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Review Article

Dietary and Topical Antioxidants in Skin Cancer: A Narrative Review on Prevention, Treatment, and Dermatological Care in Patients and Survivors

Ali Sattarian[1], Minoo Akbarzadeh Morshedi[2]*

1. School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
2. Research Center for Biochemistry and Nutrition in Metabolic Diseases, Institute for Basic Science, Kashan University of Medical Sciences, Ravand, Kashan, Iran

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**Corresponding author:*
Minoo Akbarzadeh Morshedi, BSc;
Research Center for Biochemistry and Nutrition in Metabolic Diseases, Institute for Basic Science, Kashan University of Medical Sciences, Ravand, Kashan, Iran.
Tel: +98 9392772650
Email: Mi.akbarzadeh213@gmail.com, Akbarzadeh-m@kaums.ac.ir

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ABSTRACT

Skin cancer remains a significant global health challenge, with ultraviolet (UV) radiation-induced oxidative stress playing a pivotal role in the pathogenesis. Antioxidants exhibit potent free radical scavenging properties that mitigate UV-induced DNA damage and inflammatory responses. This narrative review critically examined the role of dietary and topical antioxidants in the prevention, treatment, and dermatological care of skin cancer. Here, we conducted a comprehensive search across major medical databases for all research types. The search employed the keywords of antioxidants, oxidative stress, skin cancer, skin neoplasms and skin care. Dietary antioxidants were shown to be associated with reduced incidence and progression of various skin cancers, highlighting the importance of nutritional strategies in primary prevention. Topical antioxidants, formulated in dermatological preparations, offer localized protection by enhancing the endogenous defense mechanisms and improving repair processes of the skin post-UV exposure. In conclusion, the adjunctive use of antioxidants may improve treatment outcomes and reduce adverse effects of conventional therapies. In skin cancer survivors, sustained antioxidant therapy may contribute to improved skin health, reduced recurrence risk, and enhanced quality of life. Despite promising findings, heterogeneity in study designs and antioxidant formulations necessitates further researches to establish standardized guidelines.

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Introduction

Skin cancer, the most prevalent form of cancer globally, poses significant public health challenges, with rising incidence rates attributed to factors such as increased ultraviolet (UV) exposure, environmental pollutants, and lifestyle choices (1, 2). The two most common types of skin cancer, Basal Cell Carcinoma (BCC) and Squamous Cell Carcinoma (SCC), along with melanoma, highlight the urgent need for effective preventive and therapeutic strategies (3). In this context, the role of antioxidants - both dietary and topical - has garnered considerable attention due to their potential to mitigate oxidative stress, a key contributor to skin carcinogenesis (4, 5).

Oxidative stress arises from an imbalance between Reactive Oxygen Species (ROS) and the antioxidant defenses of human body, leading to cellular damage, inflammation, and DNA mutations (6, 7). These processes are implicated in the initiation and progression of skin cancer (8, 9). Antioxidants, which can neutralize ROS and protect cellular integrity, may therefore play a crucial role in skin cancer prevention and management (10). Dietary antioxidants, found abundantly in fruits, vegetables, nuts, and whole grains, have been associated with a reduced risk of various cancers, including skin malignancies (11-13). Compounds such as vitamins C and E, carotenoids, and polyphenols exhibit potent antioxidant properties and may enhance skin resilience against UV-induced damage (14, 15).

Topical antioxidants have also emerged as promising agents in dermatological care. Formulations containing antioxidants such as ferulic acid, vitamin C, and coenzyme Q10 are increasingly used in skin care products aimed at preventing photoaging and improving overall skin health (10, 16). Clinical studies suggested that these agents can enhance photoprotection, reduce inflammation, and promote skin repair mechanisms (17). However, the efficacy of these interventions often depends on factors such as formulation stability, penetration efficacy, and individual skin characteristics (18).

