2) application of NR to hippocampal slices (10 μM) for 4 hours abolishes the deficits in long-term potentiation recorded in the CA1 region of Tg2576 mice; (3) NR treatment promotes PGC-1α expression in the brain coinciding with enhanced degradation of BACE1 and the reduction of Aβ production in Tg2576 mice. Further in vitro studies confirmed that BACE1 protein content is decreased by NR treatment in primary neuronal cultures derived from Tg2576 embryos, in which BACE1 degradation was prevented by PGC-1α-shRNA gene silencing; and (4) NR treatment and PGC-1α overexpression enhance BACE1 ubiquitination and proteasomal degradation. Our studies suggest that **dietary treatment with NR might benefit AD cognitive function and synaptic plasticity**, in part by promoting PGC-1α-mediated BACE1 ubiquitination and degradation, thus preventing Aβ production in the brain.
https://pubmed.ncbi.nlm.nih.gov/30523581/ Nicotinamide ribose ameliorates cognitive impairment of aged and Alzheimer's disease model mice 2019
Nicotinamide adenine dinucleotide (NAD) supplementation to repair the disabled mitochondria is a promising strategy for the treatment of Alzheimer's disease (AD) and other dementia. Nicotinamide ribose (NR) is a **safe NAD precursor with high oral bioavailability**, and has beneficial effects on aging. Here, we applied NR supplied food (2.5 g/kg food) to APP/PS1 transgenic AD model mice and aged mice for 3 months. Cognitive function, locomotor activity and anxiety level were assessed by standard behavioral tests. The change of body weight, the activation of microglia and astrocytes, the accumulation of Aβ and the level of serum nicotinamide phosphoribosyltransferase (NAMPT) were determined for the evaluation of pathological processes. We found that NR supplementation improved the short-term spatial memory of aged mice, and the contextual fear memory of AD mice. Moreover, NR supplementation inhibited the activation of astrocytes and the elevation of serum NAMPT of aged mice. For AD model mice, NR supplementation inhibited the accumulation of Aβ and the migration of astrocyte to Aβ. In addition, NR supplementation inhibit the body weight gain of aged and APP/PS1 mice. Thus, **NR has selective benefits for both AD and aged mice, and the oral uptake of NR can be used to prevent the progression of dementia.**
https://pubmed.ncbi.nlm.nih.gov/34497121/ NAD+ supplementation reduces neuroinflammation and cell senescence in a transgenic mouse model of Alzheimer's disease via cGAS-STING 2021
Here, we report that levels of NAD+ are reduced and markers of inflammation increased in the brains of APP/PS1 mutant transgenic mice with beta-amyloid pathology. Treatment of APP/PS1 mutant mice with the NAD+ precursor nicotinamide riboside (NR) for 5 mo increased brain NAD+ levels, reduced expression of proinflammatory cytokines, and decreased activation of microglia and

astrocytes. **NR treatment also reduced NLRP3 inflammasome expression, DNA damage, apoptosis, and cellular senescence in the AD mouse brains**.
https://pubmed.ncbi.nlm.nih.gov/26791540/ Safety assessment of nicotinamide riboside, a form of vitamin B3 2016
Nicotinamide riboside (NR) is a **naturally occurring form of vitamin B3 present in trace amounts in some foods**. Like niacin, it has been shown to be a precursor in the biosynthesis of nicotinamide adenine dinucleotide (NAD+). The safety of Niagen™, a synthetic form of NR, was determined using a bacterial reverse mutagenesis assay (Ames), an in vitro chromosome aberration assay, an in vivo micronucleus assay, and acute, 14-day and 90-day rat toxicology studies. NR was not genotoxic. There was no mortality at an oral dose of 5000 mg/kg. Based on the results of a 14-day study, a 90-day study was performed comparing NR at 300, 1000, and 3000 mg/kg/day to an equimolar dose of nicotinamide at 1260 mg/kg/day as a positive control. Results from the study show that NR had a similar toxicity profile to nicotinamide at the highest dose tested. Target organs of toxicity were liver, kidney, ovaries, and testes. The lowest observed adverse effect level for NR was 1000 mg/kg/day, and the no observed adverse effect level was 300 mg/kg/day.
https://www.nih.gov/news-events/news-releases/compound-repairs-neurological-damage-shows-cognitive-benefits-mouse-model-alzheimers-disease
The supplement nicotinamide riboside (NR) – a form of vitamin B3 – **prevented neurological damage and improved cognitive and physical function in a new mouse model of Alzheimer's disease**. The results of the study, conducted by researchers at the National Institute on Aging (NIA) part of the National Institutes of Health, suggest a potential new target for treating Alzheimer's disease. The findings appear in the Feb. 5, 2018, issue of Proceedings of the National Academy of Sciences.
https://pubmed.ncbi.nlm.nih.gov/29432159/ NAD+ supplementation normalizes key Alzheimer's features and DNA damage responses in a new AD mouse model with introduced DNA repair deficiency 2018

