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Double-edged role of antioxidants and oxidative stress: Focusing on cancer therapy and resistance

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ABSTRACT

Oxidative stress and antioxidant systems are complex components of human physiology and pathology. Reactive oxygen species (ROS), previously viewed as undesirable byproducts of cellular metabolism, have now been identified as critical signaling agents that participate in cell proliferation, differentiation, and immune responses. Both endogenous and exogenous antioxidants play a critical role in redox homeostasis by countering surplus ROS and preventing oxidative injury. Nevertheless, growing evidence points to the paradoxical dual nature of antioxidants, casting doubt on their universally positive effects. This paradox is particularly pronounced in cancer. Although high levels of ROS promote tumor development and progression by causing genomic instability and activating oncogenic signaling, high levels of ROS can also cause cancer cell death and represent a major mechanism of action of anticancer therapies. Tumor cells respond by increasing their antioxidant capacity, which enables them to maintain ROS at levels that promote survival without causing cytotoxicity. Exogenous antioxidant supplementation can therefore disrupt this balance, potentially stimulating tumor growth, enabling metastasis, and diminishing the efficacy of ROS-dependent therapies like chemotherapy and radiotherapy. Moreover, plant-derived antioxidants, such as polyphenols and flavonoids, exhibit both antioxidant and pro-oxidant effects, highlighting the context-specificity of redox modulation in cancer. Although these compounds may have chemopreventive advantages, their impact on established malignancies is complex and requires additional research. This review provides a broad description of the duality of oxidative stress and antioxidants, specifically regarding their implications in cancer treatment and resistance. A better comprehension of redox biology is needed to develop more effective and personalized therapeutic interventions based on the specific regulation of oxidative stress.

Implication for health policy/practice/research/medical education:
The double edged nature of antioxidants suggests that routine supplementation during cancer therapy might warrant caution. Context dependent effects imply that clinical recommendations should remain tentative, and further investigation into redox modulation appears advisable before revising health policies.

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Introduction

Oxidative stress, understood as a condition in which reactive oxygen species (ROS) production tips the balance beyond what endogenous antioxidant systems can neutralize, is a fundamental biological process involved in the pathogenesis of many diseases (1,2). According to the GLOBOCAN report, close to 20 million diagnoses of cancer and roughly 9.7 million deaths attributed to the disease are recorded each year across the globe, with over 30% linked to modifiable factors including redox imbalance (1). ROS comprise a wide spectrum of chemically reactive molecules, encompassing free-radical members such as

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the superoxide anion ($O_2^{\bullet-}$) and hydroxyl radical ($\bullet\mathrm{OH}$), in addition to non-radical counterparts like hydrogen peroxide (H_2O_2). Under physiological conditions, ROS are crucial signaling molecules that coordinate cellular proliferation, differentiation, immune responses, and adaptation to environmental factors. However, excessive ROS accumulation leads to oxidative stress, damaging DNA, proteins, and lipids, which contributes to genomic instability and cellular dysfunction (3,4).

Considering the pivotal role of oxidative stress in disease pathogenesis, antioxidants have long been considered protective factors that could prevent or reduce oxidative damage (5,6). Endogenous antioxidant systems, including glutathione (GSH), superoxide dismutase (SOD), catalase, and thioredoxin, as well as exogenous antioxidants, including vitamins C and E, carotenoids, and polyphenols, collaborate to achieve redox homeostasis (6,7). Epidemiological research has long suggested that diets rich in antioxidant-containing foods are linked with a decreased risk of chronic illnesses, such as cardiovascular diseases, neurodegeneration, and cancer (8,9). Nevertheless, over the past decade, a growing body of evidence has challenged this paradigm and demonstrated paradoxical or two-sided effects of antioxidants on human health and disease (10,11). Although antioxidants can inhibit oxidative damage and disease onset, in some circumstances, they can disrupt physiological ROS signaling or even promote disease progression. For instance, antioxidant supplementation has been shown to suppress beneficial ROS-mediated adaptive responses in metabolic and cardiovascular systems, and in certain settings can be detrimental or increase disease risk (11,12). Likewise, in neurodegenerative diseases, both excessive ROS and excessive antioxidant activity can destabilize redox signaling, indicating that a delicate balance is needed rather than total elimination of ROS (13).

This contradiction is especially acute in cancer biology, where ROS have a strongly context-dependent dual role (14,15). On one hand, high ROS concentrations can cause DNA damage, mutagenesis, and oncogenic conversion, thus contributing to tumor initiation and progression. On the other hand, ROS concentrations beyond a critical threshold can trigger cell death pathways including apoptosis, ferroptosis, and senescence, which are exploited by numerous anticancer therapies (14,16). Consequently, cancer cells tend to evolve adaptive antioxidant responses to keep ROS at sublethal levels, allowing survival while maintaining pro-tumorigenic signaling (17-19).

This review aimed to answer the following specific question: why can a single antioxidant be beneficial during cancer prevention yet harmful during treatment of the same tumor, and how can this duality be managed? To address this, we critically analyze the mechanistic foundations of the antioxidant paradox, distinguish between different classes of antioxidants, and synthesize evidence from preclinical and clinical studies to propose a framework for context-specific redox modulation in cancer therapy.

