PEMF and antiOxidants, Trolox : Cancer

"Trolox is a water-soluble analog of vitamin E sold by Hoffman-LaRoche. It is an antioxidant like vitamin E and it is used in biological or biochemical applications to reduce oxidative stress or damage. "

https://www.nature.com/articles/s41598-023-46758-w

Spinning magnetic field patterns that cause oncolysis by oxidative stress in glioma cells 2023

Here, we characterized the precise configurations and timings of sOMF stimulation that produce cytotoxicity due to a critical rise in superoxide in two types of human glioma cells. We also found that the **antioxidant** Trolox reverses the cytotoxic effect of sOMF on glioma cells indicating that ROS play a causal role in producing the effect.

https://www.nature.com/articles/s41598-024-59391-y

The effect of a rotating magnetic field on the antioxidant system in healthy volunteers - preliminary study 2024

Oxidative stress is characterized by an excessive concentration of reactive oxygen species (ROS) resulting from a disturbance in the balance between ROS production and their removal by antioxidant systems (SOD, CAT, GPx). Prolonged and intense oxidative stress can cause various forms of damage to cells, which markers are total antioxidant capacity (TAC), reactive oxygen species modulator (ROMO1), and malondialdehyde (MDA). It has been demonstrated that magnetic fields can positively affect human health, for example, by reducing oxidative stress. Determination of the effect of a rotating magnetic field (RMF) on the activity/concentration of selected oxidative stress markers. A group of 30 healthy volunteers (15 women and 15 men) (mean age 24.8 ± 5.1) in the study classified into the following groups: internal control group (CG);
1 h 25 Hz (samples placed in the field for one hour at 25 Hz);
3 h 25 Hz (samples placed in the field for 3 h at 25 Hz), the 1 h 50 Hz group (placed in RMF for an hour at 50 Hz), and a group of 3 h 50 Hz (samples placed in the field for 3 h at 50 Hz). Serum samples were collected in K_2EDTA tubes.. The magnetic induction value obtained for RMF is 37.06 mT and 42.64 mT.Activity/concentration of selected oxidative stress markers was analyzed by ELISA. The influence of an RMF on the activity/concentration of SOD, MDA, TAC, and ROMO1 was demonstrated ($p < 0.001$; $p = 0.0013$; $p < 0.001$; $p = 0.003$). The RFM can reduce oxidative stress, as evidenced by higher SOD and CAT activities in the CG than in samples placed in the RFM. Prolonged exposure to the RFM at 50 Hz increased the TAC level, indicating an **intensification of oxidative stress** in these samples. The optimal conditions for staying in the RFM (reducing oxidative stress) are 1 h 50 Hz for SOD and MDA; 3 h 25 Hz for CAT and TAC. In the case of ROMO1, it is stated that 1 h 25 Hz are the optimal conditions for no increased production of ROS.
Conclusion
The rotating magnetic field may reduce oxidative stress, as evidenced by higher activities/ concentrations of SOD, CAT, or MDA in the internal control group than in the samples placed in the RMF. Too long a stay in the RMF at the frequency of 50 Hz increased the level of TAC, which proves the increase of oxidative stress in these samples.

https://pubmed.ncbi.nlm.nih.gov/17582581/

The antioxidant and pro-oxidant activity of vitamin C and trolox in vitro: a comparative study 2008

The antioxidant and pro-oxidant properties of ascorbic acid (vitamin C) and the water-soluble analogue of alpha-tocopherol (trolox) were compared. Trolox has advantages over alpha-tocopherol, the latter being only lipid-soluble due to the presence of a carboxyl group in lieu of a phytol chain which imparts trolox with water solubility. Trolox is used as a standard antioxidant in biochemical studies against which the antioxidant capacity of compounds is compared. Although ascorbic acid and tocopherols possess strong antioxidant properties, they might also exhibit pro-oxidant properties in the **presence of free transition metals**. Thus, reactions detailed in this study were performed in the presence of Cr(VI) in an effort to investigate the potential of ascorbic acid and trolox to generate hydroxyl radicals in a Fenton-like reaction. Results obtained were derived from reactions containing the same concentration of ascorbic acid and trolox under identical experimental conditions. Hydroxyl radical formation was observed in the reaction of Cr(VI) with ascorbic acid resulting from ascorbic acid auto-oxidation and H2O2 formation. Hydroxyl radical formation was only detected in the reaction mixture containing Cr(VI) and trolox following the addition of H2O2.

https://www.cancer.gov/about-cancer/causes-prevention/risk/diet/antioxidants-fact-sheet

Antioxidants and Cancer Prevention

Should people already diagnosed with cancer take antioxidant supplements?

Several randomized controlled trials, some including only small numbers of patients, have investigated whether taking antioxidant supplements during cancer treatment alters the effectiveness or reduces the toxicity of specific therapies (28). Although these trials had mixed results, some found that people who took antioxidant supplements during cancer therapy had worse outcomes, especially if they were smokers.
In some preclinical studies, antioxidants have been found to promote tumor growth and metastasis in tumor-bearing mice and to increase the ability of circulating tumor cells to metastasize (29–31). Until more is known about the effects of antioxidant supplements in cancer patients, these supplements should be used with caution. Cancer patients should inform their doctors about their use of any dietary supplement.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9220137/

Antioxidant Therapy in Cancer: Rationale and Progress 2022

2.1. Mechanisms in ROS Generation

ROS are prominently generated by transmembrane NOXs and other various oxidases from the mitochondrial electron transport chain (ETC) [25], endoplasmic reticulum (ER) [26] and peroxisomes [27], in response to intracellular signaling and extracellular stimuli. The mitochondrion functions as a highly dynamic organelle and an essential endogenous enzymatic source of ROS, which generates ROS through ETC, a series of electron transfer complexes located on the mitochondrial inner membrane [28,29]. The production of mitochondrial ROS is associated with the metabolism of glucose, fatty acids and amino acids (via glycolysis, β-oxidation and oxidative deamination, respectively), which provide precursors for tricarboxylic acid (TCA) cycle to produce metabolic substrates that enter the ETC [30,31]. In the mitochondrial ETC, ROS generation is probably due to the leak of electrons from complex I, II and III. During this process, oxygen is reduced with a single electron and thus generating $O_2^{\bullet-}$, which can be dismutated to H2O2 [32,33]. The rate of ROS generation from the mitochondrial ETC is predominantly dependent on the concentration of the one-electron donor and the reaction rate between the donor and oxygen. The primary function of NOXs is to produce ROS, which is triggered by a variety of factors and reported to be associated with tumor development [34]. The NOX family consists of seven members, namely NOX1, NOX2, NOX3, NOX4, NOX5, DUOX1 and DUOX2 [35]. They catalyze the conversion of oxygen to $O_2^{\bullet-}$ by transferring electrons to molecular oxygen in various subcellular compartments, such as the nucleus [36]. NOXs-derived ROS might activate the downstream secondary oxidase systems, such as xanthine oxidase and uncoupled endothelial nitric oxide synthase, further aggravating oxidative stress and accelerating the development of cancer [37].