Vitamin B-6 (Pyridoxine)
https://pubmed.ncbi.nlm.nih.gov/35053277/ Mechanistic Link between Vitamin B12 and Alzheimer's Disease
Several lines of evidence indicate that **B12 hypovitaminosis is linked to AD**. In this review, the biochemical pathways involved in AD that are affected by vitamin B12, focusing on APP processing, Aβ fibrillization, Aβ-induced oxidative damage as well as tau hyperphosphorylation and tau aggregation, are summarized.
https://pubmed.ncbi.nlm.nih.gov/23690582/ Preventing Alzheimer's disease-related gray matter atrophy by B-vitamin treatment
In an initial, randomized controlled study on elderly subjects with increased dementia risk (mild cognitive impairment according to 2004 Petersen criteria), **we showed that high-dose B-vitamin treatment (folic acid 0.8 mg, vitamin B6 20 mg, vitamin B12 0.5 mg) slowed shrinkage of the whole brain volume over 2 y.** Here, we go further by demonstrating that B-vitamin treatment reduces, by as much as seven fold, the cerebral atrophy in those gray matter (GM) regions specifically vulnerable to the AD process, including the medial temporal lobe. In the placebo group, higher homocysteine levels at baseline are associated with faster GM atrophy, but this deleterious effect is largely prevented by B-vitamin treatment. We additionally show that the beneficial effect of B vitamins is confined to participants with high homocysteine (above the median, 11 μmol/L) and that, in these participants, a causal Bayesian network analysis indicates the following chain of events: B vitamins lower homocysteine, which directly leads to a decrease in GM atrophy, thereby slowing cognitive decline. Our results show that **B-vitamin supplementation can slow the atrophy of specific brain regions that are a key component of the AD process and that are associated with cognitive decline.** Further B-vitamin supplementation trials focusing on elderly subjets with high homocysteine levels are warranted to see if progression to dementia can be prevented.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8832580/ Plasma Vitamin B-12 Levels and Risk of Alzheimer's Disease: A Case-Control Study
Vitamin **B-12 deficiency is a frequent condition in the elderly population**. High homocysteine levels, which can contribute to arterial damage and blood clots in blood vessels, usually indicate a deficiency in vitamin B-12. Different studies have shown an association of raised total homocysteine with incident Alzheimer's disease. Conclusion: **This study concluded that there is an association between low levels of vitamin B-12 and the risk of AD.**
https://pubmed.ncbi.nlm.nih.gov/22221769/ Cognitive impairment and vitamin B12: a review
Low serum vitamin **B12 levels are associated with neurodegenerative disease and cognitive impairment.** There is a **small subset of dementias that are reversible with vitamin B12 therapy** and this treatment is inexpensive and safe. Vitamin B12 therapy does not improve cognition in patients without pre-existing deficiency.
https://pubmed.ncbi.nlm.nih.gov/28698453/ Plasma Homocysteine and Serum Folate and Vitamin B12 Levels in Mild Cognitive Impairment and Alzheimer's Disease: A Case-Control Study
Results have shown that serum folate and vitamin B12 levels were significantly lower, but the plasma Hcy level was higher, in patients with MCI and AD than in healthy controls.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4846521/ Vitamin B1 (thiamine) and dementia
The earliest and perhaps best example of an interaction between nutrition and **dementia is related to thiamine (vitamin B1)**. Throughout the last century, research showed that thiamine deficiency is associated with neurological problems, including cognitive deficits and encephalopathy. Multiple similarities exist between classical thiamine deficiency and Alzheimer's disease (AD) in that both are associated with cognitive deficits and reductions in brain glucose metabolism. Perhaps the strongest evidence that thiamine may be involved in the etiology of AD is the relation of thiamine deficiency to plaque formation. **Thiamine deficiency greatly exacerbates plaque formation in mice** genetically engineered to make plaques (Fig. 4). All previous studies of thiamine or thiamine analogues in AD have been underpowered; therefore, neither positive nor negative results are credible. The studies with thiamine were for short time periods and included small numbers of patients. The first was a double-blind, placebo-controlled crossover study, in which each patient received either placebo or thiamine followed by 3 months of the alternate treatment. While mean Mini Mental State Examination (MMSE) scores during treatment with thiamine were significantly better than during the placebo period
https://www.alzheimersresearchuk.org/blog/b-vitamins-and-alzheimers-disease/ However, when they pooled the results of all the trials, the researchers found that – although people taking B vitamins did see a reduction in homocysteine – **there were no strong differences in memory and thinking scores between those who took B vitamins, and those who took the dummy pills.**
UPDATED:**These findings appear to be at odds with the VITACOG study from 2010, which involved 168 people and was widely reported in the media when it was first published. That two-year trial, which was part-funded by Alzheimer's Research UK, showed that people with mild memory problems and high homocysteine had a slower rate of brain shrinkage when they took B vitamins, compared to people who took a placebo. Further analysis of the same trial, published a year later, suggested that B vitamins could also slow declining memory, at least in people with high homocysteine.**
https://www.medicalnewstoday.com/articles/320879#NR-promotes-neuronal-and-cognitive-health Vitamin B-3 could be used to treat Alzheimer's
Compared with the controls, the NR(nicotinamide riboside)-treated mice had less of the protein tau in the brain, less DNA damage, and more neuroplasticity — that is, the brain's ability to "rewire" itself when it learns new things, stores new memories, or becomes damaged.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5437154/?report=reader Editorial: Impact of Diet on Learning, Memory and Cognition
Dietary intake of nutrients was compared between MCI patients and cognitively normal subjects. Carotenoids, **vitamin C**, and vitamin B6 were identified as the dietary nutrients with the highest protective capacity against MCI, potentially due to their antioxidant properties.
https://pubmed.ncbi.nlm.nih.gov/30351155/ [Nutrition strategies that improve cognitive function
Vitamins B1, B6, B12, B9 (folic acid) and D, choline, iron and iodine exert neuroprotective effects and improve intellectual performance. In parallel, antioxidants (vitamins C, E, A, zinc, selenium, lutein and zeaxanthin) have a very important role in the defense against oxidative stress associated with mental deterioration and in the improvement of cognition.
https://pubmed.ncbi.nlm.nih.gov/27116240/ Nutrient intake, nutritional status, and cognitive function with aging
With respect to nutrients, there is evidence to support the **critical role of several B vitamins in particular**, but also of vitamin D, antioxidant vitamins (including vitamin E), and omega-3 fatty acids, which are preferentially taken up by brain tissue. On the other hand, high intakes of nutrients that contribute to hypertension, atherosclerosis, and poor glycemic control may have negative effects on cognition through these conditions. Collectively, the evidence suggests that considerable slowing and reduction of cognitive decline may be achieved by following a healthy dietary pattern, which limits intake of added sugars, while maximizing intakes of fish, fruits, vegetables, nuts, and seeds.
https://pubmed.ncbi.nlm.nih.gov/19203415/ Long-term association of food and nutrient intakes with cognitive and functional decline: a 13-year follow-up study of elderly French women
Recent cognitive decline was associated with lower intakes of poultry, fish, and animal fats, as well as higher intakes of dairy desserts and ice-cream. IADL impairment was associated with a lower intake of vegetables. The odds of recent cognitive decline increased significantly with decreasing intake of soluble dietary fibre and n-3 fatty acids but with increasing intake of retinol. The odds of IADL **impairment increased significantly with decreasing intakes of vitamins B2, B6 and B12.** These results are consistent with a possible long-term neuroprotective effect of dietary fibre, n-3 polyunsaturated fats and B-group vitamins, and support dietary intervention to prevent cognitive decline.
https://pubmed.ncbi.nlm.nih.gov/28075382/ B-Vitamin Intake and Biomarker Status in Relation to Cognitive Decline in Healthy Older Adults in a 4-Year Follow-Up Study
In conclusion, lower dietary and biomarker status of vitamin B6 at baseline predicted a greater than expected rate of cognitive decline over a 4-year period in healthy older adults. **Vitamin B6 may be an important protective factor in helping maintain cognitive health in ageing.**
https://pubmed.ncbi.nlm.nih.gov/28075382/ B-Vitamin Intake and Biomarker Status in Relation to Cognitive Decline in Healthy Older Adults in a 4-Year Follow-Up Study
In conclusion, **lower dietary and biomarker status of vitamin B6 at baseline predicted a greater than expected rate of cognitive decline** over a 4-year period in healthy older adults. Vitamin B6 may be an important protective factor in helping maintain cognitive health in ageing.
https://pubmed.ncbi.nlm.nih.gov/36013492/ Plants, Plants, and More Plants: Plant-Derived Nutrients and Their Protective Roles in Cognitive Function, Alzheimer's Disease, and Other Dementias
A search was conducted on PubMed for clinical and murine studies, using combinations of the following words: "Alzheimer's disease", "dementia", "cognition", "plant-based diet", "mild cognitive impairment", "vitamin B", "vitamin C", "vitamin E, "beta carotene", "antioxidants", "fiber", "vitamin K", "Mediterranean diet", "vitamin D", and "mushrooms". Results and Conclusions: **A diet rich in vitamin B and antioxidants** can benefit the cognitive functions of individuals as shown in randomized clinical trials. **Vitamin K** is associated with improved cognition, although large randomized controlled trials need to be done. **Fiber** has been shown to prevent cognitive decline in animal studies. **Vitamin D** may contribute to cognitive health via anti-inflammatory processes. Several medical organizations have recommended a plant-based diet for optimizing cognitive health and potentially helping to prevent dementia.
https://pubmed.ncbi.nlm.nih.gov/23099812/ Hyperhomocysteinemia in Alzheimer's disease: the hen and the egg?
In conclusion, this data may argue **that folate reduction and hyperhomocysteinemia may contribute to neurodegeneration** and may also be triggered by neurodegenerative processes, i.e., represent both a cause and a consequence of neurodegeneration. Such a vicious cycle may be breakable by dietary or supplementation strategies increasing the availability of 5-MTHF. 5-methyltetrahydrofolate
https://pubmed.ncbi.nlm.nih.gov/20608755/ Folic acid and L-5-methyltetrahydrofolate: comparison of clinical