Reactive oxygen species: Sources, types, and physiological roles

ROS originate from molecular oxygen and exhibit high reactivity, encompassing radical forms such as $O_2^{\bullet-}$ and $\bullet\mathrm{OH}$, along with non-radical counterparts like H_2O_2 (2,7,18-20). These species are continuously generated in cells through endogenous pathways, primarily the mitochondrial electron transport chain (ETC), where electron leakage from complexes I and III reduces O_2 to $O_2^{\bullet-}$, accounting for approximately 90% of cellular ROS production (18,21-24). Other major endogenous sources include NADPH oxidases (NOX1–5, DUOX1–2) (25), xanthine oxidase (XO) (26), lipoxygenases (LOXs) (27), cytochrome P450 enzymes (28), peroxisomes (29), and the endoplasmic reticulum (ER) (30), with NOX enzymes directly producing $O_2^{\bullet-}$ or H_2O_2 (25), and XO generating both during purine metabolism (26). Peroxisomes contribute H_2O_2 during fatty acid oxidation, while ER generates ROS during protein folding and disulfide bond formation, and uncoupled nitric oxide synthase (NOS) produces $O_2^{\bullet-}$ instead of $\mathrm{NO}\bullet$ (29,31). Exogenous sources, including ionizing radiation (32), environmental pollutants (6), chemotherapeutic agents (18,33), and cigarette smoke (34), further elevate ROS levels through direct or indirect mechanisms. Ionizing radiation energizes oxygen electrons to produce ROS (32), while cigarette smoke chemicals (e.g., benzo[a]pyrene, formaldehyde) generate ROS directly or indirectly (35,36).

At physiological levels, ROS serve as essential secondary messengers in redox signaling, regulating processes such as cell proliferation, differentiation, immune responses, and adaptation to hypoxia by modulating pathways like MAPK, PI3K/Akt, and transcription factors, including Nrf2 and NF-κB (37-39). However, excessive ROS lead to oxidative stress, damaging DNA, proteins, and lipids, thereby contributing to mutagenesis, genomic instability, and the pathogenesis of various chronic diseases, including cancer as a prominent example (5,13,21,39,40).

ROS in cancer: Double-edged role

ROS are known to have an intricate role in cancer, which can act both as an initiator and an inhibitor of cancer formation, depending on their concentration and location in cancer cells (41,42). ROS can act as signaling molecules in cancer cells at moderate concentrations, activating oncogenic pathways such as NF-κB, MAPK, and PI3K/AKT, which are known to promote cell growth, survival, angiogenesis, and metabolic reprogramming (43,44). These signaling cascades contribute to tumor initiation and progression by enhancing cell cycle progression and inhibiting apoptosis. However, an accumulation of ROS beyond a certain threshold can cause irreversible oxidative damage to cellular macromolecules such as

DNA, lipids, and proteins, resulting in DNA strand breaks, lipid peroxidation, and protein oxidation (45). Once ROS buildup passes a certain threshold in malignant cells, several distinct pathways of regulated cell death become triggered — among them, apoptosis, ferroptosis, and necroptosis (46,47). This cytotoxic effect of ROS is therapeutically exploited by many conventional anticancer strategies, such as chemotherapy and radiotherapy, which rely on increasing oxidative stress to eliminate malignant cells (48). However, cancer cells are known to be highly adaptable in coping with oxidative stress. They can activate antioxidant defenses to counteract elevated ROS concentrations resulting from oncogenic signaling and metabolic reprogramming (49). Key regulators such as nuclear factor erythroid 2-related factor 2 (NRF2) are known to coordinate the expression of antioxidant and detoxifying enzymes in cancer cells, which can survive under conditions of oxidative stress (50). This adaptive redox reprogramming allows tumor cells to sustain proliferative signaling while avoiding ROS-induced cytotoxicity.

Endogenous and exogenous elements of antioxidant systems

Intracellular ROS levels are regulated by a highly coordinated network of enzymatic and non-enzymatic components that make up the cellular antioxidant defense system (51). The thioredoxin system, which preserves protein redox balance, catalase and glutathione peroxidase (GPx) and SODs are examples of endogenous antioxidant enzymes (52,53). Under physiological circumstances, these systems are crucial for maintaining cellular integrity and avoiding oxidative damage. In addition, exogenous antioxidants from food sources play a major role in redox regulation alongside endogenous defenses (54). These consist of a variety of polyphenolic compounds, carotenoids, and vitamins (such as C and E). Dietary antioxidants have the ability to scavenge free radicals, chelate metal ions, and alter oxidative stress-related signaling pathways (55). However, their role in disease prevention and treatment is complicated by their metabolism, bioavailability, and context-dependent effects.

Crucially, the overall redox state of the cell is determined by the interaction between endogenous and exogenous antioxidant systems. Pathological outcomes, especially in cancer, can result from upsetting this balance, either through excessive ROS production or excessive ROS suppression via antioxidant supplementation (56,57).