Despite the growing body of literature on antioxidants in skin cancer prevention and treatment, a comprehensive synthesis of current evidence remains lacking. This narrative review aimed to explore the multifaceted roles of dietary and topical antioxidants in the context of skin cancer prevention and treatment strategies. By examining existing studies, clinical trials, and expert opinions, we searched to elucidate the potential mechanisms by which these compounds exert their effects and provide insights into their application in dermatological care for patients and survivors. Ultimately, this review aimed to contribute to a deeper understanding of how antioxidants can be integrated into holistic approaches for skin cancer management, emphasizing the need for further research to optimize their use in clinical practice.

Materials and Methods

Search Strategy

A comprehensive literature search was conducted using multiple electronic databases, including PubMed, Scopus, Web of Science, and Google Scholar. The search was limited to articles published from January 2000 to May 2025 to ensure the inclusion of the most relevant and recent studies; however, the majority of included papers were from 2020 to 2025. The following keywords and phrases were utilized in various combinations: [("Antioxidants" OR "Dietary Antioxidants" OR "Topical Antioxidants" OR "Polyphenols" OR "Secondary Metabolites" OR "Nutraceuticals" OR "Plant-Derived Compounds" OR "Oxidative Stress") AND ("Skin Neoplasms" OR "Skin Cancer" OR "Basal Cell Carcinoma" OR "Squamous Cell Carcinoma" OR OR "Melanoma" OR "Acanthoma" OR "Blastic Plasmacytoid Dendritic Cell Neoplasm" OR "Cutaneous Mastocytosis" OR "Urticaria Pigmentosa" OR "Sebaceous Gland Neoplasms" OR "Dermatological Care")].

Inclusion and Exclusion Criteria

Inclusion criteria for the selected studies comprised (i) Peer-reviewed articles focusing on dietary or topical antioxidants related to skin cancer. (ii) Studies addressing prevention, treatment, or dermatological care in patients or survivors of skin cancer. (iii) Clinical trials, observational studies, meta-analyses, and systematic reviews. (iv) Articles published in English. Exclusion criteria included (a) Non-peer-reviewed articles, editorials, and opinion pieces. (b) Studies not directly related to skin cancer or antioxidants. (c) Articles lacking sufficient data or methodological rigor.

Data Extraction and Synthesis

Finally, 107 research papers were selected to be included in the review. Data were extracted from the selected articles using a standardized form that included the parameters of author(s), year of publication, study design, population characteristics, type of antioxidant, outcomes measured and key findings. The synthesis of data was performed thematically, focusing on the roles of dietary and topical antioxidants in skin cancer prevention, treatment efficacy, and dermatological care strategies for patients and survivors. The quality of the included studies was assessed using appropriate tools; and high-quality papers were finally emphasized in the review.

Narrative Synthesis

The findings from the selected articles were synthesized narratively to highlight key themes and trends regarding the role of antioxidants in skin cancer management. Emphasis was placed on contrasting results, potential mechanisms of action, and clinical implications for dietary and topical antioxidant use among skin cancer patients and survivors.

Results and Discussion

Oxidative Stress and Skin Cancer

Oxidative stress, defined as an imbalance between the production of ROS and the antioxidant defenses, is a critical factor in the pathogenesis of skin cancer (19). The skin, being the largest organ and the primary interface with the external environment, is particularly vulnerable to oxidative damage due to the constant exposure to environmental stressors, notably UV radiation (20, 21). UV radiation, particularly UVB (290-320 nm), is a major inducer of ROS, including superoxide anions, hydrogen peroxide, and hydroxyl radicals, which can exceed the antioxidant capacity of skin, resulting in oxidative damage to cellular components such as DNA, proteins, and lipids (22, 23). This imbalance is strongly associated with skin cancer, encompassing both Non-Melanoma Skin Cancers (NMSC) like BCC and SCC, highlighting the need to understand the underlying mechanisms for preventive and therapeutic strategies (24).

