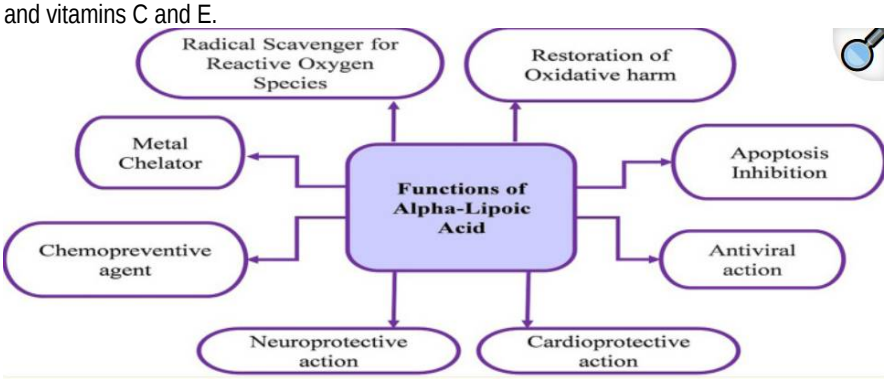
normal adult can take 300 milligrams twice a day with food, but they should always take a B-complex vitamin with it. Because B complex vitamins, especially thiamine, and biotin, and riboflavin, are depleted during this metabolic process.

https://www.aimnutrition.org/wp-content/uploads/2020/09/Vit-C-Glutathione-and-Alpha-Lipoic-Acid-Theory-202.pdf
Vitamin C, Glutathione and Alpha Lipoic Acid Theory 2020
Alpha Lipoic Acid
• ALA in combination with Vit C is cytotoxic to cancer cells.
ALA increases the killing effect of Vitamin C.
Casciari JJ, Riordan NH, Schmidt TL, Meng XL, Jackson JA, Riordan HD. Cytotoxicity of ascorbate, lipoic acid, and other antioxidants in hollow fibre in vitro tumours. Br J Cancer. 2001 Jun 1;84(11):1544-50. PMID: 11384106

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9904877/
Molecular and Therapeutic Insights of Alpha-Lipoic Acid as a Potential Molecule for Disease Prevention 2023
Alpha-lipoic acid is an organic, sulfate-based compound produced by plants, humans, and animals. As a potent antioxidant and a natural dithiol compound, it performs a crucial role in mitochondrial bioenergetic reactions. A healthy human body, on the other hand, can synthesize enough α-lipoic acid to scavenge reactive oxygen species and increase endogenous antioxidants; however, the amount of α-lipoic acid inside the body decreases significantly with age, resulting in endothelial dysfunction.
α-Lipoic acid acts as a chelating agent for metal ions, a quenching agent for reactive oxygen species, and a reducing agent for the oxidized form of glutathione and vitamins C and E.



https://pubmed.ncbi.nlm.nih.gov/29258346/
The Long-Term Survival of a Patient With Stage IV Renal Cell Carcinoma Following an Integrative Treatment Approach Including the Intravenous α-Lipoic Acid/Low-Dose Naltrexone Protocol 2018
In this case report, we describe the treatment of a 64-year-old male patient diagnosed with metastatic renal cell carcinoma (RCC) in June of 2008. In spite of a left nephrectomy and the standard oncological protocols, the patient developed a solitary left lung metastasis that continued to grow. He was informed that given his diagnosis and poor response to conventional therapy, any further treatment would, at best, be palliative. The patient arrived at the Integrative Medical Center of New Mexico in August of 2010. He was in very poor health, weak, and cachectic. An integrative program-developed by one of the authors using intravenous (IV) α-lipoic acid, IV vitamin C, low-dose naltrexone, and hydroxycitrate, and a healthy life style program-was initiated. From August 2010 to August 2015, the patient's RCC with left lung metastasis was followed closely using computed tomography and positron emission tomography/computed tomography imaging. His most recent positron emission tomography scan demonstrated no residual increased glucose uptake in his left lung. After only a few treatments of IV α-lipoic acid and IV vitamin C, his symptoms began to improve, and the patient regained his baseline weight. His energy and outlook improved, and he returned to work. The patient had stable disease with disappearance of the signs and symptoms of stage IV RCC, a full 9 years following diagnosis, with a gentle integrative program, which is essentially free of side effects. As of November 2017 the patient feels well and is working at his full-time job.

https://www.nature.com/articles/s41598-024-72309-y
Alpha lipoic acid diminishes migration and invasion in hepatocellular carcinoma cells through an AMPK-p53 axis 2024
We hypothesize that ALA can induce different antitumor events through AMPK signaling in HCC cells as well.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10707055/
Alpha-Lipoic Acid Reduces Cell Growth, Inhibits Autophagy, and Counteracts Prostate Cancer Cell Migration and Invasion: Evidence from In Vitro Studies 2023
Alpha-lipoic acid (ALA) is a natural antioxidant dithiol compound, exerting antiproliferative and antimetastatic effects in various cancer cell lines. In our study, we demonstrated that ALA reduces the cell growth of prostate cancer cells LNCaP and DU-145.
In addition, in DU-145 cells we observed that ALA affected the oxidative/redox balance system by deregulating the KEAP1/Nrf2/p62 signaling pathway. ALA decreased ROS production, SOD1 and GSTP1 protein expression, and significantly reduced the cytosolic and nuclear content of the transcription factor Nrf2, concomitantly downregulating p62, suggesting that ALA disrupted p62-Nrf2 feedback loop.
Therefore, in our experiment models, we investigated whether ALA exposure modulates the ROS content in both cell lines. Interestingly, in LNCaP cells, we observed an almost significant increase in ROS content ($p = 0.06$) after ALA compared to the control, concomitantly with a significant upregulation of the antioxidant enzyme SOD1 after 48 h. Conversely, in the same experimental conditions, our results revealed that in DU-145 cells, ALA exposure significantly reduced ROS production ($p < 0.001$) as well as SOD-1 and GSTP1 protein expression levels (Figure 3a,b).

https://www.nature.com/articles/s41598-024-54479-x
α-lipoic acid modulates prostate cancer cell growth and bone cell differentiation 2024
Prostate cancer (PCa) progression leads to bone modulation in approximately 70% of affected men. A nutraceutical, namely, α-lipoic acid (α-LA), is known for its potent anti-cancer properties towards various cancers and has been implicated in treating and promoting bone health. Our study aimed to explore the molecular

mechanism behind the role of α-LA as therapeutics in preventing PCa and its associated bone modulation. Notably, α-LA treatment significantly reduced the cell viability, migration, and invasion of PCa cell lines in a dose-dependent manner. In addition, α-LA supplementation dramatically increased reactive oxygen species (ROS) levels and HIF-1α expression, which started the downstream molecular cascade and activated JNK/caspase-3 signaling pathway.