pharmacokinetics and pharmacodynamics **L-5-methyl-tetrahydrofolate** (L-5-methyl-THF) is the predominant form of dietary folate and the only species normally found in the circulation, and hence it is the folate that is normally transported into peripheral tissues to be used for cellular metabolism. L-5-methyl-THF is also available commercially as a crystalline form of the calcium salt (Metafolin(R)), which has the stability required for use as a supplement. Studies comparing L-5-methyl-THF and folic acid have found that the two compounds have **comparable physiological activity, bioavailability and absorption** at equimolar doses. Bioavailability studies have provided **strong evidence that L-5-methyl-THF is at least as effective as folic acid in improving folate status**, as measured by blood concentrations of folate and by functional indicators of folate status, such as plasma homocysteine. Intake of **L-5-methyl-THF may have advantages over intake of folic acid**. First, the potential for masking the haematological symptoms of vitamin B(12) deficiency may be reduced with L-5-methyl-THF. Second, L-5-methyl-THF may be associated with a **reduced interaction** with drugs that inhibit dihydrofolate reductase.
https://pubmed.ncbi.nlm.nih.gov/24494987/ Folate, folic acid and 5-methyltetrahydrofolate are not the same thing
Most countries have established recommended intakes of folate through folic acid supplements or fortified foods. External supplementation of folate may occur as f**olic acid, folinic acid or 5-methyltetrahydrofolate (5-MTHF)**. 3. Naturally occurring **5-MTHF has important advantages over synthetic folic acid** - it is well absorbed even when gastrointestinal pH is altered and its bioavailability is not affected by metabolic defects. Using 5-MTHF instead of folic acid reduces the potential for masking haematological symptoms of vitamin B12 deficiency, reduces interactions with drugs that inhibit dihydrofolate reductase and overcomes metabolic defects caused by methylenetetrahydrofolate reductase polymorphism. Use of 5-MTHF also prevents the potential negative effects of unconverted folic acid in the peripheral circulation. 4. We review the evidence for the use of 5-MTHF in preventing folate deficiency.
https://pubmed.ncbi.nlm.nih.gov/27340344/#:~:text=Folic%20Acid%20Supplementation%20Mitigates%20Alzheimer%27s%20Disease%20by%20Reducing,of%20folic%20acid%20on%20AD%20itself%20is%20unclear. Folic Acid Supplementation Mitigates Alzheimer's Disease by Reducing Inflammation: A Randomized Controlled Trial
Background/Aims. Low serum folate levels can alter inflammatory reactions. Both phenomena have been linked to Alzheimer's disease (AD), but the effect of folic acid on AD itself is unclear. We quantified folate supplementation's effect on inflammation and cognitive function in patients with AD over the course of 6 months. Conclusions. **Folic acid is beneficial in patients with AD. Inflammation may play an important role in the interaction between folic acid and AD**.
https://pubmed.ncbi.nlm.nih.gov/22627695/ Folate and Alzheimer: when time matters
Folate is necessary for DNA and mtDNA integrity and via folate/B12-dependent methionine cycle for methylation of multiple substrates (epigenetic DNA and enzymes) and methylation of homocysteine. During embryogenesis, folate deficiency is a risk factor for neural tube defects and late in life for cognitive decline and Alzheimer's dementia (AD). It induces several Alzheimer pathomechanisms like oxidative stress, Ca(++) influx, accumulation of hyperphosphorylated tau and β-amyloid. But impact of folic acid supplementation on prevention or delay of dementia is a matter of debate. Six out of seven randomized controlled trials (RCT) with B vitamin intervention periods between 2 and 5.4 years reported about cognitive benefits in the supplemented groups mainly for those subjects with high homocysteine or low folate levels at baseline. This **review tries to demonstrate the connection between folate deficiency and AD**, analyses selected epidemiologic studies and RCT on folate/B12/homocysteine with long-observation periods (≥ 2 years RCT; ≥ 4 years observational) and attempts to find explanations for the controversy in literature like short follow-up, heterogeneity of subjects concerning age, recruitment, baseline cognition, inclusion criteria and probably "misleading"(not representative for the past) folate/B12/homocysteine levels due to not reported short-term use of multivitamins or food-fortification.
https://pubmed.ncbi.nlm.nih.gov/14584018/ Folic acid with or without vitamin B12 for cognition and dementia
Reviewer's conclusions: There was **no beneficial effect of 750 mcg of folic acid per day on measures of cognition** or mood in older healthy women. In patients with mild to moderate cognitive decline and different forms of dementia there was no benefit from folic acid on measures of cognition or mood. **Folic acid plus vitamin B12 was effective in reducing the serum homocysteine concentrations.** Folic acid was well tolerated and no adverse effects were reported. More studies are needed.
https://pubmed.ncbi.nlm.nih.gov/24340890/ The importance of folic acid deficiency in the pathogenesis of vascular, mixed and Alzheimer's disease dementia]
Results: In patients with dementia, compared with the control group, there were **significantly lower levels of folic acid** (p = 0.04). There was no difference in the concentration of Fol in groups of patients (p = 0.0889). In people without cognitive impairment (CDR 0) levels of folic acid were significantly higher compared to the group with moderate dementia (CDR 2, p = 0.0475).
Conclusions: The **results may suggest that folic acid deficiency is one of the possible causes of dementia**, but does not determine its type. Determination of serum Fol in the elderly and supplementation of this vitamin deficiency may play an important role in the prevention of the most common dementias.
https://pubmed.ncbi.nlm.nih.gov/25523421/ Associations between Alzheimer's disease and blood homocysteine, vitamin B12, and folate: a case-control study
Results: With the combination of normal blood Hcy, vitamin B12, and folate levels as the reference category, **low vitamin B12 in subjects with normal Hcy and folate was associated with AD** (adjusted odds ratio [OR], 4.6; 95% confidence interval [CI]: 1.6-13.2). The combination of low vitamin B12 and folate in subjects with normal Hcy was associated with AD (adjusted OR, 4.3; 95% CI: 1.3-14.6). The combination of high Hcy and low folate levels in patients with normal vitamin B12 was associated with AD (adjusted OR, 17.0; 95% CI: 5.4- 53.4). The **combination of high Hcy, low vitamin B12, and any folate level was associated with AD** (adjusted OR, 30.5; 95% CI: 9.7-95.9).
Conclusion: **Vitamin B12 was directly associated with AD**. The combination of high Hcy, low vitamin B12, and any folate level represented the poorest association with AD.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1123448/ Folic acid, ageing, depression, and dementia
It is becoming clear that folic acid affects mood and cognitive function, especially in older people. Edward Reynolds draws together the evidence
Summary points
Folate deficiency is associated with depression and dementia. In elderly people it may be related to ageing, poor diet, malabsorption, drugs, or increased demand or be unexplained. Folic acid has particular effects on mood and cognitive and social function. Impaired folate metabolism may result in a pattern of cognitive dysfunction that resembles ageing. The duration of folate deficiency and of its treatment is as important as the degree of deficiency and the dose of folic acid. **Folic acid should be used with caution in the presence of vitamin B-12 deficiency** (gdh ie folic acid can mask B12 deficiency) or epilepsy
Folic acid is important in the nervous system at all ages, but in elderly people deficiency contributes to ageing brain processes, increases the risk of Alzheimer's disease and vascular dementia and, if critically severe, can lead to a reversible dementia
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3375831/ Reduced risk of Alzheimer's disease with high folate intake: The Baltimore Longitudinal Study of Aging
These findings suggest that total i**ntake of folate at or above the RDA is associated with a reduced risk of AD.** Additional studies are necessary to further investigate whether folate or other(s) unmeasured factor(s) may be responsible for this reduction in risk.
https://www.alzinfo.org/articles/prevention-and-wellness-89/ THE LATEST ON FOLIC ACID AND ALZHEIMER'S PREVENTION
Getting **enough folic acid, a B vitamin critical for brain and nerve health**, may help ward off Alzheimer's in old age, a new study from the University of California at Irvine reports. Men and women age 60 and up who regularly consumed the daily recommended daily allowance (RDA) of 400 micrograms (mcg) of folic through foods and supplements cut their risk of developing the brain-ravaging illness by over 50 percent. It is still too early to say, however, whether folic acid also called folate or other nutrients may actually prevent the onset of Alzheimer's disease.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5028542/ Vitamin Supplementation as an Adjuvant Treatment for Alzheimer's Disease
Among **B vitamins, pyridoxine (B6), folic acid (B9), and cobalamin (B12)** have shown to have potential in managing symptoms of AD.