At the cellular level, oxidative stress induces DNA damage through the formation of mutagenic lesions such as Cyclobutane Pyrimidine Dimers (CPDs) and pyrimidine (6–4) Pyrimidone Photoproducts (6-4PPs), primarily caused by UV radiation (25, 26) (Table 1). These lesions disrupt DNA replication and transcription, and if not repaired by Nucleotide Excision Repair (NER) mechanisms, can lead to mutations in key genes, including tumor suppressor genes like TP53 and PTCH1, which are frequently altered in skin cancers (27, 28). Additionally, ROS can cause oxidative base modifications, such as 8-Hydroxy-2'-Deoxyguanosine (8-OHdG), which can mispair with adenine during DNA replication, leading to G:C to T:A transversions, a common mutation in skin cancer (29). Beyond DNA, ROS oxidize proteins, causing misfolding or loss of function in key enzymes involved in DNA repair or cell cycle regulation, and peroxidize lipids, disrupting membrane fluidity and signaling pathways (30).

At the molecular level, ROS act as signaling molecules that modulate redox-sensitive pathways, including the Nuclear Factor kappa-B (NF-κB), Mitogen-Activated Protein Kinase (MAPK), and Phosphoinositide 3-Kinase (PI3K)/AKT pathways (31, 32). These pathways regulate inflammation, cell survival, and proliferation, creating a tumorigenic microenvironment (33, 34). For instance, NF-κB activation induces proinflammatory cytokines like Tumor Necrosis Factor-α (TNF-α), Interleukin-1β (IL-1β), and IL-6, which promote angiogenesis and metastasis (35, 36), while MAPK pathways influence cell cycle progression and apoptosis resistance (37). Chronic activation of these pathways under oxidative stress can lead to uncontrolled cell growth and survival, hallmarks of cancer (38).

Understanding the role of oxidative stress in skin cancer has significant therapeutic implications, as strategies to enhance antioxidant defenses such as topical application of antioxidants or photoprotective agents thatmay help mitigate ROS levels and reduce skin cancer incidence (10). Furthermore, targeting redox-sensitive signaling pathways could offer novel approaches for skin cancer prevention and treatment, emphasizing the importance of integrating antioxidant strategies into dermatological care (39, 40). The complexity of these mechanisms, with some studies showing efficacy of antioxidants while others report mixed results, underscores the need for continued research to clarify the best preventive measures, particularly given the skin's constant exposure to environmental stressors.

The Role of Dietary and Topical Antioxidants in Skin Care

Antioxidants, both dietary and topical, play a pivotal role in skin care by mitigating oxidative stress (41) (Table 2). The skin possesses a sophisticated antioxidant defense system to counteract oxidative stress, including enzymatic antioxidants such

Table 1: Key mechanisms explaining the relationship between oxidative stress and skin cancer.

Mechanism	Description	Impact on skin cancer
DNA damage	Formation of CPDs and 6-4PPs by UV-induced ROS, leading to mutations in TP53, PTCH1	Increases mutation rate, promoting carcinogenesis
Protein oxidation	ROS oxidize proteins, causing misfolding or loss of function in repair enzymes	Disrupts DNA repair, enhances tumor growth
Lipid peroxidation	ROS peroxidize lipids, disrupting membrane integrity and signaling	Alters cell signaling, favors tumor microenvironment
Signaling pathway activation	Activation of NF-κB, MAPK, PI3K/AKT by ROS, inducing inflammation and proliferation	Promotes cell survival, angiogenesis, metastasis
Antioxidant defense	Enzymatic (SOD, catalase) and non-enzymatic (vitamins C, E) neutralize ROS	Protects against damage, but can be overwhelmed

ROS: Reactive Oxygen Species; CPDs: Cyclobutane Pyrimidine Dimers; 6-4PPs: pyrimidine (6–4) Pyrimidone Photoproducts; NF-κB: Nuclear Factor kappa-B; MAPK: Mitogen-Activated Protein Kinase; PI3K: Phosphoinositide 3-Kinase; SOD: Superoxide Dismutase.

Table 2: Key antioxidants for skin care and related mechanisms.