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8051392/

Risks and benefits of antioxidant dietary supplement use during cancer treatment: protocol for a scoping review 2021

Chemotherapy is a treatment approach designed to stop cancer growth either by preventing the reproduction of new cancer cells or killing cancer cells directly. Most chemotherapy drugs target the cell cycle, by altering or damaging DNA in the cell.[4] One of the most significant causes of oxidative stress and inflammation is related to DNA damage.[5] Additionally, anticancer drugs cannot distinguish between cancer cells and healthy cells, which is thought to be a reason for chemotherapy's negative side effects.

There is concern that antioxidant therapies may interact with the cytotoxic effects of chemotherapy, lessening adverse side effects and improving quality of life, but also rendering the cancer treatment less effective.[21] For example, a recently published secondary data analysis from a clinical trial comparing chemotherapy schedules in breast cancer identified an increased hazard of recurrence in women using antioxidant supplements both before and during chemotherapy. Recent observational data has suggested that antioxidant supplements during and after cancer treatment are associated with an increased risk of cancer recurrence, raising concern about the place of antioxidant supplements during treatment for cancer.[22]

https://www.researchgate.net/publication/263778994_The_Promise_and_Perils_of_Antioxidants_for_Cancer_Patients

The Promise and Perils of Antioxidants for Cancer Patients 2014

It has been proposed that reactive oxygen species (ROS) cause mutations, and thus cancer, and that antioxidants counter this effect, but studies suggest that antioxidants do not prevent cancer and may accelerate it. These findings may be due to the cellular location of ROS targeted by antioxidants.

https://pubmed.ncbi.nlm.nih.gov/22784609/

Role of antioxidants in cancer therapy 2013

A primary mechanism of many chemotherapy drugs against cancer cells is the formation of ROS, or free radicals. Radiotherapy is based on the fact that ionizing radiation destroys tumor cells.

Much debate has arisen about whether antioxidant supplementation alters the efficacy of cancer chemotherapy. There is still limited evidence in both quality and sample size, suggesting that certain antioxidant supplements may reduce adverse reactions and toxicities. Significant reductions in toxicity may alleviate dose-limiting toxicities so that more patients are able to complete prescribed chemotherapy regimens and thus, in turn, improve the potential for success in terms of tumor response and survival.

https://pubmed.ncbi.nlm.nih.gov/30674247/

The Role of Antioxidants in Cancer, Friends or Foes? 2018

Antioxidants were shown to assist cancer initiation, interfere with cancer treatment by reducing its efficacy and patient survival, and vice versa, there are reports of beneficial antioxidant effect during the cancer treatment.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6111235/

Antioxidants as precision weapons in war against cancer chemotherapy induced toxicity – Exploring the armoury of obscurity 2018

However, many oncologists discourage the use of antioxidant rich food supplements because these may interfere with the modalities which kill cancer by generating free radicals.

Our comprehensive data suggests that antioxidant has superior potential of ameliorating chemotherapeutic induced toxicity. Antioxidant supplementation during chemotherapy also promises higher therapeutic efficiency and increased survival times in patients.

However, in cancer chemotherapy, a mode of action of certain antineoplastic agents involves generation of free radicals further leading to cellular damage and necrosis of malignant cells. Hence use of antioxidant during chemotherapy is criticized due to fear of causing interference with efficacy of the drug. On the contrary, many integrative practitioner converse uses of antioxidant supplements allowing patients to tolerate possibly higher effective doses of chemotherapy thereby increasing the chance of better tumor response and improved survival rate. Thus concomitant use of antioxidant during chemotherapy is been highly controversial topic. The questions repeatedly put forth are "Do antioxidants increase or decrease the efficacy of anticancer agent? Do antioxidants protect normal tissue and ameliorate toxicity or protect cancer cells from the effect of chemotherapy".

https://pubmed.ncbi.nlm.nih.gov/29043851/

Antioxidants in the Treatment of Cancer 2017

Several clinical trials have produced conflicting results regarding the benefit of antioxidants in cancer therapy thus questioning the incorporation of these substances in standard treatment regimens. Vitamins E and C, selenium, carotenoids, lycopene, soy products, and green tea extract are a few substances with antioxidant properties that have been studied in detail. This article reviews the results generated over the last 20 years through in vitro and in vivo studies in various types of cancers and stages of cancer treatment. Despite the commercial popularity and the multitude of studies examining antioxidant therapy, the true role of antioxidants is yet to be determined, requiring further investigation into its propagative, causal, or protective nature.

https://pubmed.ncbi.nlm.nih.gov/23680455/

Antioxidants: friends or foe in prevention or treatment of cancer: the debate of the century 2013

Although the natural antioxidants can alone or in combination with the diet provide some benefits for chemoprevention, their position in cancer therapy, especially initial stages of carcinogenesis is breaking down. On the other hand antioxidants can promote the survival of detached cells from extra cellular medium playing dual activities with respect to tumorigenesis through inhibition of tumorigenesis by preventing oxidative injuries to DNA and otherwise maintenance of tumor by promoting cell survival via metabolic rescue. Hopefully, more details of antioxidant and anti-neoplastic mechanisms become clear day by day, which have made researchers renew the strategy for designing cancer prevention or treatment.

https://pubmed.ncbi.nlm.nih.gov/39133405/

Role of Natural Antioxidants in Cancer 2024

Several studies have been conducted to investigate whether the use of dietary antioxidant supplements is associated with decreased risks of developing cancer in humans, mixed results were reported.

https://pubmed.ncbi.nlm.nih.gov/31407778/

The conundrum of dietary antioxidants in cancer chemotherapy 2020

Although chemotherapy succeeds in reducing tumor burden, the efficacy is limited due to acquired drug resistance and often irreparable side effects. Studies show that antioxidants may influence the response to chemotherapy and its side effects, although their use remains controversial. The evidence shows that some chemo-drugs induce oxidative stress and lead to normal tissue apoptosis and the entry of cancer cells to a dormant G0 state. Through the suppression of

oxidative stress, antioxidants could protect normal cells and bring the tumor out of dormancy so as to expose it to chemotherapies. This review is focused on the redox biology of cancer/normal cells and association of reactive oxygen species with drug resistance, cancer dormancy, and side effects. To this end, evidence from cellular, animal, and clinical studies is provided to better understand the conundrum of dietary antioxidants in cancer chemotherapy.