Vitamin C

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5437154/?report=reader Editorial: Impact of Diet on Learning, Memory and Cognition
Dietary intake of nutrients was compared between MCI patients and cognitively normal subjects. Carotenoids, **vitamin C**, and vitamin B6 were identified as the dietary nutrients with the highest protective capacity against MCI, potentially due to their antioxidant properties.
https://pubmed.ncbi.nlm.nih.gov/30351155/ [Nutrition strategies that improve cognitive function
Vitamins B1, B6, B12, B9 (folic acid) and D, choline, iron and iodine exert neuroprotective effects and improve intellectual performance. In parallel, antioxidants **(vitamins C**, E, A, zinc, selenium, lutein and zeaxanthin) have a very important role in the defense against oxidative stress associated with mental deterioration and in the improvement of cognition.
https://pubmed.ncbi.nlm.nih.gov/12459890/ Effects of fruits and vegetables on levels of vitamins E and C in the brain and their association with cognitive performance
Foods are important sources of micronutrients, including vitamins E and C, which play crucial roles in optimal cell function. Vitamin E is an important component of biologic membranes, and **vitamin C acts as a cosubstrate for several enzymes**. Both E and C are involved in the antioxidant defense of cells and actively contribute to the redox status of the cell. The levels of vitamins E and C provided by diet vary significantly. Vegetable oils, nuts and seeds are the main dietary sources of vitamin E, whereas **fruits and vegetable are the primary sources of vitamin C.** Human trials of varying doses of vitamins E and C, including low, supplemental, and pharmacologic, have found that these nutrients may improve immunity, vascular function, and **brain performance**. An optimal intake of these nutrients has been associated with **decreased risk of developing cognitive impairments associated with aging**. This paper will review the scientific literature on the sources, tissue levels and roles of vitamins E and C in cognitive performance and pathologic processes of the central nervous system in the elderly.
https://pubmed.ncbi.nlm.nih.gov/12459890/ Effects of fruits and vegetables on levels of vitamins E and C in the brain and their association with cognitive performance
Foods are important sources of **micronutrients, including vitamins E and C**, which play crucial roles in optimal cell function. Vitamin E is an important component of biologic membranes, and vitamin C acts as a cosubstrate for several enzymes. **Both E and C are involved in the antioxidant defense** of cells and actively contribute to the redox status of the cell. The levels of vitamins E and C provided by diet vary significantly. **Vegetable oils, nuts and seeds are the main dietary sources of vitamin E**, whereas **fruits and vegetable are the primary sources of vitamin C.** Human **trials of varying doses of vitamins E and C, including low, supplemental, and pharmacologic, have found that these nutrients may improve immunity, vascular function, and brain performance**. An optimal intake of these nutrients has been associated with decreased risk of developing cognitive impairments associated with aging. This paper will review the scientific literature on the sources, tissue levels and roles of vitamins E and C in cognitive performance and pathologic processes of the central nervous system in the elderly.
https://www.eatthis.com/major-effect-vitamin-c-has-on-your-gut/ One Major Effect Vitamin C Has On Your Gut, Says Science

One of the major effects vitamin C has on your gut is **helping to maintain a balance between good and bad bacteria in your gut microbiome.**

Vitamin D

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9372870/pdf/WJCC-10-7631.pdf Alzheimer's and vitamin D
Vitamin D is an antioxidant hormone. There is a close linkage between vitamin D, human microbiome, and the immune system. Vitamin D can regulate innate and adaptive immune responses[93]. Vitamin D enhances the immune function and may delay aging; thus, it may play a role in the treatment of AD[94].

The key findings of the aforementioned micronutrients related to AD are summarized in Table 1
https://pubmed.ncbi.nlm.nih.gov/22202127/ The beneficial role of vitamin D in Alzheimer's disease
Patients with AD have a high prevalence of vitamin D deficiency, which is also associated with low mood and impaired cognitive performance in older people. Genetic studies have provided the opportunity to determine which proteins link vitamin D to AD pathology. In conclusion, vitamin D clearly has a beneficial role in AD and improves cognitive function in some patients with AD. Calcitriol, 1 α,25-**dihydroxyvitamin D3, is best used for AD because of its active form of vitamin D(3)** metabolite and its receptor in the central nervous system.
https://pubmed.ncbi.nlm.nih.gov/35822270/ Vitamin D supplementation worsens Alzheimer's progression: Animal model and human cohort studies
Intriguingly, we first observed that APP/PS1 mice fed a vitamin D-sufficient diet showed significantly lower levels of serum vitamin D, **suggesting its deficiency may be a consequence not a cause of AD**. Moreover, s**upplementation of vitamin D led to increased Aβ deposition and exacerbated AD.** Mechanistically, vitamin D supplementation did not rescue the genomic VDR/RXR complex but instead enhanced the non-genomic VDR/p53 complex in AD brains. Consistently, our population-based longitudinal study also showed that dementia-free older adults (n = 14,648) t**aking vitamin D3 supplements for over 146 days/year were 1.8 times more likely to develop dementia than those not taking the supplements.**
https://pubmed.ncbi.nlm.nih.gov/27116240/ Nutrient intake, nutritional status, and cognitive function with aging
With respect to nutrients, there is evidence to support the critical role of several B vitamins in particular, but **also of vitamin D**, antioxidant vitamins (including vitamin E), and omega-3 fatty acids, which are preferentially taken up by brain tissue. On the other hand, high intakes of nutrients that contribute to hypertension, atherosclerosis, and poor glycemic control may have negative effects on cognition through these conditions. Collectively, the evidence suggests that considerable slowing and reduction of cognitive decline may be achieved by following a healthy dietary pattern, which limits intake of added sugars, while maximizing intakes of fish, fruits, vegetables, nuts, and seeds.
https://pubmed.ncbi.nlm.nih.gov/36013492/ Plants, Plants, and More Plants: Plant-Derived Nutrients and Their Protective Roles in Cognitive Function, Alzheimer's Disease, and Other Dementias
A search was conducted on PubMed for clinical and murine studies, using combinations of the following words: "Alzheimer's disease", "dementia", "cognition", "plant-based diet", "mild cognitive impairment", "vitamin B", "vitamin C", "vitamin E, "beta carotene", "antioxidants", "fiber", "vitamin K", "Mediterranean diet", "vitamin D", and "mushrooms". Results and Conclusions: **A diet rich in vitamin B and antioxidants** can benefit the cognitive functions of individuals as shown in randomized clinical trials. **Vitamin K** is associated with improved cognition, although large randomized controlled trials need to be done. **Fiber** has been shown to prevent cognitive decline in animal studies. **Vitamin D** may contribute to cognitive health via anti-inflammatory processes. Several medical organizations have recommended a plant-based diet for optimizing cognitive health and potentially helping to prevent dementia.