https://www.cancertherapyadvisor.com/factsheets/alpha-lipoic-acid-and-cancer/
Few prospective in-human studies have been conducted among patients with cancer, though multiple studies have shown promising cytotoxic effects in vitro. ALA alone has been shown to decrease cell viability and proliferation in breast, ovarian, colorectal, and lung cancer cell lines, and was synergistic with chemotherapy.[2-6] ALA also decreased cell migration and invasion in thyroid cancer cell lines.[7] In prostate cancer cells, however, ALA did not affect cell proliferation compared with the control.[8]

https://www.mdpi.com/2076-3921/13/8/897
The Multifaceted Role of Alpha-Lipoic Acid in Cancer Prevention, Occurrence, and Treatment 2024
We specifically focus on the interactions between ALA and various carcinogenic and anti-carcinogenic pathways and discuss ALA's pro-oxidative capabilities in the unique redox environment of cancer cells.
ALA not only is a crucial component of glucose metabolism and ATP generation but also has antioxidant functions, protecting normal cells from the damaging effects of free radicals (FRs), also known as reactive oxygen species (ROS) [7].
In recent years, the anticancer effects of ALA have also been demonstrated, including the promotion of oxidation, inhibition of pro-cancer pathways, and activation of tumor suppressor genes, and is posited to play roles in various stages of cancer development [10].
ALA, on the other hand, has been found to increase ROS production, thereby inducing CREB/furin inhibition and preventing IGF-1R internalization and maturation.
In normal tissues, the presence of elevated levels of ROS may facilitate the transformation of normal cells into cancer cells, thereby contributing to the development of cancer. However, due to their excessive and frequent proliferative activities, cancer cells typically exhibit high levels of ROS [89]. To survive and function in this highly oxidative environment, cancer cells manage ROS levels through effective antioxidant mechanisms to prevent ROS accumulation beyond the apoptotic threshold [90,91,92]. Therefore, inducing ROS production to trigger apoptosis appears to be more advantageous than reducing ROS levels within the cancer cell microenvironment. This is the fundamental mechanism of chemotherapy.
Interestingly, research has shown that the direct anticancer effect of the antioxidant ALA is manifested as an increase in intracellular ROS levels in cancer cells [10]. This pro-oxidant characteristic may stem from the distinct cellular environments of normal and cancer cells. By increasing ROS levels, ALA effectively exploits the differences in oxidative stress response mechanisms and sensitivities between cancer and normal cells, altering the balance of anti-apoptotic and pro-apoptotic proteins to selectively induce apoptosis in cancer cells [39].
Before discussing the pro-apoptotic effects of ALA on tumor cells, it is essential to clarify that the roles and mechanisms of ROS in inducing cell damage and apoptosis differ between cancerous and normal cells [88]. In normal tissues, the presence of elevated levels of ROS may facilitate the transformation of normal cells into cancer cells, thereby contributing to the development of cancer. However, due to their excessive and frequent proliferative activities, cancer cells typically exhibit high levels of ROS [89]. To survive and function in this highly oxidative environment, cancer cells manage ROS levels through effective antioxidant mechanisms to prevent ROS accumulation beyond the apoptotic threshold [90,91,92]. Therefore, inducing ROS production to trigger apoptosis appears to be more advantageous than reducing ROS levels within the cancer cell microenvironment. This is the fundamental mechanism of chemotherapy.
In normal cells, ALA acts as an antioxidant by clearing ROS. However, in cancer cells, it can exert pro-oxidative effects, inducing pathways that restrict cancer progression. This indicates that nanostructures containing ALA, in conjunction with anticancer drugs, exhibit synergistic effects, increasing selectivity and providing protective and reparative functions against the side effects of several anticancer drugs that mediate ROS generation;

https://www.nature.com/articles/s41388-020-1211-x
Lipoic acid-induced oxidative stress abrogates IGF-1R maturation by inhibiting the CREB/furin axis in breast cancer cell lines 2020
The beneficial effects of lipoic acid (LA) in cancer treatment have been well documented in the last decade. Indeed, LA exerts crucial antiproliferative effects by reducing breast cancer cell viability, cell cycle progression and the epithelial-to-mesenchymal transition (EMT). However, the mechanisms of action (MOA) underlying these antiproliferative effects remain to be elucidated.
We unveil that LA exerts a pro-oxidant effect on these cell lines, the resulting reactive oxygen species (ROS) generated being responsible for the reduction in the expression of the major (CREB) protein.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7137803/
Alpha-lipoic acid inhibits lung cancer growth via mTOR-mediated autophagy inhibition 2020
Here, we examined the effects of alpha-lipoic acid (LA), a drug used for treating human diabetic complications, on lung cancer growth. We report that LA limited lung cancer growth in xenograft mice and reduced lung cancer A549 cell viability.

https://pubmed.ncbi.nlm.nih.gov/18237244/
alpha-Lipoic acid: the potential for use in cancer therapy 2008
This review deals with alpha-lipoic acid (LA) from the point of its chemical and biological characteristics affecting enzymatic activities that are part of cellular biochemical processes in normal and cancer cells. This includes attributes of LA that are related to its ability to act as a free-radicals scavenger and also as a radical generator.

https://pubmed.ncbi.nlm.nih.gov/16990509/
Reactive oxygen species mediate caspase activation and apoptosis induced by lipoic acid in human lung epithelial cancer cells through Bcl-2 down-regulation 2006
The antioxidant alpha-lipoic acid (LA) is a naturally occurring compound that has been shown to possess promising anticancer activity because of its ability to preferentially induce apoptosis and inhibit proliferation of cancer cells relative to normal cells. However, the molecular mechanisms underlying the apoptotic effect of LA are not well understood. We report here that LA induced reactive oxygen species (ROS) generation and a concomitant increase in apoptosis of human lung epithelial cancer H460 cells. Inhibition of ROS generation by ROS scavengers or by overexpression of antioxidant enzymes glutathione peroxidase and superoxide dismutase effectively inhibited LA-induced apoptosis, indicating the role of ROS, especially hydroperoxide and superoxide anion, in the apoptotic process. Apoptosis induced by LA was found to be mediated through the mitochondrial death pathway, which requires caspase-9 activation. Inhibition of caspase activity by the pan-caspase inhibitor (z-VAD-FMK) or caspase-9-specific inhibitor (z-LEHD-FMK) completely inhibited the apoptotic effect of LA. Likewise, the mitochondrial respiratory chain inhibitor rotenone potently inhibited the apoptotic and ROS-inducing effects of LA, supporting the role of mitochondrial ROS in LA-induced cell death. LA induced down-regulation of mitochondrial Bcl-2 protein through peroxide-dependent proteasomal degradation, and overexpression of the Bcl-2 protein prevented the apoptotic effect of LA. Together, our findings indicate a novel pro-oxidant role of LA in apoptosis induction and its regulation by Bcl-2,

which may be exploited for the treatment of cancer and related apoptosis disorders.