https://pubmed.ncbi.nlm.nih.gov/12907593/
The antioxidant conundrum in cancer 2003
The health-related effects of interactions between reactive oxygen species (ROS) and dietary antioxidants and the consequences of dietary antioxidant supplementation on human health are by no means clear. Although ROS, normal byproducts of aerobic metabolism, are essential for various defense mechanisms in most cells, they can also cause oxidative damage to DNA, proteins, and lipids, resulting in enhanced disease risk. Dietary antioxidants (e.g., vitamin E, vitamin C, beta-carotene, and selenium), as well as endogenous antioxidant mechanisms, can help maintain an appropriate balance between the desirable and undesirable cellular effects of ROS. However, any health-related effects of interactions between dietary antioxidants and ROS likely depend on the health status of an individual and may also be influenced by genetic susceptibilities. Clinical studies of antioxidant supplementation and changes in either oxidative status, disease risk, or disease outcome have been carried out in healthy individuals, populations at risk for certain diseases, and patients undergoing disease therapy. The use of antioxidants during cancer therapy is currently a topic of heated debate because of an overall lack of clear research findings. Some data suggest antioxidants can ameliorate toxic side effects of therapy without affecting treatment efficacy, whereas other data suggest antioxidants interfere with radiotherapy or chemotherapy. Overall, examination of the evidence related to potential interactions between ROS and dietary antioxidants and effects on human health indicates that consuming dietary antioxidant supplements has pros and cons for any population and raises numerous questions, issues, and challenges that make this topic a fertile field for future research. Overall, current knowledge makes it premature to generalize and make specific recommendations about antioxidant usage for those at high risk for cancer or undergoing treatment.

https://pubmed.ncbi.nlm.nih.gov/10559547/
Antioxidants in cancer therapy; their actions and interactions with oncologic therapies 1999
There is a concern that antioxidants might reduce oxidizing free radicals created by radiotherapy and some forms of chemotherapy, and thereby decrease the effectiveness of the therapy. The question has arisen whether concurrent administration of oral antioxidants is contraindicated during cancer therapeutics. Evidence reviewed here demonstrates exogenous antioxidants alone produce beneficial effects in various cancers, and except for a few specific cases, animal and human studies demonstrate no reduction of efficacy of chemotherapy or radiation when given with antioxidants. In fact, considerable data exists showing increased effectiveness of many cancer therapeutic agents, as well as a decrease in adverse effects, when given concurrently with antioxidants.

https://pubmed.ncbi.nlm.nih.gov/17283738/
Antioxidants and other nutrients do not interfere with chemotherapy or radiation therapy and can increase kill and increase survival, part 1 2007
Conclusions: Since the 1970s, 280 peer-reviewed in vitro and in vivo studies, including 50 human studies involving 8,521 patients, 5,081 of whom were given nutrients, have consistently shown that non-prescription antioxidants and other nutrients do not interfere with therapeutic modalities for cancer. Furthermore, they enhance the killing of therapeutic modalities for cancer, decrease their side effects, and protect normal tissue. In 15 human studies, 3,738 patients who took non-prescription antioxidants and other nutrients actually had increased survival

https://pubmed.ncbi.nlm.nih.gov/32768586/
Antioxidants with two faces toward cancer 2020
Taken together, antioxidants demonstrate a two-faced nature toward cancer. However, it is required to conduct further cell culture and in vivo studies to confirm the exact role of antioxidants and then use them for efficient cancer treatments.

https://ascopubs.org/doi/10.1200/JCO.2004.03.086
Antioxidants and Cancer Therapy: A Systematic Review 2004
Conclusion
These inconsistencies preclude a definitive conclusion as to the effect of chemotherapy on antioxidant status in patients undergoing anticancer therapy. However, our review suggests that total antioxidant status (measured by total radical antioxidant parameter) declines during cancer treatment. Adequately powered trials or observational studies among patients with a specific cancer diagnosis receiving a specific treatment regimen are needed to address patients' and physicians' concerns regarding these associations.

https://pubmed.ncbi.nlm.nih.gov/33849858/
Risks and benefits of antioxidant dietary supplement use during cancer treatment: protocol for a scoping review 2021
While some research indicates oral antioxidant supplementation reduces side effects and improves patient survival, other studies suggest the use of antioxidant dietary supplements may interfere with chemotherapy and reduce its curative effects.

https://www.intechopen.com/chapters/74332
The Two Sides of Dietary Antioxidants in Cancer Therapy 2020
Though there are numerous opinions about the dangers and advantages of antioxidants, it is reasonable to conclude that side effects caused by antioxidants, for now, remain unclear for patients during cancer treatment, aside from smokers during radiotherapy.

https://pubmed.ncbi.nlm.nih.gov/18839308/
Use of antioxidant supplements during breast cancer treatment: a comprehensive review 2009
Conclusion: The evidence is currently insufficient to inform clinician and patient guidelines on the use of antioxidant supplements during breast cancer treatment. Thus, well designed clinical trials and observational studies are needed to determine the short- and long-term effects of such agents.

https://isom.ca/wp-content/uploads/2020/01/JOM_2004_19_4_02_The_Use_of_Vitamin_C_with_Chemotherapy_in_Cancer-.pdf
The Use of Vitamin C with Chemotherapy in Cancer Treatment: An Annotated Bibliography 2004
In conclusion, this annotated bibliography of literature on the effectiveness of vitamin C alone, or with other vitamins, during chemotherapy confirms the conclusions of Prasad and coworkers (1999): "... antioxidants [including vitamin C] do not protect cancer cells against free radical and growth-inhibitory effects of standard therapy. On the contrary, they enhance its growth-inhibitory effects on tumor cells, but protect normal cells against its adverse effects."

https://iubmb.onlinelibrary.wiley.com/doi/abs/10.1002/biof.2117

Vitamin K3 derivative inhibits androgen receptor signaling in targeting aggressive prostate cancer cells 2024

The effect of micronutrients, including Vitamin K, on various cancer cell lines has been widely studied, but the potential anticancer effect of VK3-OCH3, an analog of vitamin K3 (Menadione), on African American prostate cancer has not been evaluated. In this study, we compared the anticancer effect of VK3-OCH3 on targeting African American derived PCa cell lines namely RC77-T and MDA-PCa-2b. Our results show that VK3-OCH3 significantly inhibits the proliferation of both RC77-T and MDA-PCa-2b African American PCa cells and promotes apoptosis, and the underlying mechanism of cell death appears to be similar in both the cell lines. Notably, VK3-OCH3 inhibits colony-forming ability and induces apoptosis by blocking the cell cycle at G0 in African American PCa cells. VK3-OCH3 also acts as an anti-metastatic agent by inhibiting the migration ability of the metastatic properties of African American PCa cells. The cell death of African American PCa cells mediated by VK3-OCH3 is associated with the production of free radicals, such as intracellular and mitochondrial reactive oxygen species (ROS). Interestingly, antioxidants such as N-Acetylcysteine (NAC) and Glutathione (GSH) effectively negated the oxidative stress induced by VK3-OCH3 on PCa cell lines derived from African American patients.

https://pmc.ncbi.nlm.nih.gov/articles/PMC2129149/

The Antioxidant Role of Glutathione and N-Acetyl-Cysteine Supplements and Exercise-Induced Oxidative Stress 2005