Vitamin E **alpha-tocopherol (major lipid-soluble antioxidant, helps mercury toxicity,)**

RDA 15mg/day, Max 1000mg/day
https://www.drugs.com/dosage/vitamin-e.html Vitamin E Dosage
US Recommended Dietary Allowance **(RDA):15 mg** alpha-tocopherol. Tolerable **Upper Intake Level (UL): 1000 mg** alpha-tocopherol
https://pubmed.ncbi.nlm.nih.gov/31409980/ Vitamin E and Alzheimer's disease: what do we know so far?
Thus, **despite a strong rationale in support of a beneficial role for vitamin E for the treatment of AD, the evidence remains inconclusive.** Several factors may partly explain this discrepancy and represent the difficulties of translating complex laboratory evidence and dietary interactions into clinical interventions. Methodological design limitations of existing randomised trials and restrictions to supplementation with a single vitamin E isoform may also limit the influence of effect. Moreover, several factors influence individual responsiveness to vitamin E intake and recent findings suggest variation in the underlying genetic architecture attenuates vitamin E biological availability and activity which likely contributes to the variation in clinical responsiveness and the failure of randomised trials to date.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5618073/ For the last two decades, it has been **hotly debated whether vitamin E—**the major lipid-soluble antioxidant, which functions to maintain neurological integrity—**is efficacious as a therapy for Alzheimer's disease**. Several factors key to the debate, include (1) which of the eight naturally-occurring vitamin E forms should be used; (2) how combination treatments affect vitamin E efficacy; and (3) safety concerns that most-recently resurfaced after the results of the Selenium and vitamin E Cancer prevention trial SELECT prostate cancer trial. Although there are eight naturally-occurring forms of vitamin E, alpha-tocopherol has garnered the most attention. Since vitamin E is an essential micronutrient, humans must consume the vitamin in order to maintain adequate levels. **Alarmingly, 90% of the population does not consume the RDA of 15 mg/day but average closer to half that value—around 7 mg/day [17].** The **consequences of low vitamin E intake on cognitive decline are exemplified in several studies.** In a group of nearly 3000 elderly healthy women who were followed for three years, it was found that individuals who consumed higher vitamin E-containing foods exhibited reduced cognitive decline per an adaptation of the Mini Mental State Examination (MMSE) [18,19]. Similarly, healthy individuals who participated in the Women's Health Study were shown to have **less cognitive decline when consuming higher levels of vitamin E** supplementation [20]. Together, these studies support the notion that adequate vitamin E supports neurological health and raises the concern that unrecognized sub-clinical deficiency of vitamin E may contribute to cognitive decline as individuals age. A concrete connection between vitamin E and AD is the significant decrease of vitamin E in the cerebrospinal fluid (CSF) and plasma of AD patients [26,27]. Other studies have individually corroborated the results of lower CSF [28] or lower plasma [29,30] vitamin E. **However, in smaller studies, there was no difference in vitamin E CSF or plasma levels [31,32].** Interestingly, a recent randomized control study using human samples from the Rush Memory and Aging Project (MAP) determined there were micro-locations of gamma-tocopherol that correlate with amyloid-beta plaques burdens [42]. These results indeed give credence to investigating other vitamin E forms. **Vitamin E may be an effective agent in pre-emptively slowing the progression of AD**, **but it is not likely to be efficacious in reversing disease symptoms in advanced phases.** The debate regarding safe supplementation dosing of alpha-tocopherol seems to be eternal [46,65]. No AD trials —even at 2000 IU alpha-tocopherol—demonstrated an increased risk of mortality. However, we cannot ignore that there have been several clinical trials that have shown increased all-cause mortality of high-dose vitamin E treatment.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5651431/ Serum concentrations of vitamin E and carotenoids are altered in Alzheimer's disease: A case-control study
Serum concentrations of retinol, two forms of **vitamin E (α- and γ-tocopherol)** and six carotenoids were quantified by high-performance liquid chromatography from patients with AD. Serum levels of **α-tocopherol and all six carotenoids were significantly lower** in patients with AD compared with cognitively intact controls ($P < .001$). **In contrast, γ-tocopherol was significantly higher in the serum of patients with AD.** Our findings implicate compromised serum antioxidant defenses in AD pathogenesis and differing biological roles for vitamin E isoforms. AD patients had significantly lower serum levels of retinol ($P = .02$), α-tocopherol, lutein, zeaxanthin, β-cryptoxanthin, α-carotene, β-carotene, and lycopene ($P < .001$) compared to controls. By contrast, the mean serum level of the vitamin E compound, γ-tocopherol, was significantly higher among AD cases compared to cognitively intact controls ($P < .001$). Of interest, a 1 μmol/L increase in γ-tocopherol resulted in a 19% increase in risk associated with AD (OR per μmol/L increase, 1.19 [CI: 1.10–1.30]), **whereas all other antioxidant vitamins and carotenoids analyzed were negatively correlated with AD**. In addition, the opposing associations we observed for α- and γ-tocopherol may highlight a potential limitation of previous vitamin E trials, as proposed by La Fata et al. in a recent systematic review of vitamin E trials in AD. The authors, Zandi et al., found the use of **vitamin E and C supplements in combination** to be associated with reduced incidence of AD thus providing further support for the synergistic benefit of a combined supplementation approach.
https://alz-journals.onlinelibrary.wiley.com/doi/full/10.1016/j.trci.2017.06.006 Serum concentrations of vitamin E and carotenoids are altered in Alzheimer's disease: A case-control study
Serum concentrations of retinol, two forms of vitamin E (α- and γ-tocopherol) and six carotenoids were quantified by high-performance liquid chromatography from patients with AD ($n = 251$) and cognitively intact controls ($n = 308$) and assessed by regression analyses. **Serum levels of α-tocopherol and all six carotenoids were significantly lower in patients with AD** compared with cognitively intact controls ($P < .001$). In contrast, **γ-tocopherol was significantly higher in the serum of patients with AD** (odds ratio = 1.17 [confidence intervals: 1.05–1.31]).
https://pubmed.ncbi.nlm.nih.gov/12097694/ Cognitive function in elderly people is influenced by vitamin E status
, demonstrating a greater number of errors in comparison to participants with a greater intake of the vitamin. This study shows there to be a **relationship between vitamin E status and cognitive function,** and that vitamin E status could be improved in this population of elderly individuals.
https://pubmed.ncbi.nlm.nih.gov/27116240/ Nutrient intake, nutritional status, and cognitive function with aging
With respect to nutrients, there is evidence to support the critical role of several B vitamins in particular, but also of vitamin D, **antioxidant vitamins (including vitamin E)**, and omega-3 fatty acids, which are preferentially taken up by brain tissue. On the other hand, high intakes of nutrients that contribute to hypertension, atherosclerosis, and poor glycemic control may have negative effects on cognition through these conditions. Collectively, the evidence suggests that considerable slowing and reduction of cognitive decline may be achieved by following a healthy dietary pattern, which limits intake of added sugars, while maximizing intakes of fish, fruits, vegetables, nuts, and seeds.
https://pubmed.ncbi.nlm.nih.gov/12459890/ Effects of fruits and vegetables on levels of vitamins E and C in the brain and their association with cognitive performance
Foods are important sources of micronutrients, including **vitamins E** and C, which play crucial roles in optimal cell function. **Vitamin E is an important component of biologic membranes**, and vitamin C acts as a cosubstrate for several enzymes. Both E and C are involved in the antioxidant defense of cells and actively contribute to the redox status of the cell. The levels of vitamins E and C provided by diet vary significantly. **Vegetable oils, nuts and seeds are the main dietary sources of vitamin E**, whereas fruits and vegetable are the primary sources of vitamin C. Human trials of varying doses of vitamins E and C, including low, supplemental, and pharmacologic, have found that these nutrients may improve immunity, vascular function, and **brain performance**. An optimal intake of these nutrients has been **associated with decreased risk of developing cognitive impairments associated with aging**. This paper will review the scientific literature on the sources, tissue levels and roles of vitamins E and C in cognitive performance and pathologic processes of the central nervous system in the elderly.