https://pubmed.ncbi.nlm.nih.gov/37453954/
Alpha-lipoic acid induced apoptosis of PC3 prostate cancer cells through an alteration on mitochondrial membrane depolarization and MMP-9 mRNA expression 2023
The present study aimed to evaluate the anti-proliferative and apoptotic activity of α-lipoic acid in human PC3 prostate carcinoma cells considering different concentrations and exposure durations. The findings showed that, α-lipoic acid significantly decreased PC3 cell viability with an IC_{50} value of 1.71 mM at 48 h ($p < 0.05$). Additionally, the compound significantly increased Annexin-V binding in cells compared to control and induced a significant alteration in mitochondrial membrane potential and caspase levels ($p < 0.05$). Furhermore, the RT-PCR analyses have revealed that α-lipoic acid reduced MMP-9 mRNA expression in PC3 cells compared to the control ($p < 0.05$). In conclusion, this study highlights that α-lipoic acid induced apoptosis in human PC3 prostate cancer cells and inhibited the MMP-9 gene at the mRNA level, which is known to play a role in metastasis development.

https://pubmed.ncbi.nlm.nih.gov/20650348/
alpha-Lipoic acid reduces matrix metalloproteinase activity in MDA-MB-231 human breast cancer cells 2010
We conclude that in this cell culture model, LA treatment inhibits cancer metastasis, and this inhibition is likely due to the decrease in the activity and mRNA expression levels of MMP-2 and MMP-9 caused by LA.

https://pubmed.ncbi.nlm.nih.gov/31669587/
Lipoic acid a multi-level molecular inhibitor of tumorigenesis 2020
We discuss how lipoic acid (LA), a natural antioxidant, induces apoptosis and inhibits proliferation, EMT, metastasis and stemness of cancer cells. Furthermore, owing to its ability to reduce chemotherapy-induced side effects and chemoresistance, LA appears to be a promising compound for cancer treatment.

https://jeffreydachmd.com/2016/05/alpha-lipoic-acid-anticancer-agent-burt-berkson-md/
Addition of Hydroxy Citrate improves effect of ALA
In a series of studies authored by Laurent Schwartz, the addition of hydroxycitrate increases the effect of ALA. Hydroxycitrate is a known inhibitor of ATP citrate lyase (also called ATP-citric synthase), an enzyme frequently upregulated in cancer cells, a useful anti-cancer target, and the subject of a patent.

https://aacrjournals.org/cancerres/article/72/8_Supplement/3832/580877/Abstract-3832-Tolerance-of-oral-lipoid-acid-and
Abstract 3832: Tolerance of oral lipoid acid and hydroxycitrate combination in cancer patients: first approach of the cancer metabolism research group 2012
Introduction: our previous publications demonstrate that lipoïc acid (ALA) and hydroxycitrate (HCA) combination decreases the tumor growth in mice with either lung cancer, bladder cancer or melanoma. ALA is a well known treatment of the diabetic neuropathy but its interest in cancer is growing. In fact, ALA is a cofactor in mitochondrial energy metabolism and a potent regulator of the cell's redox status with effects on P13K and AMPK signaling and related transcriptional pathways. These mechanisms increase its interest in cancer and aging relative diseases.
French experience: Jan 08 to Nov 11, 13 p. with local relapse and/or metastatic cancer with a combination of ALA -HCA, 7 M, 6 F, median age 45 y (28 –74) 2 colon, 1 lung, 1 hepatocarcinoma, 5 sarcomas, 1 neuro-endocrine. HCA was administered orally, 3 g / d (1 g x3/d). ALA 1,8 g /D (600 m g x3/d) and from Oct 11 increased to 6 g /d for 3 last 6 p. Median duration: 3 months (15 d - 5 m, 1 pt 20m). Results: This association was well tolerated with few clinical disturbances: vomiting, nausea, 5 patients had a gastric protective treatment and 2 because of corticotherapy. The increased dose of ALA was well tolerated. No hepatic toxicity found, no weight loss, no hypoglycemia. A problem was the bad and discontinued observance for patients in relation with the cost of these medicines, the difficulty to buy them (only by online pharmacy for ALA in France).The tolerance of HCA was mild because of gastric pain but patients continue the treatment. Conclusion: ALA - HCA a combination well tolerated is a promising treatment in cancer patients. The switch to IV ALA will permit to obtain higher blood peaks and better observance.

https://pubmed.ncbi.nlm.nih.gov/20931262/
Adding a combination of hydroxycitrate and lipoic acid (METABLOC™) to chemotherapy improves effectiveness against tumor development: experimental results and case report 2012
We recently published results obtained with a combination of two drugs, lipoic acid and hydroxycitrate, targeting metabolic enzymes particularly affected in cancer: ATP citrate lyase and pyruvate dehydrogenase kinase. This treatment was as efficient as chemotherapy in the three mouse cancer models that were tested. In this work, we asked if our drug combination could be used in conjunction with standard cytotoxic chemotherapy, in particular cisplatin, to improve basic protocol efficacy.
We demonstrate that the triple combination lipoic acid + hydroxycitrate + cisplatin or methotrexate is more efficient than cisplatin or methotrexate used individually or the combination of lipoic acid and hydroxycitrate administered alone. Of particular note are the results obtained in the treatment of an 80 year-old female who presented with ductal adenocarcinoma of the pancreas accompanied by liver metastases. A treatment course using gemcitabine plus α-lipoic acid and hydroxycitrate gave highly promising results.

https://pubmed.ncbi.nlm.nih.gov/24511042/
Metabolic treatment of cancer: intermediate results of a prospective case series 2014
Background: The combination of hydroxycitrate and lipoic acid has been demonstrated by several laboratories to be effective in reducing murine cancer growth.
Patients and methods: All patients had failed standard chemotherapy and were offered only palliative care by their referring oncologist. Karnofsky status was between 50 and 80. Life expectancy was estimated to be between 2 and 6 months. Ten consecutive patients with chemoresistant advanced metastatic cancer were offered compassionate metabolic treatment. They were treated with a combination of lipoic acid at 600 mg i.v. (Thioctacid), hydroxycitrate at 500 mg t.i.d. (Solgar) and low-dose naltrexone at 5 mg (Revia) at bedtime.
Results: One patient was unable to receive i.v. lipoic acid and was switched to oral lipoic acid (Tiobec). Toxicity was limited to transient nausea and vomiting. Two patients died of progressive disease within two months. Two other patients had to be switched to conventional chemotherapy combined with metabolic treatment, one of when had a subsequent dramatic tumor response. Disease in the other patients was either stable or very slowly progressive. The patient with hormone-resistant prostate cancer had a dramatic fall in Prostate-Specific Antigen (90%), which is still decreasing.