Antioxidant	Mechanism of action (Cellular/Molecular)	Specific effects/Studies
Vitamin E (Tocopherol)	Neutralizes singlet oxygen in cell membrane; stabilizes membrane, prevents lipid peroxidation of unsaturated fatty acids like arachidonic acid	Proven action on UV-induced damage; high doses may inhibit glutathione-S-transferase, linked to tumorigenesis
Vitamin C (Ascorbic acid)	Extensive removal of free radicals; repairs oxidized vitamin E bound to cell membrane	Reduces dopaquinone in melasma, prevents free radical formation; positive impact on SOD reduction states
Polypodium leucotomos	Inhibits UV-induced ROS generation, including superoxide anion	Neutralizes ROS, blocks lipid peroxidation, activates natural antioxidant systems; used in photoaging, melasma
Lycopene	Carotenoid with greatest biological action in neutralizing singlet oxygen	Daily intake of tomato paste for 12 weeks reduced MMP-1 expression; no photoprotective effect orally
Lutein	Protects fibroblasts from UVA-induced oxidative action, prevents decrease in catalase and SOD	Absorbs blue light, protective against visible light damage; oral and topical combination superior after 12 weeks
Resveratrol	Inhibits UV-induced oxidative and mutagenic action to DNA	Bioactive in nanometric doses from phytochemicals; conflicting data on doses
Epigallocatechin gallate (Green Tea)	Broad scavenging of free radicals, inhibits ROS production and lipid peroxidation, protects endogenous systems	Prevents UVB-induced leukocyte infiltration, oxidative stress
Lipoic Acid	Repairs endogenous antioxidant systems, neutralizes free radicals	Conflicting results were reported
Delphinidin	Inhibits lipid peroxidation and formation of 8-OHdG, marker of oxidative stress to DNA; improves Ox-LDL and F2-isoprostanes	Increases skin brightness and collagen content, and improves facial skin redness
Coenzyme Q10 (Ubiquinol)	Reduces free radical production, regenerates vitamin E; reduces keratinocyte DNA damage, UVA-induced metalloproteinase production	Influences synthesis of cutaneous proteins, inhibits collagenase, preserves collagen content; declines with age

SOD: Superoxide Dismutase; ROS: Reactive Oxygen Species; UV: Ultraviolet; 8-OHdG, 8-Hydroxy-2'-Deoxyguanosine; MMP-1: Matrix Metallopeptidase 1; Ox-LDL: Oxidized Low-Density Lipoprotein.

as Superoxide Dismutase (SOD), catalase, and glutathione peroxidase, as well as non-enzymatic antioxidants like vitamins C and E, and polyphenols (42, 43). These defenses neutralize ROS and repair oxidative damage, thereby protecting against skin carcinogenesis (44, 45). However, chronic exposure to UV radiation or other stressors can overwhelm these defenses, leading to sustained oxidative stress and increased cancer risk (46).

Researches indicate that combinations of antioxidants, such as vitamins A, C, E, selenium, and phytochemicals like green tea and pomegranate, can enhance the skin's ability to neutralize ROS and improve its resilience against UV-induced erythema, particularly when administered both orally and topically (14, 47, 48). For instance, some studies have shown that oral and topical combinations, such as lutein/zeaxanthin, can improve epidermal lipids, hydration, photoprotective activity, skin elasticity, and reduce lipid peroxidation under UV exposure, with oral administration often proving superior (49, 50).

At the cellular and molecular level, antioxidants exert their protective effects through diverse and synergistic mechanisms, crucial for maintaining skin integrity and combating oxidative stress. Vitamin E (tocopherol) is effective in both dietary and topically forms and neutralizes singlet oxygen in the cell membrane, stabilizes it and prevents lipid peroxidation of unsaturated fatty acids like arachidonic acid (51). Vitamin C (ascorbic acid) not only extensively removes free radicals but also repairs oxidized vitamin E bound to the cell membrane, demonstrating a synergistic effect (52), and has been shown to reduce dopaquinone in melasma and prevent free radical formation, positively impacting SOD reduction states (53).