Distinguishing endogenous, dietary, and pharmacological antioxidants

It is essential to distinguish between three categories of antioxidants, which differ fundamentally in pharmacokinetics, tissue concentration, and mechanism of action. Endogenous antioxidants (e.g., SOD, catalase, GSH, thioredoxin), synthesized by the body, are under tight transcriptional control (primarily by NRF2), and function in a compartment-specific manner (51-53). Dietary antioxidants (e.g., vitamins C and E, polyphenols from fruits and vegetables), consumed through food, have variable bioavailability (often low for polyphenols), and undergo extensive first-pass metabolism, limiting their tissue concentrations. Pharmacological antioxidants (e.g., N-acetylcysteine, high-dose vitamin E supplements) are administered at supraphysiological doses, achieving systemic concentrations that can profoundly alter redox balance. This distinction is maintained throughout the revised manuscript (54-57). For example, endogenous GSH upregulation by tumors promotes resistance, while dietary flavonoids at physiological doses may have negligible direct scavenging effects but significant signaling modulation, and pharmacological N-acetylcysteine has been shown to promote metastasis in preclinical models (19,52,53,55).

Mechanistic crosstalk: NRF2, MAPK, and NF-κB in redox-driven therapy resistance

The transcription factor NRF2 serves as the primary orchestrator of cellular antioxidant defenses. Under normal, unstressed conditions, KEAP1 sequesters NRF2 in the cytosol, thereby routing it toward breakdown by the proteasome. Oxidative stress or electrophilic signals modify KEAP1 cysteine residues, stabilizing NRF2, which then translocates to the nucleus and upregulates over 200 genes, including GCLC, GCLM (glutathione synthesis), SOD1, CAT, NQO1, and HO-1. In many cancers, constitutive NRF2 activation (via KEAP1 or NRF2 mutations) confers broad chemoresistance by neutralizing ROS generated by chemotherapy and radiotherapy (42-45,48,50).

MAPK signaling (particularly JNK and p38) is redox-sensitive. Moderate ROS activate MAPK pathways to promote proliferation, whereas excessive ROS causes sustained JNK/p38 activation leading to apoptosis (42-45). Antioxidants can blunt this pro-apoptotic signal. NF-κB, a pro-inflammatory and survival transcription factor, is also redox-regulated: ROS promote IκB kinase (IKK) activation and NF-κB nuclear translocation, inducing anti-apoptotic genes (e.g., BCL-XL, XIAP, survivin). Paradoxically, high ROS can inhibit NF-κB by oxidizing critical cysteine residues in the DNA-binding domain. Thus, antioxidants may either suppress or enhance NF-κB depending on the cellular context (42-45,48). This complex crosstalk explains why indiscriminate antioxidant use can unintentionally protect tumors (42,44,45).

Paradoxical effects of antioxidants in cancer progression

Although antioxidants have long been thought to protect against cancer, new research suggests that, in some circumstances, they may actually promote tumor growth (19,58). The reduction of ROS below levels necessary for initiating tumor-suppressive pathways, such as p53-mediated apoptosis and senescence, is one of the primary mechanisms underlying this paradox (59). Antioxidants may unintentionally help damaged or altered cells survive by reducing oxidative stress.

In certain cancer models, preclinical research has shown that antioxidant supplementation can hasten tumor growth and metastasis (60). For instance, antioxidants have been shown to enhance the metastatic potential of cancer cells by reducing oxidative stress during detachment, circulation, and colonization at distant sites (61). Because circulating tumor cells undergo high levels of oxidative stress and rely on antioxidant defenses to survive, this effect is especially significant.

Antioxidants may also obstruct immune responses against tumors that are mediated by ROS. Cytotoxic T lymphocytes and natural killer (NK) cells are among the immune cells that are activated by ROS (62,63). Overproduction of antioxidants may suppress these immune reactions, which would lessen immune-mediated tumor removal and facilitate immune evasion.

Antioxidants and resistance to cancer therapy

A major clinical implication of the antioxidant paradox is its impact on resistance to cancer therapy. Many standard cancer treatments, including chemotherapy and radiotherapy, exert their cytotoxic effects through the induction of oxidative stress (64). These treatments cause DNA damage and trigger cancer cell apoptosis by raising intracellular ROS levels. Treatment resistance, however, may result from tumor cells' increased antioxidant capacity neutralizing therapy-induced ROS (65). Common mechanisms contributing to this resistance include increased expression of detoxifying enzymes, activation of NRF2 signaling, and upregulation of GSH (66). Numerous cancer types, including lung, breast, and pancreatic cancers, have been shown to exhibit this phenomenon. Furthermore, by shielding tumor cells from oxidative damage, exogenous antioxidant supplementation during cancer treatment may worsen resistance (67). Antioxidants may lessen the effectiveness of radiotherapy and chemotherapeutic drugs, according to clinical and experimental research, though results are still context-specific and occasionally debated (68).

Plant-derived antioxidants: Opportunities and challenges

Plant antioxidants, such as terpenoids, phenolic acids, and flavonoids, have been thoroughly investigated for their possible applications in cancer treatment and prevention (69,70). Antioxidant, anti-inflammatory, and antiproliferative compounds like quercetin, curcumin, and resveratrol have demonstrated encouraging outcomes in preclinical cancer models.