Conclusion: These very primary results suggest the lack of toxicity and the probable efficacy of metabolic treatment in chemoresistant advanced carcinoma. It is also probable that metabolic treatment enhances the efficacy of cytotoxic chemotherapy. These results are in line with published animal data. A randomized clinical trial is warranted.

https://pubmed.ncbi.nlm.nih.gov/22797854/

Tumor regression with a combination of drugs interfering with the tumor metabolism: efficacy of hydroxycitrate, lipoic acid and capsaicin 2013

Cellular metabolic alterations are now well described as implicated in cancer and some strategies are currently developed to target these different pathways. In previous papers, we demonstrated that a combination of molecules (namely alpha-lipoic acid and hydroxycitrate, i.e. Metabloc™) targeting the cancer metabolism markedly decreased tumor cell growth in mice. In this work, we demonstrate that the addition of capsaicin further delays tumor growth in mice in a dose dependant manner. This is true for the three animal model tested: lung (LLC) cancer, bladder cancer (MBT-2) and melanoma B16F10. There was no apparent side effect of this ternary combination. The addition of a fourth drug (octreotide) is even more effective resulting in tumor regression in mice bearing LLC cancer. These four compounds are all known to target the cellular metabolism not its DNA. The efficacy, the apparent lack of toxicity, the long clinical track records of these medications in human medicine, all points toward the need for a clinical trial. The dramatic efficacy of treatment suggests that cancer may simply be a disease of dysregulated cellular metabolism.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9960359/

Cancer Metabolism: Fasting Reset, the Keto-Paradox and Drugs for Undoing 2023

In previous works, we tested lipoic acid and hydroxycitrate in pursuit of this goal; more information can be found in Refs. [11,12]. We found that, respectively, these substances inhibit the citrate formation and ACL, beginning the cytosolic synthesis of fatty acids. However, tumor cells are still able to incorporate exogenous acetate, converting it into acetyl-CoA in the cytosol; "via" acetyl-CoA synthetase, we can inhibit this entry with allicine [13] or orotic acid [14].
In earlier works we showed that Lipoic acid and Hydroxycitrate from Garcinia were able to limit the citrate efflux from mitochondria and inhibit ATP citrate lyase (ACL) in the cytosol, which cuts the lipogenic supply. These effects are strengthened if one uses allicine or orotic acid to block the direct incorporation of external acetate via acetyl-CoA synthetase. Moreover, one can impair the synthesis of lipid membranes with DHA through the inhibition of AMP deaminase, which leaves more AMP to stimulate AMP kinase.

https://pubmed.ncbi.nlm.nih.gov/20372858/

A combination of alpha lipoic acid and calcium hydroxycitrate is efficient against mouse cancer models: preliminary results 2010

The impact of metabolic dysregulation on tumor development has long been established. We have targeted two enzymes that are altered during carcinogenesis: pyruvate dehydrogenase (PDH), which is down-regulated, and ATP citrate lyase, which is overexpressed in cancer cells. Alpha lipoic acid is a cofactor of PDH, while hydroxycitrate is a known inhibitor of ATP citrate lyase. Our hypothesis is that a combination of these drugs may have antitumoral potential.
When hydroxycitrate and lipoic acid were used together, there was a major cytotoxic effect: complete cell death was seen following 8 microM lipoic acid and 300 microM hydroxycitrate treatment for 72 h. The combination of alpha lipoic acid and hydroxycitrate was administered to healthy mice, at doses currently utilized for other indications than cancer; no demonstrable toxicity was observed. The combination was used to treat mouse syngenic cancer models: MBT-2 bladder transitional cell carcinoma, B16-F10 melanoma and LL/2 Lewis lung carcinoma. The efficacy of this combination appears similar to conventional chemotherapy (cisplatin or 5-fluorouracil) as it resulted in significant tumor growth retardation and enhanced survival.

https://www.nature.com/articles/s41598-019-39109-1

Metabolic therapies inhibit tumor growth in vivo and in silico 2019

In the early 20th century, Otto Warburg revealed that cancer cells rely on the cytoplasmic fermentation of glucose to lactic acid for energy synthesis (called "Warburg effect"). Our investigations aim to reverse this effect in reprogramming cancer cells' metabolism. In this work, we present a metabolic therapy specifically targeting the activity of specific enzymes of central carbon metabolism, combining the METABLOC bi-therapeutic drugs combination (Alpha Lipoic Acid and Hydroxycitrate) to Metformin and Diclofenac, for treating tumors implanted in mice. Furthermore, a dynamic metabolic model describing central carbon metabolism as well as fluxes targeted by the drugs allowed to simulate tumors progression in both treated and non-treated mice, in addition to draw hypotheses on the effects of the drugs on tumor cells metabolism. Our model predicts metabolic therapies-induced reversed Warburg effect on tumor cells.

https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-017-0873-x

When less may be more: calorie restriction and response to cancer therapy 2017

Given the nutritional concerns of CR and fasting in some cancer patients, CR mimetics, namely pharmacological agents that target pathways affected by CR, such as rapamycin, metformin, resveratrol, and hydroxycitrate, are attractive strategies to mimic the protective effects of CR both for cancer prevention and as adjuvant therapies without dietary restriction. These CR mimetics affect systemic and tumor-specific inflammation and metabolism, and targeting these pathways may sensitize cancers to traditional and emerging anti-cancer therapies by reducing tumor-associated inflammation or causing metabolic stress in the cancer cell.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9268148/

Hydroxycitric Acid Inhibits Chronic Myelogenous Leukemia Growth through Activation of AMPK and mTOR Pathway 2022

We found that hydroxycitric acid (HCA), a natural, safe bioactive from the plant *Garcinia gummi-gutta* (*cambogia*), has potent AMPK activity in chronic myelogenous leukemia (CML) cell line K562. HCA is a known competitive inhibitor of ATP citrate lyase (ACLY) and is widely used as a weight loss inducer. We found that HCA was able to inhibit the growth of K562 cells in in vitro and in vivo xenograft models.

https://pubmed.ncbi.nlm.nih.gov/32439410/

Hydroxycitric acid potentiates the cytotoxic effect of tamoxifen in MCF-7 breast cancer cells through inhibition of ATP citrate lyase 2020