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https://pubmed.ncbi.nlm.nih.gov/12459890/ Effects of fruits and vegetables on levels of vitamins E and C in the brain and their association with cognitive performance
Foods are important sources of **micronutrients, including vitamins E and C**, which play crucial roles in optimal cell function. Vitamin E is an important component of biologic membranes, and vitamin C acts as a cosubstrate for several enzymes. **Both E and C are involved in the antioxidant defense** of cells and actively contribute to the redox status of the cell. The levels of vitamins E and C provided by diet vary significantly. **Vegetable oils, nuts and seeds are the main dietary sources of vitamin E**, whereas **fruits and vegetable are the primary sources of vitamin C.** Human **trials of varying doses of vitamins E and C, including low, supplemental, and pharmacologic, have found that these nutrients may improve immunity, vascular function, and brain performance**. An optimal intake of these nutrients has been associated with decreased risk of developing cognitive impairments associated with aging. This paper will review the scientific literature on the sources, tissue levels and roles of vitamins E and C in cognitive performance and pathologic processes of the central nervous system in the elderly.
https://pubmed.ncbi.nlm.nih.gov/1304229/ Selenium in the treatment of heavy metal poisoning and chemical carcinogenesis 1992
Selenium (Se) has been shown to counteract the toxicity of heavy metals such as cadmium, inorganic mercury, methylmercury, thallium and to a limited extent silver. Although not as effective as Se, **vitamin E significantly alters methylmercury toxicity** and is more effective than Se against silver toxicity. Vitamin E is very effective against lead toxicity but Se has little effect.

Vitamin K K1 (phylloquinone) and K2 (menaquinone)(uncommon, animal sources).

https://pubmed.ncbi.nlm.nih.gov/34199021/ Vitamin K2 Holds Promise for Alzheimer's Prevention and Treatment
Recent studies have highlighted the importance of **vitamin K2 (VK2)** in human health. However, there have been no clinical studies investigating the role of VK2 in the prevention or treatment of Alzheimer's disease (AD), a debilitating disease for which currently there is no cure. we have found a growing body of evidence demonstrating that VK2 has the **potential to slow the progression of AD** and contribute to its prevention. In our review, we consider the **antiapoptotic and antioxidant effects** of VK2 and its impact on **neuroinflammation**, mitochondrial dysfunction, cognition, cardiovascular health, and comorbidities in AD.
https://pubmed.ncbi.nlm.nih.gov/11461163/ The possible role of vitamin K deficiency in the pathogenesis of Alzheimer's disease and in augmenting brain damage associated with cardiovascular disease
A relative deficiency of vitamin K, affecting the extrahepatic functions of the vitamin, is common in ageing men and women. Evidence is accumulating that vitamin K has important functions in the brain, including the regulation of sulfotransferase activity and the activity of a growth factor/tyrosine kinase receptor (Gas 6/Axl). The **hypothesis is now proposed that vitamin K deficiency contributes to the pathogenesis of AD** and that vitamin K supplementation may have a beneficial effect in preventing or treating the disease.
https://www.alzheimersorganization.org/vegetables-vitamin-k-and-alzheimers Vitamin K and Alzheimers
Studies have shown that Vitamin K, and other nutrients present in leafy greens **slow the speed at which the brain ages**.
Vitamin K is not well-absorbed through supplementation; the **best way to add it to your diet is through vegetables high in Vitamin K**.
In a cognitive study of over 950 older participants, researchers found that individuals whom ate one or two servings of mustard greens, spinach, collards, or kale daily had the same mental ability as individuals **11 years their junior**.
https://pubmed.ncbi.nlm.nih.gov/36013492/ Plants, Plants, and More Plants: Plant-Derived Nutrients and Their Protective Roles in Cognitive Function, Alzheimer's Disease, and Other Dementias
A search was conducted on PubMed for clinical and murine studies, using combinations of the following words: "Alzheimer's disease", "dementia", "cognition", "plant-based diet", "mild cognitive impairment", "vitamin B", "vitamin C", "vitamin E, "beta carotene", "antioxidants", "fiber", "vitamin K", "Mediterranean diet", "vitamin D", and "mushrooms". Results and Conclusions: **A diet rich in vitamin B and antioxidants** can benefit the cognitive functions of individuals as shown in randomized clinical trials. **Vitamin K** is associated with improved cognition, although large randomized controlled trials need to be done. **Fiber** has been shown to prevent cognitive decline in animal studies. **Vitamin D** may contribute to cognitive health via anti-inflammatory processes. Several medical organizations have recommended a plant-based diet for optimizing cognitive health and potentially helping to prevent dementia.

https://www.healthline.com/nutrition/foods-high-in-vitamin-k#TOC_TITLE_HDR_2 Which foods contain vitamin K
The following 20 foods are good sources of vitamin K (4Trusted Source).