Numerous cellular pathways, such as NF-κB signaling inhibition, apoptotic cascade activation, and cell cycle progression regulation, can be modulated by these phytochemicals (71). Plant antioxidants may reduce oxidative DNA damage and prevent tumor initiation in the early stages of carcinogenesis. But like synthetic antioxidants, they have complicated effects in established tumors that can change based on the tumor microenvironment, timing, and dosage (72).

Notably, some plant-derived compounds can exhibit pro-oxidant activity under specific conditions, leading to increased ROS production and selective killing of cancer cells (73,74). This dual behavior further highlights the context-dependent nature of antioxidant activity and suggests potential therapeutic applications when precisely targeted.

Critical analysis of conflicting evidence

The literature contains apparent contradictions regarding antioxidants in cancer. For example, the SELECT study (Selenium and Vitamin E Cancer Prevention Trial) indicated that vitamin E supplementation increased prostate cancer risk, while observational studies suggested protective effects (75). Similarly, N-acetylcysteine (NAC) reduces lung tumor burden in some KRAS mutant models but accelerates metastasis in melanoma and lung cancer models (76). These discrepancies arise from several factors: (1) Timing: Antioxidants may prevent initiation (by reducing DNA damage) but promote progression (by allowing damaged cells to survive); (2) Tumor type: KRAS or BRAF mutant tumors with high basal ROS depend on antioxidant defenses, making exogenous antioxidants potentially harmful; (3) Model system: Three-dimensional culture and in vivo studies reveal effects (e.g., on metastasis) not seen in 2D cultures; (4) Dose: Physiological doses may differ from pharmacological doses. Rather than inconsistency, these findings indicate that antioxidant effects are highly context-dependent, necessitating a personalized approach (Table 1) (2,19,42,43,48,49,77).

Clinical evidence from phase 3 trials and meta-analyses

The following clinical studies and meta-analyses provide critical translational context. The SELECT trial demonstrated that vitamin E significantly increased prostate cancer risk among healthy men, contradicting earlier observational studies (75). The vitamin E and Beta-Carotene Cancer Prevention Study found that beta-carotene supplementation increased lung cancer incidence and mortality in male smokers (78). In the therapeutic setting, D'Andrea and Block et al systematically reviewed evidence suggesting that antioxidant supplementation during chemotherapy or radiotherapy may reduce treatment efficacy, although results vary by cancer type and specific antioxidant (79,80). More recently, Ambrosone et al reported that dietary supplement use during chemotherapy for breast cancer was associated with worse recurrence-free survival (81). Preclinical mechanistic studies by Le Gal et al and Sayin et al demonstrated that pharmacological antioxidants (NAC and vitamin E)

Table 1. Fruits with high antioxidant capacity and their dual roles in cancer

Fruit/Plant	Main phytochemical	Dual role in cancer	References
Barberry	Berberine	Induces apoptosis in colon cancer cells; inhibits proliferation	(84)
Green Tea	EGCG (Epigallocatechin gallate)	Inhibits angiogenesis at low dose; pro-oxidant cytotoxicity at high dose	(85)
Turmeric	Curcumin	Antioxidant in healthy tissue; pro-oxidant and apoptosis inducer in tumor cells	(86)
Pomegranate	Ellagic acid & Punicalagin	Inhibits metastasis in breast cancer models; modulates estrogen signaling	(87)
Blueberry	Anthocyanins	Neuroprotective; conflicting evidence with chemotherapy (may reduce efficacy)	(88)
Grape (seed/skin)	Resveratrol	Activates SIRT1; pro-oxidant at high doses inducing apoptosis	(89)

accelerate tumor progression and metastasis in mouse models of lung cancer and melanoma, respectively (82,83). These findings collectively recommend caution against indiscriminate antioxidant use in cancer patients without careful consideration of tumor redox status.

Conclusion

The dynamic interplay between oxidative stress and antioxidant systems represents a central axis in cancer biology. ROS exhibit a dual role: they contribute to tumor initiation while also serving as key mediators of cancer cell death at cytotoxic levels. Antioxidants, traditionally viewed as protective, can paradoxically enhance metastatic dissemination and reduce the efficacy of ROS-dependent therapies. Cancer cells exploit this balance by upregulating endogenous antioxidant systems, including NRF2 signaling, to develop therapy resistance. Future research must focus on targeted redox modulation, selectively disrupting antioxidant defenses in cancer cells while preserving normal function. Perhaps it is time to move from universal antioxidant prescription to decisions based on the specific redox profile of each tumor. Remaining knowledge gaps include the lack of validated biomarkers for tumor redox status and the need for prospective trials stratifying patients by tumor NRF2/KEAP1 mutational status.

Authors' contribution

Conceptualization: All authors.
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Writing–original draft: All authors.
Writing–review & editing: Ali Rafieian, Mohammad Kordkatouli, Manal Sami Abduridha

Conflict of interests

The authors declare no conflict of interest.