An increase in exercise intensity is one of the many ways in which oxidative stress and free radical production has been shown to increase inside our cells. Effective regulation of the cellular balance between oxidation and antioxidation is important when considering cellular function and DNA integrity as well as the signal transduction of gene expression. Many pathological states, such as cancer, Parkinson's disease, and Alzheimer's disease have been shown to be related to the redox state of cells. In an attempt to minimize the onset of oxidative stress, supplementation with various known antioxidants has been suggested. Glutathione and N-acetyl-cysteine (NAC) are antioxidants which are quite popular for their ability to minimize oxidative stress and the downstream negative effects thought to be associated with oxidative stress.

https://onlinelibrary.wiley.com/doi/full/10.1155/2021/9965916

The Involvement of the Oxidative Stress Status in Cancer Pathology: A Double View on the Role of the Antioxidants 2021

Oxygen-free radicals, reactive oxygen species (ROS) or reactive nitrogen species (RNS), are known by their “double-sided” nature in biological systems. The beneficial effects of ROS involve physiological roles as weapons in the arsenal of the immune system (destroying bacteria within phagocytic cells) and role in programmed cell death (apoptosis). On the other hand, the redox imbalance in favor of the prooxidants results in an overproduction of the ROS/RNS leading to oxidative stress. This imbalance can, therefore, be related to oncogenic stimulation. High levels of ROS disrupt cellular processes by nonspecifically attacking proteins, lipids, and DNA. It appears that DNA damage is the key player in cancer initiation and the formation of 8-OH-G, a potential biomarker for carcinogenesis. The harmful effect of ROS is neutralized by an antioxidant protection treatment as they convert ROS into less reactive species. However, contradictory epidemiological results show that supplementation above physiological doses recommended for antioxidants and taken over a long period can lead to harmful effects and even increase the risk of cancer. Thus, we are describing here some of the latest updates on the involvement of oxidative stress in cancer pathology and a double view on the role of the antioxidants in this context and how this could be relevant in the management and pathology of cancer.

In general, it is suggested that the continuous use of antioxidants like glutathione, superoxide dismutase, catalase, and thioredoxin may prevent the ROS levels from inducing anticancer mechanisms (mainly apoptosis) by keeping them in check [14]. Also, since tumor cells themselves produce antioxidants to overcome oxidative damage, the additional supplements may allow tumor cells to store surplus antioxidants and promote its survival and further proliferation [335]. A recent observational study of 2014 patients demonstrated an association between antioxidant supplements (including vitamins, carotenoids, and coenzyme Q_{10}) and increased risk for breast cancer recurrence and death [336].

However, inclusion of antioxidants in cancer therapy is controversial due to their unpredictable interaction with chemodrugs. Furthermore, recent research has revealed the overconsumption of antioxidants (and in particular synthetic antioxidants) can promote the survival and growth of cancer cells; a phenomenon known as the antioxidant paradox. A high antioxidant supplementation that exceeds safe levels can cause “antioxidant stress” and can fuel the metastasis-promoting physiological imbalance. In light of all these data, great caution is advised in the use of large doses of supplements. The natural state of health is a question of balance. A balanced diet of antioxidants can thus hold the key to cancer prevention.

https://pmc.ncbi.nlm.nih.gov/articles/PMC8799102/

The interplay between reactive oxygen species and antioxidants in cancer progression and therapy: a narrative review 2021

The suggested rationale for using antioxidant supplementation during chemotherapy, is to compensate the total antioxidant decline (measured by total radical antioxidant parameter/serum micronutrients) due to depletion of antioxidants after treatment, as some studies tried to investigate the effect of a single or a combination of antioxidants with chemotherapy; yet the evidence for such depletion isn’t conclusive (67).

In this regard, several studies concluded that polyphenols in higher concentrations then serve as prooxidants (75,76), e.g., quercetin at higher concentrations (>50 μM) can initiate ROS generation especially $O_2^{\bullet-}$;

https://pubmed.ncbi.nlm.nih.gov/26708754/

Antioxidant supplementation accelerates cachexia development by promoting tumor growth in C26 tumor-bearing mice 2016

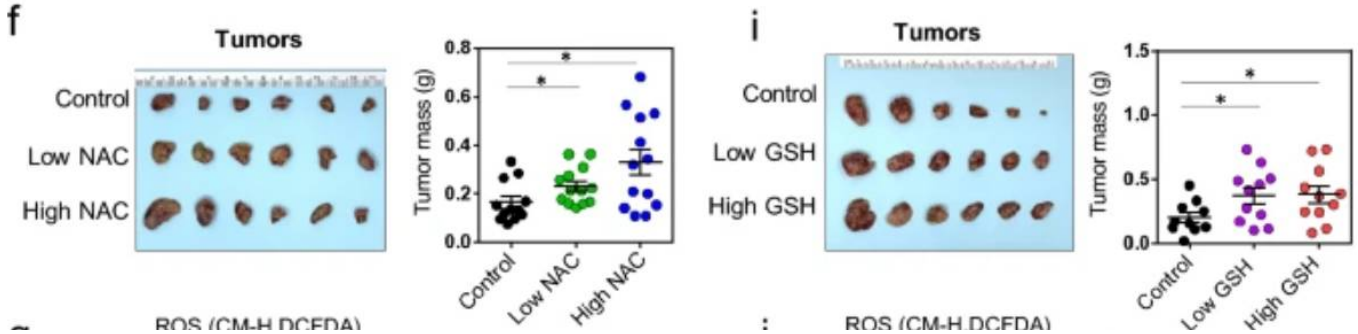
More than 50% of patients with advanced stages of colon cancer suffer from progressive loss of skeletal muscle, called cachexia, resulting in reduced quality of life and shortened survival. It is becoming evident that reactive oxygen species (ROS) regulate pathways controlling skeletal muscle atrophy. Herein we tested the hypothesis that antioxidant supplementation could prevent skeletal muscle atrophy in a model of cachectic Colon 26 (C26) tumor-bearing mice. Seven-week-old BALB/c mice were subcutaneously inoculated with colon 26 (C26) cancer cells or PBS. Then C26-mice were daily gavaged during 22 days either with PBS (vehicle) or an antioxidant cocktail whose composition is close to that of commercial dietary antioxidant supplements (rich in catechins, quercetin and vitamin C). We found that antioxidants enhanced weight loss and caused premature death of mice. Antioxidants supplementation failed to prevent (i) the increase in plasma TNF-α levels and systemic oxidative damage, (ii) skeletal muscle atrophy and (iii) activation of the ubiquitin-proteasome system (MuRF-1, MAFbx and polyubiquitinated proteins). Accordingly, immunohistological staining for Ki-67 and the expression of cell cycle inhibitors demonstrated that tumor of supplemented mice developed faster with a concomitant decrease in oxidative damage. Previous studies have shown that the use of catechins and quercetin separately can improve the musculoskeletal function in cachectic animals. However, our results indicate that the combination of these antioxidants reduced survival and enhanced cachexia in C26-mice.

https://cellandbioscience.biomedcentral.com/articles/10.1186/s13578-021-00731-0

Antioxidant supplements promote tumor formation and growth and confer drug resistance in hepatocellular carcinoma by reducing intracellular ROS and induction of TMBIM1 2021

Controversy over the benefits of antioxidants supplements in cancers persists for long. Using hepatocellular carcinoma (HCC) as a model, we investigated the effects of exogenous antioxidants *N*-acetylcysteine (NAC) and glutathione (GSH) on tumor formation and growth.