Hydroxycitric acid (HCA), a dietary-derived weight loss supplement, competitively inhibits ATP citrate lyase (ACLY). Tamoxifen (TAM) is the most frequently used therapy for estrogen receptor (ER)-positive breast cancer patients, but its application was restricted due to efficacy related issues. Lipid metabolic reprogramming plays a key role in cancer progression and response to treatment. This study will test the hypothesis that targeting lipid metabolic enzymes could enhance TAM effect against breast cancer cells. MCF-7 ER-positive breast cancer cell line was used, and the cytotoxic effect of TAM treatment, alone and in combination with HCA was evaluated.
Treatment with TAM or HCA significantly reduced cell viability in a concentration-dependent manner whereas co-treatment synergistically reduced cell viability, promoted apoptosis, and decreased the expression of ACLY, ACC-α, and FAS. Intracellular triglyceride and cholesterol were accumulated in response to treatment with TAM and/or HCA. Moreover, either solitary TAM or TAM/ HCA co-treatment increased ER-α protein levels non significantly. Our results revealed that TAM effects on breast cancer are mediated, in part, through the regulation of key genes involved in lipid metabolism. Accordingly, inhibition of ACLY by HCA might be beneficial to enhance the therapeutic index of TAM against breast cancer.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3424601/

In Vitro and In Vivo Toxicity of Garcinia or Hydroxycitric Acid: A Review 2012

Obesity is one of the pandemic chronic diseases commonly associated with health disorders such as heart attack, high blood pressure, diabetes or even cancer. Among the current natural products for obesity and weight control, *Garcinia* or more specifically hydroxycitric acid (HCA) extracted from *Garcinia* has been widely

used. The evaluation of the potential toxicity of weight control supplement is of the utmost importance as it requires long term continuous consumption in order to maintain its effects. Majority of reports demonstrated the efficacy of *Garcinia*/HCA without any toxicity found. However, a few clinical toxicity reports on weight-loss diet supplements of which some were combinations that included *Garcinia*/HCA as an active ingredient showed potential toxicity towards spermatogenesis. Nonetheless, it cannot be concluded that *Garcinia*/HCA is unsafe. Those products which have been reported to possess adverse effects are either polyherbal or multi-component in nature. To date, there is no case study or report showing the direct adverse effect of HCA. The structure, mechanism of action, long history of the use of *Garcinia*/HCA and comprehensive scientific evidence had shown "no observed adverse effect level (NOAEL)" at levels up to 2800 mg/day, suggesting its safety for use.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3882485/

α-Lipoic acid suppresses migration and invasion via downregulation of cell surface β1-integrin expression in bladder cancer cells 2014

Our previous study showed α-lipoic acid (LA) downregulated cell surface β1-integrin expression of v-H-ras-transformed derivative of rat fibroblast with amelioration of their malignant phenotype. Here, we evaluated the ameliorating effect of LA on the malignant characters in H-ras-transformed bladder cancer cells.

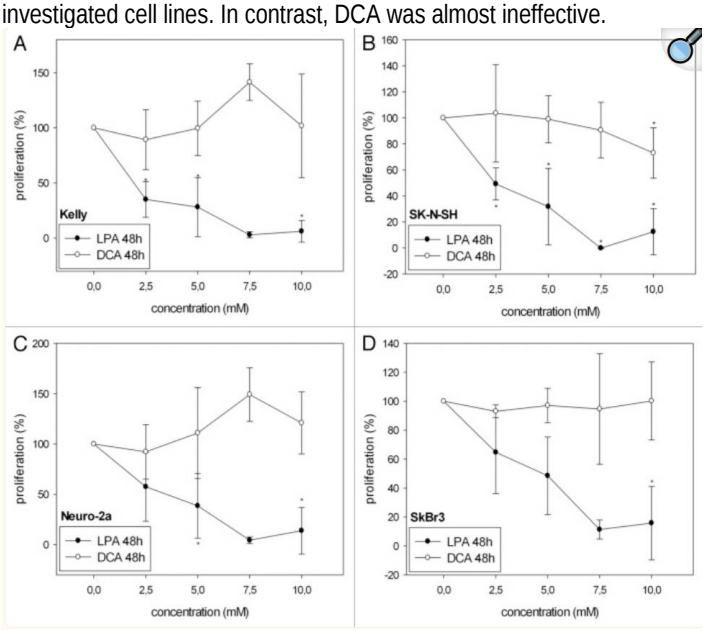
LA clearly inhibited cell migration and invasion of T24 cells, which were mimicked by extracellular signal-regulated kinase (ERK) and Akt pathway inhibition. Actually, LA significantly downregulated the phosphorylated ERK and Akt levels. Moreover, LA downregulated phosphorylated focal adhesion kinase level with disappearance of stress fiber formation. Finally, although LA induced the internalization of cell surface β1-integrin, disruption of the raft did not affect the action of LA. Taken together, LA is a promising agent to improve malignant character of bladder cancer cells through regulation of cellular β1-integrin localization.

https://pmc.ncbi.nlm.nih.gov/articles/PMC3542233/

Lipoic acid inhibits cell proliferation of tumor cells in vitro and in vivo 2012

Cancer cells convert glucose preferentially to lactate even in the presence of oxygen (aerobic glycolysis–Warburg effect). New concepts in cancer treatment aim at inhibition of aerobic glycolysis. Pyruvate dehydrogenase converts pyruvate to acetylCoA thus preventing lactate formation. Therefore, the aim of this study was to evaluate compounds that could activate pyruvate dehydrogenase in cancer cells. We investigated the effects of (R)-(+)-α-lipoic acid (LPA) and dichloroacetate (DCA), possible activators of pyruvate dehydrogenase, on suppression of aerobic glycolysis and induction of cell death.

These data suggests that LPA can reduce (1) cell viability/proliferation, (2) uptake of [18F]-FDG and (3) lactate production and increase apoptosis in all investigated cell lines. In contrast, DCA was almost ineffective.



The hypothesis that LPA could possibly change the glucose uptake in Kelly, Neuro-2a, SK-N-SH and SkBr3 cells was investigated by [18F]-FDG uptake experiments. The data support this idea because in our in vitro experiments all cells showed a dose dependent decrease of uptake. The impaired uptake might be in part due to decreased cell proliferation and/or cell death caused by LPA. However, it is also possible that a shift to oxidative turnover caused cells to reduce uptake since less glucose is needed to meet the demands for energy by switching over to oxidative respiration.[3,22]

https://pmc.ncbi.nlm.nih.gov/articles/PMC6723188/

Insights on the Use of α-Lipoic Acid for Therapeutic Purposes 2019

α-lipoic acid (ALA, thioctic acid) is an organosulfur component produced from plants, animals, and humans. It has various properties, among them great antioxidant potential and is widely used as a racemic drug for diabetic polyneuropathy-associated pain and paresthesia. Naturally, ALA is located in mitochondria, where it is used as a cofactor for pyruvate dehydrogenase (PDH) and α-ketoglutarate dehydrogenase complexes. Despite its various potentials, ALA therapeutic efficacy is relatively low due to its pharmacokinetic profile. Data suggests that ALA has a short half-life and bioavailability (about 30%) triggered by its hepatic degradation, reduced solubility as well as instability in the stomach. However, the use of various innovative formulations has greatly improved ALA bioavailability. The R enantiomer of ALA shows better pharmacokinetic parameters, including increased bioavailability as compared to its S enantiomer. Indeed, the use of amphiphilic matrices has capability to improve ALA bioavailability and intestinal absorption. Also, ALA's liquid formulations are associated with greater plasma concentration and bioavailability as compared to its solidified dosage form. Thus, improved formulations can increase both ALA absorption and bioavailability, leading to a raise in therapeutic efficacy. Interestingly, ALA bioavailability will be dependent on age, while no difference has been found for gender.