Declaration of AI-assisted tools in the writing procedure

This manuscript was prepared with the assistance of artificial intelligence software, specifically DeepSeek and ChatGPT, which were used solely for improving writing quality and correcting grammatical errors; these tools were not used for data analysis, interpretation, or any other aspects of the research. All AI-suggested edits were reviewed and approved by the authors, who take full responsibility for the final content of the manuscript.

Ethical considerations

This article is a review study and did not involve any original research on human or animal subjects. Therefore, no ethical approval from a committee was required. The authors have adhered to ethical principles in scientific writing, including avoiding plagiarism, fabrication, and falsification of data. All sources cited have been properly acknowledged.

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References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229-263. doi: 10.3322/caac.21834.
2. Pizzino G, Irrera N, Cucinotta M, Pallio G, Mannino F, Arcoraci V, et al. Oxidative Stress: Harms and benefits for human health. Oxid Med Cell Longev. 2017;2017:8416763.
3. Sena LA, Chandel NS. Physiological roles of mitochondrial reactive oxygen species. Mol Cell. 2012;48(2):158-67.
4. Lennicke C, Cochemé HM. Redox metabolism: ROS as specific molecular regulators of cell signaling and function. Mol Cell. 2021;81(18):3691-707.
5. Ratnam DV, Ankola DD, Bhardwaj V, Sahana DK, Kumar MN. Role of antioxidants in prophylaxis and therapy: A pharmaceutical perspective. J Control Release. 2006;113(3):189-207.
6. Pham-Huy LA, He H, Pham-Huy C. Free radicals,

antioxidants in disease and health. Int J Biomed Sci. 2008;4(2):89-96.