Conclusions
Our data implicate that exogenous antioxidants NAC and GSH, by reducing the intracellular ROS levels and inducing TMBIM expression, promoted HCC formation and tumor growth, and counteracted the therapeutic effect of Sorafenib. Our study provides scientific insight regarding the use of exogenous antioxidant supplements in cancers.



https://pubmed.ncbi.nlm.nih.gov/25496272/
Antioxidant supplementation on cancer risk and during cancer therapy: an update 2015
Radiation and some chemotherapeutic agents used in conventional cancer treatment generate reactive oxygen species (ROS), and a high ROS level diminishes cellular antioxidant capacity and leads to apoptosis and cancer cell death. Antioxidant supplements are consumed widely by cancer patients in order to prevent toxic side effects of cancer treatment to normal tissues and organs. However, the effects of antioxidant supplementation in cancer therapy were largely disappointing. There is still no consensus on the efficacy and safety of dietary antioxidant supplementation during conventional cancer therapy. In some studies, antioxidant supplements did not reduce the risk for cancer or prevent tumour growth; at the contrary, these interventions resulted in some cases to be harmful to the patients. Therefore, a guidance on antioxidant supplementation based on large clinical trials is urgently needed in order to obtain the best possible care and to avoid risky treatments for cancer patients.

https://www.cancer.gov/news-events/cancer-currents-blog/2015/antioxidants-metastasis
Antioxidants Accelerate the Growth and Invasiveness of Tumors in Mice 2015
Evidence from two new studies in mice shows that antioxidants—dietary supplements commonly used in the belief that they may help prevent disease—may actually promote tumor growth and metastasis.
The new findings, authors from both studies said, suggest that cancer patients and people with an increased risk of cancer should avoid taking antioxidant supplements.
To investigate how antioxidants might affect cancer progression, Martin Bergö, Ph.D., of the University of Gothenburg in Sweden, led a 2014 study in mouse models of human lung cancer. The researchers found that adding the antioxidants N-acetylcysteine (NAC) or vitamin E to the diet of mice with small lung tumors substantially increased the number, size, and stage of the tumors. Additional work showed that the NAC and vitamin E reduced levels of ROS and DNA damage in cancer cells, and essentially eliminated expression of the gene p53—a tumor suppressor gene that is typically activated by DNA damage.
These findings, Dr. Bergö said, provided a plausible explanation for why the male smokers who received antioxidants in the Alpha-Tocopherol, Beta Carotene Cancer Prevention Study in Finland had a higher incidence of lung cancer than those who received a placebo. The simplest explanation, Dr. Bergö said, is that when the trial recruited patients, many of them had small, undiagnosed lung tumors, which progressed more rapidly when they were given antioxidants.
The findings support the idea that antioxidants, by reducing oxidative stress, benefit tumor cells more than they benefit normal healthy cells, Dr. Morrison added. The results also support the idea that treating patients with pro-oxidants might be a way to prevent metastasis, he said.

https://pmc.ncbi.nlm.nih.gov/articles/PMC3093095/
Are antioxidants helpful for disease prevention? 2010
Evidence from basic research and observational epidemiologic studies suggest that individuals with high intakes of fruits and vegetables experience lower risks of developing cancer. Although there are many compounds in fruits and vegetables that may potentially influence cancer risk, it is generally assumed that certain antioxidants such as vitamin E, Vitamin C and beta-carotene may be responsible for the lower cancer rates. However, the few randomized trials of vitamin E, vitamin C or beta-carotene supplementation show no overall benefits; some even suggest harm. The findings of recent trials are summarized below:
The Physicians' Health Study II Random-ized Controlled Trial also evaluated whether long-term vitamin E (400 IU every other day) or vitamin C (500 mg daily) supplementation decreases the risk of prostate and total cancer events among men(23). During a mean follow-up of 8.0 years, there were 1943 confirmed incident cases of total cancers and 1008 cases of prostate cancer. Compared with placebo, vitamin E had no effect on the incidence of total cancer (vitamin E and placebo groups, 17.8 and 17.3 cases per 1000 person-years; HR, 1.04; 95% CI, 0.95-1.13; *P*=0.41) or prostate cancer (vitamin E and placebo groups, 9.1 and 9.5 events per 1000 person-years; HR, 0.97; 95% CI, 0.85-1.09; *P*=0.58). There was also no significant effect of vitamin C on total cancer (vitamin C and placebo groups, 17.6 and 17.5 events per 1000 person-years; HR, 1.01; 95%CI, 0.92-1.10; *P*=0.86) or prostate cancer (vitamin C and placebo groups, 9.4 and 9.2 cases per 1000 person-years; HR, 1.02; 95% CI, 0.90-1.15; *P*=0.80). Neither vitamin E nor vitamin C had a significant effect on colorectal, lung, or other site-specific cancers. Stratification by various cancer risk factors demonstrated no significant modification of the effect of vitamin E on prostate cancer risk or either supplement on total cancer risk. In this large, long-term trial neither vitamin E nor vitamin C supplementation reduced the risk of prostate or total cancer in middle-aged and older men(23).
A Systematic Review and Meta-analysis evaluated randomized clinical trails of anti-oxidants on the prevention of cancer(25). The review examined literature up to August 2005 and identified 12 high quality trails (including the women's health study) with a combined population of 104,196. Eligible antioxidants included beta-carotene, selenium, zinc, vitamin C and vitamin E alone or in combination with other antioxidant supplements. The review concludes that antioxidant supplementation, particularly with beta-carotene and vitamin E, does not reduce primary cancer incidence or cancer mortality. Beta-carotene supplementation might increase the risk of smoking-related cancers, as well as cancer mortality, and should be avoided by tobacco users. Selenium supplementation might reduce cancer incidence and cancer mortality in men, but not in women. Further research is needed to confirm the chemopreventive effect of selenium(25).

https://www.mdpi.com/2076-3921/11/11/2149
The Self-Administered Use of Complementary and Alternative Medicine (CAM) Supplements and Antioxidants in Cancer Therapy and the Critical Role of Nrf-2—A Systematic Review 2022
Drug–drug interactions with dietary supplements or vitamins involving multiple signaling pathways are well described. Since most of the anticancer drugs generate reactive oxygen species (ROS), an adaptive stress response of healthy and malignant cells, mainly driven by the Nrf-2-Keap I network, can be observed. On the one hand, healthy cells should be protected from ROS-overproducing chemotherapy and radiotherapy; on the other hand, ROS production in cancer cells is a