ALA plays a vital role in glucose humiliation during metabolism.

ALA is found in many vegetables (spinach, broccoli, tomato, brussels sprouts, and rice bran), meats and entrails (e.g., liver and kidney) in lipoyllysine form (ALA with binding lysine residues). Moreover, ALA can also be synthesized by enzymatic reactions in mitochondria from octanoic acid and cysteine (as a sulfur donor) [24,25].

3.4. **α-Lipoic Acid and Cancer**

An increasing body of literature highlight on the potential application of ALA in cancer therapy [68,69]. Cancer cells convert glucose preferentially to lactate for ATP generation, a phenomenon known as the Warburg effect or aerobic glycolysis. The persistent activation of aerobic glycolysis in cancerous cells lead to oncogenes activation or loss of tumor suppressors, thereby causing cancer progression. In this respect, the inhibition of aerobic cycle may contribute to anticancer

effects [70,71]. Pyruvate dehydrogenase catalyzes pyruvate to acetyl CoA conversion, thus preventing lactate production. Feuerecker et al. investigated whether ALA is capable of activating pyruvate dehydrogenase in tumor cells. The results show that ALA inhibited cell proliferation, [18F]-FDG uptake and lactate formation and increased apoptosis in neuroblastoma cell lines Kelly, SK-N-SH, Neuro-2a and in the breast cancer cell line SkBr3. In the mouse xenograft model with subcutaneously SkBr3 cells, daily treatment with ALA has delayed tumor growth [72].
Studies have also shown that ALA is able to generate ROS, which promote ALA-dependent cell death in lung cancer [75], breast cancer [76] and colon cancer [77,78], suggesting that it triggers the mitochondrial pathway of apoptosis in cancer cells.
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 after ALA administration [92]. In addition, it has been suggested that acidic pH of the stomach is favorable for ALA absorption through the gastrum. Therefore, ALA supplements are preferably taken on an empty stomach to benefit of the acidic stomach pH.
It was observed that ALA is rapidly absorbed after oral ingestion of 50 to 600 mg thioctic acid. The time required to reach the maximum plasma concentrations was about 0.5 to 1 h.
Similarly, another study determined the ALA bioavailability through different oral and intravenous (IV) formulations. The study used 200 mg ALA through the two administration routes to determine the pharmacokinetic parameters of ALA. The IV solution was given over 4 min, while the oral one consisted of 317.6 mg trometanlole salt, which corresponded to 200 mg of free ALA, 4 tablets of 50 mg and 1 tablet of 200 mg, given to 12 healthy subjects. The IV solution was the same as the oral solution. ALA could be detected for up to 2 h after IV drug administration and for up to 4 h after oral administration. However, it was determined that the maximum plasma concentration of ALA was greater through the IV route when compared to oral administration; in addition, the terminal half-lives for both routes were comparable.
Indeed, the bioavailability and peak plasma concentrations of ALA were found to be considerably higher in adults with mean age greater than 75 years as compared to young adults between the ages of 18 and 45 years.

https://pubmed.ncbi.nlm.nih.gov/33321563/
Synergistic Tumoricidal Effects of Alpha-Lipoic Acid and Radiotherapy on Human Breast Cancer Cells via HMGB1 2021
Results: Our data showed that ALA significantly promoted apoptotic cell death when combined with RT, as reflected by Annexin V staining, expression of apoptosis-related factors, mitochondrial damages as well as cell morphological changes and reduction of cell numbers. In addition, ALA significantly enhanced radiation-induced cellular senescence, which was shown by increased HMGB1 expression in the cytosol fraction compared to the control, increased p53 expression compared to the control, activation of p38 as well as nuclear factor κB, and G2/M cell cycle arrest.
Conclusion: The current study is the first report showing a new mode of action (senescence induction) of ALA beyond apoptotic cell death in MDA-MB-231 cancer cells known to be resistant to RT.

https://pubmed.ncbi.nlm.nih.gov/38578399/
Anti-cancer effects of alpha lipoic acid, cisplatin and paclitaxel combination in the OVCAR-3 ovarian adenocarcinoma cell line 2024
Conclusions: This study is the first one to investigate the combined treatment of ALA, Cisplatin, Paclitaxel on OVCAR-3. While ALA alone was not effective, combined therapy with ALA, has been found to reduce cell invasion, especially wound healing in the first 24 h, along with tumor cell adhesion.

https://pubmed.ncbi.nlm.nih.gov/39493360/
Combination of High-Dose Parenteral Ascorbate (Vitamin C) and Alpha-Lipoic Acid Failed to Enhance Tumor-Inhibitory Effect But Increased Toxicity in Preclinical Cancer Models 2024
Background: Intravenous vitamin C (IVC, ascorbate [Asc]) and alpha-lipoic acid (ALA) are frequently coadministered in integrative oncology clinics, with limited understanding of combination effects or drug-drug interactions. As high-dose IVC has anticancer activity through peroxide (H_2O_2), it is hypothesized that IV ALA, a thiol antioxidant, might have untoward effects when combined with IVC.
Results: Cancer cell lines were sensitive to Asc treatment but not to ALA. There is no evidence ALA becomes a prooxidant at higher doses. The CIs showed a mixture of synergistic and antagonistic effects with different ALA and Asc combination ratios, with a "U" shape response to Asc concentrations. The ALA concentrations did not influence the CIs or cellular H2O2 formation. Adding ALA to Asc dampened the increase of H2O2. Toxicity was observed in mice receiving prolonged treatment of ALA at all doses. The Asc at all doses was nontoxic. The combination of ALA and Asc increased toxicity. The ALA at all doses did not inhibit tumor growth. The Asc at 4 g/kg inhibited tumor growth. Adding ALA 50 mg/kg to Asc 4 g/kg did not enhance the effect, but lower doses of ALA (10 or 20 mg/kg) dampened the inhibitory effect of Asc.
Conclusions: These data do not support the concurrent or relative concurrent use of high-dose intravenous ALA with prooxidative high-dose IVC in clinical oncology care with potentially increased toxicity.