7. Sies H, Belousov VV, Chandel NS, Davies MJ, Jones DP, Mann GE, et al. Defining roles of specific reactive oxygen species (ROS) in cell biology and physiology. Nat Rev Mol Cell Biol. 2022;23(7):499-515.
8. Hercberg S, Galan P, Preziosi P, Alfarez MJ, Vazquez C. The potential role of antioxidant vitamins in preventing cardiovascular diseases and cancers. Nutrition. 1998;14(6):513-520. doi:10.1016/s0899-9007(98)00040-9
9. Briguglio G, Costa C, Pollicino M, Giambò F, Catania S, Fenga C. Polyphenols in cancer prevention:new insight (review). International Journal of Functional Nutrition. 2020;1(2):9. doi:10.3892/ijfn.2020.9
10. Chaiswing L, St Clair WH, St Clair DK. Redox Paradox: A Novel Approach to Therapeutics-Resistant Cancer. Antioxid Redox Signal. 2018;29(13):1237-1272. doi:10.1089/ars.2017.7485
11. Salehi B, Martorell M, Arbiser JL, Sureda A, Martins N, Maurya PK, et al. Antioxidants: Positive or Negative Actors?. Biomolecules. 2018;8(4):124. doi:10.3390/biom8040124
12. Bjelakovic G, Nikolova D, Gluud C. Antioxidant supplements and mortality. Curr Opin Clin Nutr Metab Care. 2014;17(1):40-4.
13. Chen X, Guo C, Kong J. Oxidative stress in neurodegenerative diseases. Neural Regen Res. 2012;7(5):376-85.
14. Huang R, Chen H, Liang J, Li Y, Yang J, Luo C, et al. Dual role of reactive oxygen species and their application in cancer therapy. J Cancer. 2021;12(18):5543-61.
15. Nakamura H, Takada K. Reactive oxygen species in cancer: Current findings and future directions. Cancer Sci. 2021;112(10):3945-52.
16. Aggarwal V, Tuli HS, Varol A, Thakral F, Yerer MB, Sak K, et al. Role of reactive oxygen species in cancer progression: molecular mechanisms and recent advancements. Biomolecules. 2019;9(11):735. doi:10.3390/biom9110735
17. Jomova K, Alomar SY, Valko R, Fresser L, Nepovimova E, Kuca K, et al. Interplay of oxidative stress and antioxidant mechanisms in cancer development and progression. Arch Toxicol. 2026;100(1):27-73.
18. Conklin KA. Chemotherapy-associated oxidative stress: impact on chemotherapeutic effectiveness. Integr Cancer Ther. 2004;3(4):294-300.
19. Le Gal K, Ibrahim MX, Wiel C, Sayin VI, Akula MK, Karlsson C, et al. Antioxidants can increase melanoma metastasis in mice. Sci Transl Med. 2015;7(308):308re8. doi:10.1126/scitranslmed.aad3740
20. Zhang YJ, Gan RY, Li S, Zhou Y, Li AN, Xu DP, et al. Antioxidant phytochemicals for the prevention and treatment of chronic diseases. Molecules. 2015;20(12):21138-56.
21. Zhou Y, Zheng J, Li Y, Xu DP, Li S, Chen YM, et al. Natural Polyphenols for Prevention and Treatment of Cancer. Nutrients. 2016;8(8):515. doi:10.3390/nu8080515
22. Pereira AG, Echave J, Jorge AOS, Nogueira-Marques R, Nur Yuksek E, Barciela P, et al. Therapeutic and Preventive Potential of Plant-Derived Antioxidant Nutraceuticals. Foods. 2025;14(10):1749. doi:10.3390/foods14101749
23. Sarniak A, Lipińska J, Tytman K, Lipińska S. Endogenous mechanisms of reactive oxygen species (ROS) generation. Postepy Hig Med Dosw (Online). 2016;70(0):1150-65.
24. Yang Y, Karakhanova S, Hartwig W, D'Haese JG, Philippov PP, Werner J, et al. Mitochondria and Mitochondrial ROS in Cancer: Novel Targets for Anticancer Therapy. J Cell Physiol. 2016;231(12):2570-81.
25. Kim TH, Lee HC, Kim JH, Hewawaduge CY, Chathuranga K, Chathuranga WAG, et al. Fas-associated factor 1 mediates NADPH oxidase-induced reactive oxygen species production and proinflammatory responses in macrophages against Listeria infection. PLoS Pathog. 2019;15(8):e1008004. doi:10.1371/journal.ppat.1008004
26. Bonini MG, Miyamoto S, Di Mascio P, Augusto O. Production of the carbonate radical anion during xanthine oxidase turnover in the presence of bicarbonate. J Biol Chem. 2004;279(50):51836-43.
27. Zheng Y, Boeglin WE, Schneider C, Brash AR. A 49-kDa mini-lipoxygenase from Anabaena sp. PCC 7120 retains catalytically complete functionality. J Biol Chem. 2008;283(8):5138-47.
28. Furge LL, Guengerich FP. Cytochrome P450 enzymes in drug metabolism and chemical toxicology: An introduction. Biochem Mol Biol Educ. 2006;34(2):66-74. doi:10.1002/bmb.2006.49403402066
29. Yin J, Wang H, Hong Y, Ren A, Wang H, Liu L, et al. Identification of an at-risk subpopulation with high immune infiltration based on the peroxisome pathway and TIM3 in colorectal cancer. BMC Cancer. 2022;22(1):44. doi:10.1186/s12885-021-09085-9
30. Farooqi AA, Li KT, Fayyaz S, Chang YT, Ismail M, Liaw CC, et al. Anticancer drugs for the modulation of endoplasmic reticulum stress and oxidative stress. Tumour Biol. 2015;36(8):5743-52.
31. Zeeshan HM, Lee GH, Kim HR, Chae HJ. Endoplasmic Reticulum Stress and Associated ROS. Int J Mol Sci. 2016;17(3):327.
32. Azzam EI, Jay-Gerin JP, Pain D. Ionizing radiation-induced metabolic oxidative stress and prolonged cell injury. Cancer Lett. 2012;327(1-2):48-60. doi:10.1016/j.canlet.2011.12.012
33. Mizutani H, Tada-Oikawa S, Hiraku Y, Kojima M, Kawanishi S. Mechanism of apoptosis induced by doxorubicin through the generation of hydrogen peroxide. Life Sci. 2005;76(13):1439-53.
34. Yanbaeva D, Dentener M, Creutzberg E, Wesseling G, Wouters EFM. Systemic Effects of Smoking. Chest. 2007;131:1557-66.
35. Phaniendra A, Jestadi DB, Periyasamy L. Free radicals: properties, sources, targets, and their implication in various diseases. Indian J Clin Biochem. 2015;30(1):11-26.
36. Li Y, Hecht SS. Carcinogenic components of tobacco and tobacco smoke: A 2022 update. Food Chem Toxicol. 2022;165:113179. doi:10.1016/j.fct.2022.113179
37. Son Y, Cheong YK, Kim NH, Chung HT, Kang DG, Pae HO. Mitogen-Activated Protein Kinases and Reactive Oxygen Species: How Can ROS Activate MAPK Pathways? J Signal Transduct. 2011;2011:792639.
38. Takata T, Araki S, Tsuchiya Y, Watanabe Y. Oxidative Stress orchestrates MAPK and nitric-oxide synthase signal. Int J Mol Sci. 2020;21(22):8750. doi:10.3390/ijms21228750
39. Bardaweel SK, Gul M, Alzweiri M, Ishaqat A, HA AL, Bashatwah RM. Reactive Oxygen Species: the Dual Role in

Physiological and Pathological Conditions of the Human Body. Eurasian J Med. 2018;50(3):193-201.