“desirable side effect” during anticancer drug treatment. We here describe the paradoxical use of antioxidants and supplements during cancer therapy, possible interactions with anticancer drugs, and the involvement of the Nrf-2 transcription factor.
Considering these inconclusive findings discussed in the literature [22,48], the intake of supplements by cancer patients, especially during their conventional treatment, seems at least questionable. According to different authors, dietary supplements, and especially antioxidants taken during conventional treatment, may exert various effects by reducing the toxicity of conventional anticancer therapies (and thus their side effects), but in consequence also by reducing the effectiveness of anticancer drugs and radiotherapy [46,48,88,99]. In fact, chemotherapeutic agents and radiotherapy exert their effectiveness by producing ROS, increasing oxidative stress in cancer cells. On the contrary, antioxidants such as vitamins (A, C, and E), minerals, and polyphenols reduce ROS, thus not only protecting normal cells, but also potentially cancer cells from oxidative stress [22,46,88,99]. Based on this mechanism, Andersen et al. [99], who investigated antioxidant use in cancer patients receiving chemotherapy, found that more than one-quarter of participants treated with anthracyclines (doxorubicin) and platinum-based anticancer drugs (carboplatin and cisplatin) were at potential risk of reduced effectiveness due to antioxidants. An even higher proportion of possibly compromised anticancer therapies was found in a similar newer study [88].
.1.2. Nrf-2 Dual Role in Cancer
Several outstanding reviews described Nrf-2 as a hallmark of malignant cells [108,109,110,111]. The role of Nrf-2 in cancer development is a double-edged sword. Nrf-2 maintains redox homeostasis in normal cells and thus acts as tumor-suppressive, while it is constitutively activated in many cancer cells to maintain an enhanced resistance against hypoxic conditions. The transcription factor activates pro-survival genes to enhance proliferation, promotes tumor progression and metastasis, and inhibits pro-apoptotic cell signals. From a clinical perspective, patients with a high expression of Nrf-2 in their tumor tissue have a higher risk of recurrence and a poor survival prognosis, mainly due to the increased chemo- and/or radioresistance of the tumor [112,113].
However, as mentioned above, Nrf-2 activation also fosters cancer cell resistance and therefore might limit the success of the therapy. This dilemma often leads to a paradoxical use of antioxidants during chemotherapy, either by the doctor’s prescription (reviewed by Yasueda et al. [22])

https://www.cell.com/trends/cell-biology/abstract/S0962-8924(20)30058-1
The Complex Interplay between Antioxidants and ROS in Cancer 2020
Highlights
New tools allow in vivo measurements of ROS in tumors.
Mouse modeling and genetic screening approaches have revealed novel complexities and redundancies in endogenous antioxidant systems.
Exogenous antioxidants may promote cancer through complex mechanisms.
Aberrant NRF2 activation has diverse, and sometimes contradictory, impacts on tumor growth and metastasis.
Tissue of origin, tumor stage, and the microenvironment greatly influence the influence of ROS on cancer.

https://pmc.ncbi.nlm.nih.gov/articles/PMC7062457/
Dietary Supplement Use During Chemotherapy and Survival Outcomes of Patients With Breast Cancer Enrolled in a Cooperative Group Clinical Trial (SWOG S0221) 2019
Despite reported widespread use of dietary supplements during cancer treatment, few empirical data with regard to their safety or efficacy exist. Because of concerns that some supplements, particularly antioxidants, could reduce the cytotoxicity of chemotherapy, we conducted a prospective study ancillary to a therapeutic trial to evaluate associations between supplement use and breast cancer outcomes.
There were indications that use of any antioxidant supplement (vitamins A, C, and E; carotenoids; coenzyme Q10) both before and during treatment was associated with an increased hazard of recurrence (adjusted hazard ratio [adjHR], 1.41; 95% CI, 0.98 to 2.04; *P* = .06) and, to a lesser extent, death (adjHR, 1.40; 95% CI, 0.90 to 2.18; *P* = .14). Relationships with individual antioxidants were weaker perhaps because of small numbers. For nonantioxidants, vitamin B12 use both before and during chemotherapy was significantly associated with poorer disease-free survival (adjHR, 1.83; 95% CI, 1.15 to 2.92; *P* < .01) and overall survival (adjHR, 2.04; 95% CI, 1.22 to 3.40; *P* < .01). Use of iron during chemotherapy was significantly associated with recurrence (adjHR, 1.79; 95% CI, 1.20 to 2.67; *P* < .01) as was use both before and during treatment (adjHR, 1.91; 95% CI, 0.98 to 3.70; *P* = .06). Results were similar for overall survival. Multivitamin use was not associated with survival outcomes.

https://pubmed.ncbi.nlm.nih.gov/24477002/
Antioxidants accelerate lung cancer progression in mice 2014
Antioxidants are widely used to protect cells from damage induced by reactive oxygen species (ROS). The concept that antioxidants can help fight cancer is deeply rooted in the general population, promoted by the food supplement industry, and supported by some scientific studies. However, clinical trials have reported inconsistent results. We show that supplementing the diet with the antioxidants N-acetylcysteine (NAC) and vitamin E markedly increases tumor progression and reduces survival in mouse models of B-RAF- and K-RAS-induced lung cancer. RNA sequencing revealed that NAC and vitamin E, which are structurally unrelated, produce highly coordinated changes in tumor transcriptome profiles, dominated by reduced expression of endogenous antioxidant genes. NAC and vitamin E increase tumor cell proliferation by reducing ROS, DNA damage, and p53 expression in mouse and human lung tumor cells. Inactivation of p53 increases tumor growth to a similar degree as antioxidants and abolishes the antioxidant effect. Thus, antioxidants accelerate tumor growth by disrupting the ROS-p53 axis. Because somatic mutations in p53 occur late in tumor progression, antioxidants may accelerate the growth of early tumors or precancerous lesions in high-risk populations such as smokers and patients with chronic obstructive pulmonary disease who receive NAC to relieve mucus production.

https://pubmed.ncbi.nlm.nih.gov/27383327/
Vitamin E promotes breast cancer cell proliferation by reducing ROS production and p53 expression 2016
Results: Vitamin E supplement in the chow significantly accelerated breast cancer cell growth in vivo. ROS level and p53 expression were decreased in tumor tissues. Water-solvable vitamin E Trolox significantly promoted MCF7 cell proliferation in vitro, while reducing intracellular ROS level and p53 expression. p53 knowdown by p53-siRNA transfection inMCF7 cells significantly reduced p53 expression and increased MCF7 cell proliferation.
Conclusions: Vitamin E accelerated breast cancer growth by reducing ROS production and p53 expression.