1. Kale (cooked) — 443% of the DV per serving	1/2 cup: 531 mcg (443% of the DV)	100 grams: 817 mcg (681% of the DV)
2. Mustard greens (cooked) — 346% of the DV per serving	1/2 cup: 415 mcg (346% of the DV)	100 grams: 593 mcg (494% of the DV)
3. Swiss chard (raw) — 332% of the DV per serving	1 leaf: 398 mcg (332% of the DV)	100 grams: 830 mcg (692% of the DV)
4. Collard greens (cooked) — 322% of the DV per serving	1/2 cup: 386 mcg (322% of the DV)	100 grams: 407 mcg (339% of the DV)
5. Natto — 261% of the DV per serving	1 ounce: 313 mcg (261% of the DV)	100 grams: 1,103 mcg (920% of the DV)
6. Spinach (raw) — 121% of the DV per serving	1 cup: 145 mcg (121% of the DV)	100 grams: 483 mcg (402% of the DV)
7. Broccoli (cooked) — 92% of the DV per serving	1/2 cup: 110 mcg (92% of the DV)	100 grams: 141 mcg (118% of the DV)
8. Brussels sprouts (cooked) — 91% of the DV per serving	1/2 cup: 109 mcg (91% of the DV)	100 grams: 140 mcg (117% of the DV)
9. Beef liver — 60% of the DV per serving	1 slice: 72 mcg (60% of the DV)	100 grams: 106 mcg (88% of the DV)
10. Pork chops — 49% of the DV per serving	3 ounces: 59 mcg (49% of the DV)	100 grams: 69 mcg (57% of the DV)
11. Chicken — 43% of the DV per serving	3 ounces: 51 mcg (43% of the DV)	100 grams: 60 mcg (50% of the DV)
12. Goose liver paste — 40% of the DV per serving	1 tablespoon: 48 mcg (40% of the DV)	100 grams: 369 mcg (308% of the DV)
13. Green beans (cooked) — 25% of the DV per serving	1/2 cup: 30 mcg (25% of the DV)	100 grams: 48 mcg (40% of the DV)
14. Prunes — 24% of the DV per serving	5 pieces: 28 mcg (24% of the DV)	100 grams: 60 mcg (50% of the DV)
15. Kiwi — 23% of the DV per serving	1 fruit: 28 mcg (23% of the DV)	100 grams: 40 mcg (34% of the DV)
16. Soybean oil — 21% of the DV per serving	1 tablespoon: 25 mcg (21% of the DV)	100 grams: 184 mcg (153% of the DV)
17. Hard cheeses — 20% of the DV per serving	1 ounce: 25 mcg (20% of the DV)	100 grams: 87 mcg (72% of the DV)
18. Avocado — 18% of the DV per serving	Half of a fruit, medium: 21 mcg (18% of the DV)	100 grams: 21 mcg (18% of the DV)
19. Green peas (cooked) — 17% of the DV per serving	1/2 cup: 21 mcg (17% of the DV)	100 grams: 26 mcg (22% of the DV)
20. Soft cheeses — 14% of the DV per serving	1 ounce: 17 mcg (14% of the DV)	100 grams: 59 mcg (49% of the DV)

1. Beet greens (cooked) — 290% of the DV per serving	1/2 cup: 349 mcg (290% of the DV)	100 grams: 484 mcg (403% of the DV)
2. Parsley (fresh) — 137% of the DV per serving	1 sprig: 164 mcg (137% of the DV)	100 grams: 1,640 mcg (1,367% of the DV)
3. Cabbage (cooked) — 68% of the DV per serving	1/2 cup: 82 mcg (68% of the DV)	100 grams: 109 mcg (91% of the DV)

1. Blackberries — 12% of the DV per serving	1/2 cup: 14 mcg (12% of the DV)	100 grams: 20 mcg (17% of the DV)
2. Blueberries — 12% of the DV per serving	1/2 cup: 14 mcg (12% of the DV)	100 grams: 19 mcg (16% of the DV)
3. Pomegranate — 12% of the DV per serving	1/2 cup: 14 mcg (12% of the DV)	100 grams: 16 mcg (14% of the DV)

Egg yolk — 5% of the DV per serving	1 large: 5.8 mcg (5% of the DV)	100 grams: 34 mcg (29% of the DV)

Walnuts (source of alpha-linolenic acid -omega3)

ALA: **Walnuts(2500mg/ounce(28g)=6 walnuts), 5g/Walnut (446mg/whole Walnut)**
:**potassium**(441mg/100g) (22mg/whole Walnut)

https://pubmed.ncbi.nlm.nih.gov/32093220/ Beneficial Effects of Walnuts on Cognition and Brain Health
Walnuts contain several components that have **antioxidant and anti-inflammatory effects**. Animal and human studies from our and other groups suggest that s**upplementation with walnuts in the diet may improve cognition and reduce the risk and/or progression of MCI and AD.** In the transgenic AD mouse model (AD-tg), we have reported the b**eneficial effects of a diet with walnuts on memory, learning, motor coordination, anxiety, and locomotor activity.** Human clinical trials have also suggested an association of **walnut consumption with better cognitive performance and improvement in memory when compared to baseline in adults.** Our recent study in AD-tg mice has shown that a **walnut-enriched diet significantly improves antioxidant defense and decreases free radicals' levels,** lipid peroxidation, and protein oxidation when compared to a control diet without walnuts. These findings suggest that a diet with walnuts can reduce oxidative stress

by decreasing the generation of free radicals and by boosting antioxidant defense, thus resulting in decreased oxidative damage to lipids and proteins. An in vitro study with synthetic Aβ showed that walnut extract can inhibit Aβ fibrillization and solubilize the preformed Aβ fibrils, suggesting an anti-amyloidogenic property of walnuts. Because it takes many years for cognitive impairment and dementia to develop, **we suggest that early and long-term dietary supplementation with walnuts may help to maintain cognitive functions and may reduce the risk of developing, or delay the onset and/or slow the progression of, MCI and dementia by decreasing Aβ fibrillization, reducing oxidative damage, increasing antioxidant defense, and decreasing neuroinflammation.** Furthermore, several animal and human studies have suggested that walnuts may also decrease the risk or progression of other brain disorders such as Parkinson's disease, stroke, and depression, as well as of cardiovascular disease and type 2 diabetes. Together, these reports suggest the benefits of a walnut-enriched diet in brain disorders and in other chronic diseases, due to the additive or synergistic effects of walnut components for protection against oxidative stress and inflammation in these diseases.

https://pubmed.ncbi.nlm.nih.gov/25024344/ Dietary supplementation of walnuts improves memory deficits and learning skills in transgenic mouse model of Alzheimer's disease

the age of 4 months, the experimental groups of AD-tg mice were fed custom-mixed diets containing 6% walnuts (T6) or 9% walnuts (T9), i.e., e**quivalent to 1 or 1.5 oz, respectively, of walnuts per day in humans**.

The AD-tg mice receiving the diets with 6% or 9% walnuts (T6 and T9) showed a s**ignificant improvement in memory, learning ability, anxiety, and motor development compared to the AD-tg mice on the control diet** (T0). There was no statistically significant difference in behavioral performance between the T6/T9 mice on walnuts-enriched diets and the Wt group on the control diet. These findings suggest that dietary supplementation with walnuts may have a beneficial effect in reducing the risk, delaying the onset, or slowing the progression of, or preventing AD.

https://pubmed.ncbi.nlm.nih.gov/29208493/ **Almond, hazelnut and walnut, three nuts for neuroprotection in Alzheimer's disease:** A neuropharmacological review of their bioactive constituents

There is special attention to the three types of nuts including almond, hazelnut and walnut in manuscripts of traditional Persian medicine (PM) as the preventive agents against brainatrophy and memory loss

https://pubmed.ncbi.nlm.nih.gov/28119602/ The Walnuts and Healthy Aging Study (WAHA): Protocol for a Nutritional Intervention Trial with Walnuts on Brain Aging

Results: From May 2012 to May 2014, 708 participants (mean age 69 years, 68% women) were randomized. The study ended in May 2016 with a 90% retention rate. Discussion: The results of WAHA might provide high-level evidence of the benefit of regular **walnut consumption in delaying the onset of age-related cognitive impairment and retinal pathology**. The findings should translate into public health policy and sound recommendations to the general population (ClinicalTrials.gov identifier NCT01634841).