40. Ottaviano FG, Handy DE, Loscalzo J. Redox regulation in the extracellular environment. Circ J. 2008;72(1):1-16.
41. Reczek CR, Chandel NS. The Two Faces of Reactive Oxygen Species in Cancer. Annu Rev Cancer Biol. 2017;1:79-98. doi:10.1146/annurev-cancerbio-041916-065808
42. Moloney JN, Cotter TG. ROS signalling in the biology of cancer. Semin Cell Dev Biol. 2018;80:50-64. doi:10.1016/j.semcdb.2017.05.023
43. Schieber M, Chandel NS. ROS function in redox signaling and oxidative stress. Curr Biol. 2014;24(10):R453-R462. doi:10.1016/j.cub.2014.03.034
44. Liou GY, Storz P. Reactive oxygen species in cancer. Free Radic Res. 2010;44(5):479-96
45. Klaunig JE. Oxidative Stress and Cancer. Curr Pharm Des. 2018;24(40):4771-8.
46. Dixon SJ, Lemberg KM, Lamprecht MR, Skouta R, Zaitsev EM, Gleason CE, et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death. Cell. 2012;149(5):1060-1072. doi:10.1016/j.cell.2012.03.042
47. Redza-Dutordoir M, Averill-Bates DA. Activation of apoptosis signalling pathways by reactive oxygen species. Biochim Biophys Acta. 2016;1863(12):2977-2992. doi:10.1016/j.bbamcr.2016.09.012
48. Srinivas US, Tan BWQ, Vellayappan BA, Jeyasekharan AD. ROS and the DNA damage response in cancer. Redox Biol. 2019;25:101084.
49. Hayes JD, Dinkova-Kostova AT. The Nrf2 regulatory network provides an interface between redox and intermediary metabolism. Trends Biochem Sci. 2014;39(4):199-218.
50. Rojo de la Vega M, Chapman E, Zhang DD. NRF2 and the Hallmarks of Cancer. Cancer Cell. 2018;34(1):21-43. doi:10.1016/j.ccell.2018.03.022
51. Birben E, Sahiner UM, Sackesen C, Erzurum S, Kalayci O. Oxidative stress and antioxidant defense. World Allergy Organ J. 2012;5(1):9-19.
52. Brigelius-Flohé R, Maiorino M. Glutathione peroxidases. Biochim Biophys Acta. 2013;1830(5):3289-303.
53. Arnér ES, Holmgren A. The thioredoxin system in cancer. Semin Cancer Biol. 2006;16(6):420-6.
54. Halliwell B. Free radicals and antioxidants - quo vadis?. Trends Pharmacol Sci. 2011;32(3):125-130. doi:10.1016/j.tips.2010.12.002
55. Pandey KB, Rizvi SI. Plant polyphenols as dietary antioxidants in human health and disease. Oxid Med Cell Longev. 2009;2(5):270-8.
56. Zuo J, Zhang Z, Luo M, Zhou L, Nice EC, Zhang W, et al. Redox signaling at the crossroads of human health and disease. MedComm (2020). 2022;3(2):e127. Published 2022 Mar 31. doi:10.1002/mco2.127
57. Forman HJ. Redox signaling: An evolution from free radicals to aging. Free Radic Biol Med. 2016;97:398-407.
58. Sayin VI, Ibrahim MX, Larsson E, Nilsson JA, Lindahl P, Bergo MO. Antioxidants accelerate lung cancer progression in mice. Sci Transl Med. 2014;6(221):221ra15. doi:10.1126/scitranslmed.3007653
59. Liu B, Chen Y, St Clair DK. ROS and p53: a versatile partnership. Free Radic Biol Med. 2008;44(8):1529-1535. doi:10.1016/j.freeradbiomed.2008.01.011
60. Schmidt S, Qiao X, Bergö MO. Effects of antioxidants on cancer progression. EMBO Mol Med. 2025;17(8):1896-901.
61. Piskounova E, Agathocleous M, Murphy MM, Hu Z, Huddlestun SE, Zhao Z, et al. Oxidative stress inhibits distant metastasis by human melanoma cells. Nature. 2015;527(7577):186-91.
62. Yang Y, Bazhin AV, Werner J, Karakhanova S. Reactive oxygen species in the immune system. Int Rev Immunol. 2013;32(3):249-70.
63. Shah R, Ibis B, Kashyap M, Boussiotis VA. The role of ROS in tumor infiltrating immune cells and cancer immunotherapy. Metabolism. 2024;151:155747.
64. Trachootham D, Alexandre J, Huang P. Targeting cancer cells by ROS-mediated mechanisms: a radical therapeutic approach? Nat Rev Drug Discov. 2009;8(7):579-91.
65. Gorrini C, Harris IS, Mak TW. Modulation of oxidative stress as an anticancer strategy. Nat Rev Drug Discov. 2013;12(12):931-47.
66. DeNicola GM, Karreth FA, Humpton TJ, Gopinathan A, Wei C, Frese K, et al. Oncogene-induced Nrf2 transcription promotes ROS detoxification and tumorigenesis. Nature. 2011;475(7354):106-9.
67. Lawenda BD, Kelly KM, Ladas EJ, Sagar SM, Vickers A, Blumberg JB. Should supplemental antioxidant administration be avoided during chemotherapy and radiation therapy? J Natl Cancer Inst. 2008;100(11):773-83.
68. Conklin KA. Dietary antioxidants during cancer chemotherapy: impact on chemotherapeutic effectiveness and development of side effects. Nutr Cancer. 2000;37(1):1-18.
69. Scalbert A, Johnson IT, Saltmarsh M. Polyphenols: antioxidants and beyond. Am J Clin Nutr. 2005;81(1 Suppl):215s-7s.
70. Abotaleb M, Samuel SM, Varghese E, Varghese S, Kubatka P, Liskova A, et al. Flavonoids in Cancer and Apoptosis. Cancers (Basel). 2018;11(1):28. doi:10.3390/cancers11010028
71. Wani AK, Akhtar N, Mir TUG, Singh R, Jha PK, Mallik SK, et al. Targeting Apoptotic Pathway of Cancer Cells with Phytochemicals and Plant-Based Nanomaterials. Biomolecules. 2023;13(2):194. doi:10.3390/biom13020194
72. Mileo AM, Miccadei S. Polyphenols as Modulator of Oxidative Stress in Cancer Disease: New Therapeutic Strategies. Oxid Med Cell Longev. 2016;2016:6475624.
73. Isnaini I, Permatasari N, Mintaroem K, Prihardina B, Widodo MA. Oxidants-Antioxidants Profile in the Breast Cancer Cell Line MCF-7. Asian Pac J Cancer Prev. 2018;19(11):3175-8.
74. Costa PSD, Ramos PS, Ferreira C, Silva JL, El-Bacha T, Fialho E. Pro-Oxidant Effect of Resveratrol on Human Breast Cancer MCF-7 Cells is Associated with CK2 Inhibition. Nutr Cancer. 2022;74(6):2142-51.
75. Klein EA, Thompson IM Jr, Tangen CM, Crowley JJ, Lucia MS, Goodman PJ, et al. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA. 2011;306(14):1549-56. doi: 10.1001/jama.2011.1437.
76. Obrador E, Salvador-Palmer R, López-Blanch R, Oriol-Caballo M, Moreno-Murciano P, Estrela JM.