https://pubmed.ncbi.nlm.nih.gov/31578304/
The antioxidant N-acetylcysteine protects from lung emphysema but induces lung adenocarcinoma in mice 2019
Here, we investigated chronic NAC treatment in aging mice displaying lung oxidative stress and cell senescence due to inactivation of the transcription factor JunD, which is downregulated in diseased human lungs. NAC treatment decreased lung oxidative damage and cell senescence and protected from lung emphysema but concomitantly induced the development of lung adenocarcinoma in 50% of JunD-deficient mice and 10% of aged control mice. This finding constitutes the first evidence to our knowledge of a carcinogenic effect of antioxidant therapy in the lungs of aged mice with chronic lung oxidative stress and warrants the utmost caution when considering the therapeutic use of antioxidants.

https://pubmed.ncbi.nlm.nih.gov/33557356/

Antioxidants Promote Intestinal Tumor Progression in Mice 2021

Dietary antioxidants and supplements are widely used to protect against cancer, even though it is now clear that antioxidants can promote tumor progression by helping cancer cells to overcome barriers of oxidative stress. Although recent studies have, in great detail, explored the role of antioxidants in lung and skin tumors driven by RAS and RAF mutations, little is known about the impact of antioxidant supplementation on other cancers, including Wnt-driven tumors originating from the gut. Here, we show that supplementation with the antioxidants N-acetylcysteine (NAC) and vitamin E promotes intestinal tumor progression in the ApcMin mouse model for familial adenomatous polyposis, a hereditary form of colorectal cancer, driven by Wnt signaling. Both antioxidants increased tumor size in early neoplasias and tumor grades in more advanced lesions without any impact on tumor initiation. Importantly, NAC treatment accelerated tumor progression at plasma concentrations comparable to those obtained in human subjects after prescription doses of the drug. These results demonstrate that antioxidants play an important role in the progression of intestinal tumors, which may have implications for patients with or predisposed to colorectal cancer.

https://pmc.ncbi.nlm.nih.gov/articles/PMC9945759/

ROS-lowering doses of vitamins C and A accelerate malignant melanoma metastasis 2023

Oxidative stress is a barrier of migration and metastasis for malignant melanoma cells. Consequently, reducing oxidative stress with the antioxidant N-acetylcysteine (NAC) stimulates melanoma cell migration in vitro and metastasis in vivo. However, it is not yet known whether the NAC effect is shared with other antioxidants. Here, we screened 104 redox-active compounds and identify 27 that increase migration of human malignant melanoma cells in two doses. Validation experiments in four cell lines and four drug doses resulted in a list of 18 compounds which were ranked based on their ability to increase migration and reduce ROS levels; vitamin C (VitC) ranked as number one, followed by the vitamin E analogue Trolox and several carotenoids and Vitamin A–related compounds. Four diet-relevant compounds from this list—VitC, β-carotene, retinyl palmitate, and canthaxanthin—were selected and found to accelerate metastasis in mice with BRAFV600E-driven malignant melanoma. Genomics analyses revealed that the transcription factor BACH1 is activated following antioxidant administration and knockout of Bach1 in mouse melanoma cells reduced lymph node and liver metastasis in xenograft mouse models. We conclude that a broad range of antioxidants accelerate melanoma migration and metastasis and that BACH1 is functionally linked to melanoma metastasis in vivo.

https://www.mdpi.com/2072-6694/8/10/92

Antioxidant Activity during Tumor Progression: A Necessity for the Survival of Cancer Cells? 2016

Antioxidant defenses encompass a variety of distinct compounds and enzymes that are linked together through their capacity to neutralize and scavenge reactive oxygen species (ROS). While the relationship between ROS and tumorigenesis is clearly complex and context dependent, a number of recent studies have suggested that neutralizing ROS can facilitate tumor progression and metastasis in multiple cancer types through distinct mechanisms. These studies therefore infer that antioxidant activity may be necessary to support the viability and/or the invasive capacity of cancer cells during tumor progression and metastasis. Here, we discuss some of the accumulating evidence suggesting a role for antioxidant activity in facilitating tumor progression.

Early evidence of a potential pro-tumorigenic role for antioxidant activity came from the results of a clinical trial in 1996 that surprisingly demonstrated worse outcomes for lung cancer patients who had a history of smoking and were given dietary supplements of β-carotene and vitamin A [1]. Following the publication of these unexpected data, additional studies were published that seemed to corroborate the idea that antioxidant activity could facilitate tumorigenesis [2,3,4]. However, a molecular mechanism that could clarify how cancer cells can benefit from antioxidant activity in a fashion that promotes tumor formation and/or progression remained elusive until the publication of several recent studies.

https://www.researchgate.net/publication/276475050_Abstract_503_Antioxidants_markedly_accelerate_tumor_growth_and_reduce_survival_in_mice_with_KRAS-_and_BRAF-induced_lung_cancer_by_disrupting_the_ROS-p53_axis

Abstract 503: Antioxidants markedly accelerate tumor growth and reduce survival in mice with KRAS- and BRAF-induced lung cancer by disrupting the ROS-p53 axis 2014

Antioxidants are widely used to protect cells from damage induced by reactive oxygen species (ROS). The concept that antioxidants can help fight cancer is deeply rooted in the general population, promoted by the food supplement industry, and supported by some scientific studies. However, clinical trials have reported inconsistent results. Here, we show that supplementing the diet with the antioxidants N-acetylcysteine (NAC) or vitamin E markedly increases tumor progression and reduces survival by 50-60% in mouse models of B-RAF- and K-RAS-induced lung cancer

https://pmc.ncbi.nlm.nih.gov/articles/PMC7445980/

Antioxidant Antagonises Chemotherapeutic Drug Effect in Lung Cancer Cell Line A549 2020

Methods:

Small lung Cancer cell line (A549) was treated with anticancer drug 6-Thioguanine (6-TG) at different concentration viz., 1, 10, 50 and 100µM and the proliferation was measured using MTT assay. The antioxidant N-Acetyl Cysteine (NAC) in different ratios viz., 1mM, 5mM and 10mM were assayed for their effect in proliferation on the A549 cells alone and in combination with 6-TG.

Results:

Our experiment proves that anticancer drug 6-TG decreases the proliferation and the antioxidant NAC enhances the proliferation of A549 cells. Strikingly when co-treated with 6-TG, the antioxidant NAC diminished the proliferation reduction action of 6-TG on A549 cells.