https://www.nature.com/articles/s41416-020-0729-6
Lipoic acid decreases breast cancer cell proliferation by inhibiting IGF-1R via furin downregulation 2020
Conclusion
LA exerts its anti-proliferative effect by inhibiting the maturation of IGF-1R via the downregulation of furin

https://pmc.ncbi.nlm.nih.gov/articles/PMC6395653/
Metabolic therapies inhibit tumor growth in vivo and in silico 2019
We used Alpha Lipoic Acid (ALA) and Hydroxycitrate (HCA), two old drugs from the pharmacopoeia targeting PDH and ACL, respectively. Interestingly, we managed to show that combination of ALA and HCA deeply inhibits cultures of three cancer cell lines (MBT-2 bladder carcinoma, B16-F10 melanoma and LL/2 lung carcinoma)[21]. These results agree with that from Hatzivassiliou and colleagues who reported the inhibition of cancer cells growth when using specific silencing RNA (SiRNA) to vanish ACL protein expression[22]. Similarly, a study from Bonnet and colleagues (2006) demonstrated the efficacy of a small molecule, Dichloroacetate, in restoring PDH activity in cancer cells[23]. Taken together, these experimental results show the potential of targeting enzymes involved in programming the Warburg effect. These therapeutic approaches show a similar efficacy as for conventional therapies but without any side effects. Furthermore, we have also investigated the efficacy of our drug combination, namely METABLOC (ALA and HCA), used in synergy with standard chemotherapy drugs such as Cisplatin or Methotrexane[24]. We reported an enhanced delay in tumor growth when Cisplatin and Methotrexane are applied in combination with METABLOC.

https://link.springer.com/article/10.1007/s12010-024-04994-4
Antistress and Antiaging Potentials of Alpha-Lipoic Acid: Insights from Cell Culture–Based Experiments 2024
Chronic stress has been linked to a large number of pathologies, including cancer, premature aging, and neurodegenerative diseases. The accumulation of molecular waste resulting from oxidative and heavy metal–induced stress has been ascribed as a major factor contributing to these diseases. With this in mind, we started by screening 13 small molecules to determine their antistress potential in heavy metal stress–exposed C6 glioblastoma and found that alpha-lipoic acid (ALA) (a natural antioxidant abundantly present in yeast, spinach, broccoli, and meat) was the most effective candidate. We then conducted molecular analyses to

validate its mechanism of action. Dose-dependent toxicity assays of cells treated with two ALA enantiomers, R-ALA and S-ALA, showed that they are nontoxic and can be tolerated at relatively high doses. Cells exposed to heavy metal, heat, and oxidative stress showed better recovery when cultured in R-ALA-/S-ALA-supplemented medium, supported by reduction of reactive oxygen species (ROS), aggregated proteins, and mitochondrial and deoxyribonucleic acid (DNA) damage. Molecular analyses revealed protection against stress-induced apoptosis and induction of autophagy in R-ALA- and S-ALA-treated C6/U2OS cells. Consistent with these findings, normal human fibroblasts showed lifespan extension. Taken together, this study demonstrates that lipoic acid has antiaging and antistress potential and warrants further attention in laboratory and clinical studies.

https://pubmed.ncbi.nlm.nih.gov/31958458/
α-Lipoic acid prevents the ionizing radiation-induced epithelial-mesenchymal transition and enhances the radiosensitivity in breast cancer cells 2020
Radiotherapy is routinely used in the treatment of breast cancer. However, its efficiency is often limited by the development of radioresistance and metastasis. The cancer cells surviving irradiation show epithelial-mesenchymal transition (EMT) along with increased migration, invasion and metastasis. In this study, we have evaluated the role of α-lipoic acid in preventing the radiation-induced EMT and in sensitizing the breast cancer cells to radiation. The breast cancer cell lines, MCF-7 and MDA-MB-231 were pretreated with lipoic acid, irradiated and the changes associated with cell growth, clonogenicity, migration, matrix metalloproteinases (MMPs), EMT and TGFβ signaling were measured. Our data showed that lipoic acid pretreatment sensitized the breast cancer cells to the ionizing radiation and inhibited the radiation-induced migration and the release of MMP2 and MMP9. Lipoic acid also prevented the TGFβ1 release and inhibited the radiation-induced EMT in breast cancer cells. The inhibition of TGFβ signaling by lipoic acid is associated with the inhibition of radiation-induced activation and translocation of NF-κB. These results suggest that α-lipoic acid inhibits the radiation-induced TGFβ signaling and nuclear translocation of NF-κB, thereby inhibiting the radiation-induced EMT and sensitizing the breast cancer cells to ionizing radiation.

https://pubmed.ncbi.nlm.nih.gov/37165582/
The Chemoprotective Potentials of Alpha-lipoic Acid against Cisplatin-induced Ototoxicity: A Systematic Review 2024
Ototoxicity is one of the major adverse effects of cisplatin therapy which restrict its clinical application. Alpha-lipoic acid administration may mitigate cisplatin-induced ototoxicity. In the present study, we reviewed the protective potentials of alpha-lipoic acid against the cisplatin-mediated ototoxic adverse effects.
Conclusion: The findings of audiometry, biochemical parameters, and histological evaluation showed that alpha-lipoic acid co-administration alleviates the cisplatin-induced ototoxicity. The protective role of alpha-lipoic acid against the cisplatin-induced ototoxicity can be due to different mechanisms of anti-oxidant, anti-apoptotic, anti-inflammatory activities, and regulation of cell cycle progression.

https://pmc.ncbi.nlm.nih.gov/articles/PMC9385783/
Role of alpha-lipoic acid in counteracting paclitaxel- and doxorubicin-induced toxicities: a randomized controlled trial in breast cancer patients 2022
Conclusion
Alpha-lipoic acid may represent a promising adjuvant therapy to attenuate paclitaxel-associated neuropathy and doxorubicin-induced cardiotoxicity in women with breast cancer.

https://pubmed.ncbi.nlm.nih.gov/31915505/
The Antioxidant Alpha-Lipoic Acid Inhibits Proliferation and Invasion of Human Gastric Cancer Cells via Suppression of STAT3-Mediated MUC4 Gene Expression 2019
Metastasis and invasion are the main causes of mortality in gastric cancer. To improve the treatment of gastric cancer, the development of effective and innovative antitumor agents toward invasion and proliferation is needed. Alpha-lipoic acid (ALA), a naturally occurring thiol antioxidant, showed antiproliferative and cytotoxic effects on several cancers. So it is feasible to explore whether ALA can be used to inhibit proliferation and invasion in human gastric cancer.
Conclusion: ALA inhibits both proliferation and invasion of gastric cancer cells by suppression of STAT3-mediated MUC4 gene expression

https://pmc.ncbi.nlm.nih.gov/articles/PMC11124255/
Hepatic-Metabolic Activity of α-Lipoic Acid—Its Influence on Sphingolipid Metabolism and PI3K/Akt/mTOR Pathway in a Rat Model of Metabolic Dysfunction-Associated Steatotic Liver Disease 2024
Our study aimed to evaluate the potential protective effect of α-lipoic acid (α-LA) administration on the intrahepatic metabolism of sphingolipid and insulin signaling transduction in rats with metabolic dysfunction-associated steatotic liver disease (MASLD).
Based on these data, we concluded that α-lipoic acid may alleviate glucose intolerance and may have a protective influence on the sphingolipid metabolism under HFD; thus, this antioxidant appears to protect from MASLD development and steatosis deterioration.