N-Acetylcysteine Promotes Metastatic Spread of Melanoma in Mice. Cancers (Basel). 2022;14(15):3614. doi: 10.3390/cancers14153614.

77. Schmidt S, Qiao X, Bergö MO. Effects of antioxidants on cancer progression. EMBO Mol Med. 2025(8):1896-1901. doi: 10.1038/s44321-025-00269-5.
78. Blumberg J, Block G. The alpha-tocopherol, beta-carotene cancer prevention study in Finland. Nutr Rev. 1994;52(7):242-5. doi: 10.1111/j.1753-4887.1994.tb01430.x.
79. D'Andrea GM. Use of antioxidants during chemotherapy and radiotherapy should be avoided. CA Cancer J Clin. 2005;55(5):319-21. doi: 10.3322/canjclin.55.5.319.
80. Block KI, Koch AC, Mead MN, Tothy PK, Newman RA, Gyllenhaal C. Impact of antioxidant supplementation on chemotherapeutic efficacy: a systematic review of the evidence from randomized controlled trials. Cancer Treat Rev. 2007;33(5):407-18. doi: 10.1016/j.ctrv.2007.01.005.
81. Ambrosone CB, Zirpoli GR, Hutson AD, McCann WE, McCann SE, Barlow WE, et al. Dietary Supplement Use During Chemotherapy and Survival Outcomes of Patients With Breast Cancer Enrolled in a Cooperative Group Clinical Trial (SWOG S0221). J Clin Oncol. 2020;38(8):804-814. doi: 10.1200/JCO.19.01203.
82. Sayin VI, Ibrahim MX, Larsson E, Nilsson JA, Lindahl P, Bergo MO. Antioxidants accelerate lung cancer progression in mice. Sci Transl Med. 2014;6(221):221ra15. doi: 10.1126/scitranslmed.3007653.
83. Le Gal K, Ibrahim MX, Wiel C, Sayin VI, Akula MK, Karlsson C, et al. Antioxidants can increase melanoma metastasis in mice. Sci Transl Med. 2015;7(308):308re8. doi: 10.1126/scitranslmed.aad3740.
84. Wu K, Yang Q, Mu Y, Zhou L, Liu Y, Zhou Q, et al. Berberine inhibits the proliferation of colon cancer cells by inactivating Wnt/β-catenin signaling. Int J Oncol. 2012;41(1):292-8. doi: 10.3892/ijo.2012.1423. Epub 2012 Apr 2.
85. Capasso L, De Masi L, Sirignano C, Maresca V, Basile A, Nebbioso A, et al. Epigallocatechin Gallate (EGCG): Pharmacological Properties, Biological Activities and Therapeutic Potential. Molecules. 2025;30(3):654. doi: 10.3390/molecules30030654
86. Mahdavi H, Hadadi Z, Ahmadi M. A review of the anti-oxidation, anti-inflammatory and anti-tumor properties of curcumin. Traditional and Integrative Medicine. 2017 7(2):188-95.
87. Sharma P, McClees SF, Afaq F. Pomegranate for prevention and treatment of cancer: an update. Molecules. 2017;22(1):177.
88. Tran PHL, Tran TTD. Blueberry supplementation in neuronal health and protective technologies for efficient delivery of blueberry anthocyanins. Biomolecules. 2021;11(1):102. doi: 10.3390/biom11010102.
89. Wen S, Zhang J, Yang B, Elias PM, Man MQ. Role of resveratrol in regulating cutaneous functions. Evid Based Complement Alternat Med. 2020;2020:2416837. doi: 10.1155/2020/2416837.