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7071526/ Beneficial Effects of Walnuts on Cognition and Brain Health

Oxidative stress and neuroinflammation have important roles in the aging process, mild cognitive impairment (MCI), Alzheimer's disease (AD), and other brain disorders. Amyloid beta protein (Aβ) is the main component of amyloid plaques in the brains of people with AD. Several studies suggest that Aβ increases the generation of free radicals in neurons, which leads to oxidative damage and cell death. Aβ can also induce neuroinflammation by increasing pro-inflammatory cytokines and enzymes. **Walnuts contain several components that have antioxidant and anti-inflammatory effects.**

https://www.forbes.com/sites/alicegwalton/2017/09/11/why-the-omega-3s-in-walnuts-are-not-the-same-as-the-ones-in-fish-and-algae/?sh=27abbb3d6e06

Why The Omega-3s In Walnuts Are Not The Same As The Ones In Fish And Algae

The variety of omega-3s in plants is α-linolenic acid (ALA). The omega-3s in fish are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Humans aren't able to make EPA or DHA from scratch; we need either to eat them or to form them from shorter fatty acids (like ALA). The **body *is* able to convert ALA into EPA and DHA through a chain of chemical reactions that generally take place in the liver.** In this sequence of events, DHA is the final product, arriving a couple of steps after EPA. (For a detailed breakdown of all the reactions needed to take ALA to DHA, see this.) The problem is that the conversion isn't very efficient, with **only a small percentage of ALA making it all the way to DHA**. This is partly due to competition from omega-6 fatty acids, which people tend to eat in higher quantities than omega-3s in general.

https://journals.lww.com/co-clinicalnutrition/Fulltext/2018/11000/Beneficial_effects_of_walnut_consumption_on_human.15.aspx

Alpha-linolenic acid, a critical walnut component, is metabolized into bioactive oxylipins, has been shown to protect microglial cells from inflammation, and is associated with lower fatal myocardial infarction rates through a putative antiarrhythmic effect. Phytosterols relate to the cholesterol-lowering effect of nut consumption. Nonsodium minerals are associated with better cardiometabolic health. Walnut phytomelatonin has anticancer effects that are shared by the main walnut polyphenols and their metabolites, ellagitannins and urolithins, respectively.

ALA

Phytosterols(95-279mg/100g) (anti-oxidant)+displace Cholesterol-→LDL cholesterol reduction

Minerials:**potassium**(441mg/100g-raising dietary K+ blunts the effects of high dietary Na+)(control blood pressure/reduce stroke),

magnesium and **calcium**(100mg/100g)

VITAMIN E (γ-TOCOPHEROL) As long as intestinal function is preserved, tocopherols are bioavailable because, being small fatty molecules, they are absorbed along with dietary fat in the intestine and enter the circulation via chylomicron particles [36]. Walnuts are an excellent source of γ-tocopherol, supplying 21 mg/100 g [37], and there is evidence that the liver hydroxylation and oxidation products of this form of vitamin E are potent free radical scavengers and reduce pro-inflammatory eicosanoids and the inflammatory response, actions that are not shared by α-tocopherol.

Melatonin: 350 ng/100 g

Polyphenols:2500mg/100g

https://academic.oup.com/jn/article/144/4/561S/4571638?login=false Role of Walnuts in Maintaining Brain Health with Age 2014 (THIS STUDY HAS LOTS OF INFO)

Primary prevention in many of these neurodegenerative diseases could be achieved earlier in life by consuming a healthy diet, rich in antioxidant and anti-inflammatory phytochemicals, which offers one of the most effective and least expensive ways to address the crisis. English walnuts (*Juglans regia* L.) are rich in numerous phytochemicals, including high amounts of polyunsaturated fatty acids, and offer potential benefits to brain health. **Polyphenolic compounds found in walnuts not only reduce the oxidant and inflammatory load on brain cells** but also improve interneuronal signaling, increase neurogenesis, and enhance sequestration of insoluble toxic protein aggregates. **Evidence for the beneficial effects of consuming a walnut-rich diet i**s reviewed in this article.

English walnuts (*Juglans regia* L.) are rich in α-linolenic acid (ALA; 18:3n−3) and linoleic acid (LA; 18:2n−6) as well as other polyphenolics, phytosterols, and micronutrients. Feeding studies from our laboratory have shown that **dietary supplementation with walnuts can improve memory, cognition, and motor function in aged animals** (8–10). Although most of these studies have linked walnuts' effects to their high PUFA content, walnuts' notable polyphenol content plays an important role in reducing the inflammation and oxidative stress in the aging brain.

Walnuts are a rich source of nutrients and bioactive phytochemicals. Walnuts contain large amounts of PUFAs such as ALA and LA, which have been shown to boost brain health and function even with an increase in age (8, 21). Every 100 g of walnuts (*Juglans regia*) contain **38 g of LA and 9 g of ALA, as well as 4.4 g of saturated (palmitic acid, 16:0) and 8.7 g of monounsaturated (oleic acid**, 18:1n–9) FAs. In humans, ALA from walnuts is then converted through a series of sequential desaturation and elongation reactions into essential PUFAs such as **EPA (20:5n–3) and DHA (22:6n–3) in the liver.** Both **EPA and DHA play an important role in brain health not only by reducing oxidative stress and altering the immune function but also in maintaining synaptic plasticity, neuronal membrane stability, gene expression, and neurogenesis** (8, 22).

Melatonin is another bioactive compound found in walnuts. Endogenous melatonin, which is primarily synthesized by the pineal gland, plays a critical role in regulating circadian rhythms (30). Melatonin deficiency has been linked to degeneration of cholinergic neurons in the basal forebrain and the deposition of aggregated proteins, such as amyloid β (Aβ) peptides, leading to cognitive impairment and dementia (31). **Reiter et al. (30) reported that consumption of walnuts increased blood melatonin concentrations**, which correlated with an increase in "total antioxidant capacity" of the serum with "total antioxidant capacity," indicating the ability of the blood to detoxify free radicals.

When BV-2 mouse microglial cells were treated with walnut extract prior to LPS stimulation, production of NO and expression of inducible NO synthase were substantially reduced. In the same study, walnut extract also **reduced the production of TNF-α, a proinflammatory mediator**. We have also shown that calcium buffering in hippocampal cells was substantially altered by LPS and 6-hydroxy dopamine (DA) stressors (33). Walnut extract protected against LPS-induced, but not DA-induced, loss of calcium recovery (34). Another study showed that walnut extract counteracted Aβ-induced oxidative stress and cytotoxicity in PC12 cells of rat adrenal medulla (35).

Results indicated that **walnut oil extract**, ALA, and DHA provided substantial p**rotection against cell death and calcium dysregulation**; the effects were pretreatment concentration-dependent and stressor-dependent.

Withania somnifera (see Ashawagandha)