https://pubmed.ncbi.nlm.nih.gov/16484716/
The long-term survival of a patient with pancreatic cancer with metastases to the liver after treatment with the intravenous alpha-lipoic acid/low-dose naltrexone protocol 2006
The authors describe the long-term survival of a patient with pancreatic cancer without any toxic adverse effects. The treatment regimen includes the intravenous alpha-lipoic acid and low-dose naltrexone (ALA-N) protocol and a healthy lifestyle program. The patient was told by a reputable university oncology center in October 2002 that there was little hope for his survival. Today, January 2006, however, he is back at work, free from symptoms, and without appreciable progression of his malignancy. The integrative protocol described in this article may have the possibility of extending the life of a patient who would be customarily considered to be terminal. The authors believe that life scientists will one day develop a cure for metastatic pancreatic cancer, perhaps via gene therapy or another biological platform. But until such protocols come to market, the ALA-N protocol should be studied and considered, given its lack of toxicity at levels reported. Several other patients are on this treatment protocol and appear to be doing well at this time.

https://www.researchgate.net/publication/40819400_Revisiting_the_ALAN_-Lipoic_AcidLow-Dose_Naltrexone_Protocol_for_People_With_Metastatic_and_Nonmetastatic_Pancreatic_Cancer_A_Report_of_3_New_Cases
Revisiting the ALA/N (-Lipoic Acid/Low-Dose Naltrexone) Protocol for People With Metastatic and Nonmetastatic Pancreatic Cancer: A Report of 3 New Cases 2009
The authors, in a previous article, described the long-term survival of a man with pancreatic cancer and metastases to the liver, treated with intravenous alpha-lipoic acid and oral low-dose naltrexone (ALA/N) without any adverse effects. He is alive and well 78 months after initial presentation. Three additional pancreatic cancer case studies are presented in this article. At the time of this writing, the first patient, GB, is alive and well 39 months after presenting with adenocarcinoma of the pancreas with metastases to the liver. The second patient, JK, who presented to the clinic with the same diagnosis was treated with the ALA/N protocol and after 5 months of therapy, PET scan demonstrated no evidence of disease. The third patient, RC, in addition to his pancreatic cancer with liver and retroperitoneal metastases, has a history of B-cell lymphoma and prostate adenocarcinoma. After 4 months of the ALA/N protocol his PET scan demonstrated no signs of cancer. In this article, the authors discuss the poly activity of ALA: as an agent that reduces oxidative stress, its ability to stabilize NF(k)B, its ability to stimulate pro-

oxidant apoptosic activity, and its discriminative ability to discourage the proliferation of malignant cells. In addition, the ability of lowdose naltrexone to modulate an endogenous immune response is discussed. This is the second article published on the ALA/N protocol and the authors believe the protocol warrants clinical trial.

https://pmc.ncbi.nlm.nih.gov/articles/PMC5924730/
Oral Alpha-Lipoic Acid to Prevent Chemotherapy-Induced Peripheral Neuropathy: A Randomized, Double-Blind, Placebo-Controlled Trial 2013
Chemotherapy-induced peripheral neuropathy is frequently a dose-limiting factor in cancer treatment and may cause pain and irreversible function loss in cancer survivors. We tested whether alpha-lipoic acid (ALA) could decrease the severity of peripheral neuropathy symptoms in patients undergoing platinum-based chemotherapy.
This strategy of oral ALA administration was ineffective at preventing neurotoxicity caused by oxaliplatin or cisplatin. High attrition rates due to poor patient compliance and manner of dosage administration in this trial demonstrated a lack of feasibility for this intervention. Future studies to explore ALA as a neuroprotective agent should take heed of the barriers confronted in this study.

https://pubmed.ncbi.nlm.nih.gov/15843897/
alpha-Lipoic acid induces apoptosis in human colon cancer cells by increasing mitochondrial respiration with a concomitant O2-*-generation 2005
The antioxidant alpha-lipoic acid (ALA) has been shown to affect a variety of biological processes associated with oxidative stress including cancer. We determined in HT-29 human colon cancer cells whether ALA is able to affect apoptosis, as an important parameter disregulated in tumour development. Exposure of cells to ALA or its reduced form dihydrolipoic acid (DHLA) for 24 h dose dependently increased caspase-3-like activity and was associated with DNA-fragmentation. DHLA but not ALA was able to scavenge cytosolic O2-* in HT-29 cells whereas both compounds increased O2-*-generation inside mitochondria. Increased mitochondrial O2-*-production was preceded by an increased influx of lactate or pyruvate into mitochondria and resulted in the down-regulation of the anti-apoptotic protein bcl-X(L). Mitochondrial O2-*-generation and apoptosis induced by ALA and DHLA could be prevented by the O2-*-scavenger benzoquinone. Moreover, when the lactate/pyruvate transporter was inhibited by 5-nitro-2-(3-phenylpropylamino) benzoate, ALA- and DHLA-induced mitochondrial ROS-production and apoptosis were blocked. In contrast to HT-29 cells, no apoptosis was observed in non-transformed human colonocytes in response to ALA or DHLA addition. In conclusion, our study provides evidence that ALA and DHLA can effectively induce apoptosis in human colon cancer cells by a prooxidant mechanism that is initiated by an increased uptake of oxidizable substrates into mitochondria.

https://pmc.ncbi.nlm.nih.gov/articles/PMC5840773/
Early alpha-lipoic acid therapy protects from degeneration of the inner retinal layers and vision loss in an experimental autoimmune encephalomyelitis-optic neuritis model 2018
Alpha-lipoic acid (LA) is a naturally occurring antioxidant which has recently been demonstrated to reduce the rate of brain atrophy in progressive MS.

https://pmc.ncbi.nlm.nih.gov/articles/PMC6023526/
Do Anti-Oxidants Vitamin D3, Melatonin, and Alpha-Lipoic Acid Have Synergistic Effects with Temozolomide on Cultured Glioblastoma Cells? 2018
Conclusions: Anti-oxidants may have synergistic effects with TMZ. LA offers the most promise, followed by melatonin.