Conclusion:

Our results suggest that antioxidants in fact benefit the tumor cell growth when treated alone and when in combination with anticancer drug, it severely impair the activity of the drug. **We propose that extreme care should be taken when prescribing antioxidants alone or in combination with chemotherapeutics.**

https://pubmed.ncbi.nlm.nih.gov/31257027/

BACH1 Stabilization by Antioxidants Stimulates Lung Cancer Metastasis 2019

For tumors to progress efficiently, cancer cells must overcome barriers of oxidative stress. Although dietary antioxidant supplementation or activation of endogenous antioxidants by NRF2 reduces oxidative stress and promotes early lung tumor progression, little is known about its effect on lung cancer metastasis. Here, we show that long-term supplementation with the antioxidants N-acetylcysteine and vitamin E promotes KRAS-driven lung cancer metastasis. The antioxidants stimulate metastasis by reducing levels of free heme and stabilizing the transcription factor BACH1. BACH1 activates transcription of Hexokinase 2 and Gapdh and increases glucose uptake, glycolysis rates, and lactate secretion, thereby stimulating glycolysis-dependent metastasis of mouse and human lung cancer cells. Targeting BACH1 normalized glycolysis and prevented antioxidant-induced metastasis, while increasing endogenous BACH1 expression stimulated glycolysis and promoted metastasis, also in the absence of antioxidants. We conclude that BACH1 stimulates glycolysis-dependent lung cancer metastasis and that BACH1 is activated under conditions of reduced oxidative stress.

https://www.researchgate.net/publication/282772360_Antioxidants_can_increase_melanoma_metastasis_in_mice

Antioxidants can increase melanoma metastasis in mice 2015

Antioxidants in the diet and supplements are widely used to protect against cancer, but clinical trials with antioxidants do not support this concept. Some trials show that antioxidants actually increase cancer risk and a study inmice showed that antioxidants accelerate the progression of primary lung tumors. However, little is known about the impact of antioxidant supplementation on the progression of other types of cancer, including malignant melanoma. We show that administration of N-acetylcysteine (NAC) increases lymph node metastases in an endogenous mousemodel of malignant melanoma but has no impact on the number and size of primary tumors. Similarly, NAC and the soluble vitamin E analog Trolox markedly increased the migration and invasive properties of human malignant melanoma cells but did not affect their proliferation. Both antioxidants increased the ratio between reduced and oxidized glutathione in melanoma cells and in lymph node metastases, and the increased migration depended on new glutathione synthesis. Furthermore, both NAC and Trolox increased the activation of the small guanosine triphosphatase (GTPase) RHOA, and blocking downstream RHOA signaling abolished antioxidant-induced migration. These results demonstrate that antioxidants and the glutathione system play a previously unappreciated role in malignant melanoma progression.

https://www.researchgate.net/publication/369072109_ANTI-OXIDANTS_AND_LUNG_CANCER

ANTI-OXIDANTS AND LUNG CANCER 2022

Number of clinical studies indicates that antioxidants increase the risk of some malignancies, particularly lung cancer (1, 2). Additionally, study published by Sayin et al, suggested that treatment with NAC or vitamin-E accelerated tumour growth in mice with lung cancer caused by a Ras gene mutation, although it reduced oxidative stress and DNA damage as would be predicted causing decrease in the activity of the p53 protein associated with the suppression of oxidative stress. The use of antioxidants is often cited as one of the possible therapeutic approaches, both preventive as well as curative. However, further research is warranted to confirm its actual role.

https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4653529

Antioxidants Accelerate Hepatocellular Carcinoma Initiation and Progression by Inhibiting Gst-Pi-Mapk Axis 2023

Non-alcohol fatty liver diseases are increasingly becoming a major risk factor of hepatocellular carcinoma (HCC). And accumulating evidence indicates that antioxidants promote tumor growth or metastasis after tumor onset in several cancer types. However, whether antioxidants can prevent or accelerate hepatic tumorigenesis with steatosis remains unknown. In this study, we investigated effects of resveratrol (RES) and N-acetylcystein (NAC) on HCC formation in a fatty liver setting. In both high fat diet (HFD) plus DEN and AKT/Ras-induced primary HCC mouse models, RES or NAC reduced lipid accumulation.
Our study indicates that antioxidants may increase the incidence of HCC in the population with fatty liver although reduce the ROS production.

https://www.cell.com/cell-metabolism/fulltext/S1550-4131(15)00575-6

Metastasis and Oxidative Stress: Are Antioxidants a Metabolic Driver of Progression? 2015

Tumor metastasis is the main cause of death in cancer patients. The acquisition of specific traits by cancer cells, including migration, invasion, and survival in the bloodstream, permits metastasis. Of all the tumor cells that reach the circulation, only a few are able to generate metastases in distant organs. Emerging evidence suggests that oxidative stress acts as a key driver of the malignant transformation observed in primary tumors that enhances their metastatic potential. In a recent Nature paper, Piskounova et al. show that increased production of reactive oxygen species (ROS) is essential to enable and sustain a highly metastatic phenotype (Piskounova et al., 2015).

ROS, including hydrogen peroxide (H_2O_2) and superoxide ($O_2^{\bullet-}$) and hydroxyl ($HO^{\bullet}$) free radicals, are mainly produced during oxygen-consuming metabolic reactions that occur in peroxisomes, the endoplasmic reticulum, and the mitochondria, which is their major source. Moderate ROS levels have been shown to support cell proliferation and migration and activate stress-induced signaling pathways involved in cell survival, therefore contributing to tumor development (Gorrini et al., 2013). Accordingly, the use of antioxidants to quench oxidative stress has been postulated as a preventive and therapeutic anticancer strategy. Thus, large-scale clinical trials using antioxidant supplementation have been conducted, though they failed to benefit patients and even increased cancer incidence (Sayin et al., 2014). Considering the relevance of oxidative stress in cancer development, why have many clinical trials based on antioxidant supplementation not shown therapeutic efficacy? One possibility is that excessive ROS accumulation promotes severe cellular damage and triggers apoptosis, which makes a tight redox regulation essential for the cell. Indeed, cancer cells depend on an increased antioxidant capacity, which keeps ROS levels higher than in normal cells, but below a critical threshold able to maintain their viability. It has been observed that the same stimuli that promote oxidative stress, such as detachment from the cell matrix, also increase the selective pressure on cells to adapt by building up a powerful antioxidant response (Gorrini et al., 2013).

The study performed by Piskounova et al. supports that notion. To identify the mechanistic differences in the metastatic activity of several melanomas, the authors performed a metabolomics analysis on patient-derived melanoma xenografts and the metastases that they generated. Cancer cells isolated from blood and from metastatic sites displayed higher levels of cytoplasmic and mitochondrial-derived ROS than those from the primary subcutaneous tumors (Figure 1A). Paradoxically, treatment with the antioxidant N-acetyl-cysteine (NAC) increased the presence of circulating cancer cells and metastatic burden, indicating that cellular oxidative stress limits metastasis in vivo. Moreover, metastatic tumors showed a reversible increase in the overall production of the endogenous antioxidants glutathione and NADPH, which was linked to a higher folate pathway activity, indicating that tumor cells adopt adaptive measures to neutralize oxidative stress. Indeed, blocking the folate pathway either by genetically downregulating the expression of enzymes of this pathway or by pharmacologically inhibiting it using methotrexate decreased melanoma metastasis in mice (Figure 1A) (Piskounova et al., 2015). In conclusion, the authors show that efficient spread and metastatic seeding of melanoma cells not only depends on their high ROS production but also on their **ability to withstand the cellular oxidative stress** they experience, as they travel through the bloodstream and initiate new metastatic lesions (Figure 1B).