Polypodium leucotomos, a tropical fern available in both oral capsules and topical creams, inhibits UV-induced ROS generation, including superoxide anion, and activates natural antioxidant systems, making it effective in treating photoaging and melasma by neutralizing ROS and blocking lipid peroxidation (54). Resveratrol that is effective in both ways can inhibit UV-induced oxidative and mutagenic

actions to DNA (55), while Epigallocatechin gallate (EGCG) from green tea broadly scavenges free radicals, inhibits ROS production, and prevents UVB-induced leukocyte infiltration and oxidative stress (56). Coenzyme Q10 (ubiquinol) that is used in both dietary and topically forms can, reduce free radical production, regenerates vitamin E, and supports collagen synthesis by inhibiting collagenase activity, preserving collagen content, which declines with age (57).

A trial showed that delphinidin, extracted from maqui berry, has the potential to improve Oxidized Low-Density Lipoprotein (Ox-LDL) and F2-isoprostanes in healthy adults, overweight adults, and adult smokers (58). Moreover, a research revealed the beneficial effects of delphinidin supplementation on skin brightness, collagen content, and facial skin redness (59). These evidences highlight the multifaceted roles of antioxidants in maintaining skin health, though controversies exist regarding their effectiveness, particularly with topical applications, necessitating further research to clarify their clinical benefits.

Key Dietary Antioxidants in Skin Cancer Prevention and Treatment

Vitamin C

Dietary vitamin C, also known as ascorbic acid, has been extensively studied for the potential role in the prevention and treatment of skin cancer, particularly NMSC, which includes BCC and SCC (60). Preliminary human studies suggested a potential protective role for dietary vitamin C in skin cancer prevention. For instance, individuals diagnosed with BCC have been found to have lower serum levels of dietary antioxidants, including vitamin C, indicating that higher intake might reduce risk (61). This aligns with broader epidemiological evidence that found strong protection against non-hormone-dependent cancers, including those of the esophagus, larynx, oral cavity, and pancreas, with high vitamin C intake conferring approximately a twofold protective effect compared to low intake (62-64).

While skin cancer was not explicitly detailed in this review, the shared mechanisms of oxidative stress and DNA damage suggest potential relevance. However, specific epidemiological studies on skin cancer and dietary vitamin C are limited, highlighting a gap in direct evidence. Researches have provided mixed results regarding the efficacy of vitamin C supplementation in preventing NMSC. Pauling *et al.* conducted a study on hairless mice exposed to UV light, finding that supplemental vitamin C significantly reduced the incidence of malignant and precancerous lesions, suggesting a direct protective effect against UV-induced carcinogenesis (65). Additionally, Roomi *et al.* demonstrated that a nutrient mixture including vitamin C significantly inhibited skin tumor incidence and multiplicity in mice treated with a carcinogen, reinforcing the protective role in a chemically induced model (66). The animal studies collectively suggest that dietary vitamin C can mitigate skin cancer development, particularly under conditions of UV exposure or chemical carcinogenesis (67).

Vitamin E

Dietary vitamin E, particularly alpha-tocopherol, has been extensively studied on skin cancer prevention and treatment due to the antioxidant properties (68). Researches have consistently demonstrated protective effects; for instance, Peus *et al.* found that Trolox, a water-soluble vitamin E analog, differentially modulates the activation of UVB-induced signaling pathway (69). Findings suggest that vitamin E can mitigate UV-induced skin damage and tumorigenesis in animal models by neutralizing ROS and preventing lipid peroxidation (14, 70). However, human studies have yielded less conclusive results. A research by Vural *et al.* found that plasma samples and blood cells of patients with BCC had significantly lower levels of alpha-tocopherol. While vitamin E may offer protective benefits, its efficacy in human populations, particularly through supplementation, remains uncertain and may depend on factors such as dosage, form, and interaction with other nutrients (71).

At the cellular and molecular levels, vitamin E exerts the protective effects primarily as a lipid-soluble antioxidant (72). It integrates into cell membranes, where it neutralizes ROS generated by UV radiation, thereby preventing lipid peroxidation and maintaining membrane integrity (73). This is crucial in skin cells, as ROS can cause DNA damage, protein oxidation, and lipid peroxidation, all of which are implicated in carcinogenesis. It was shown that pretreatment with vitamin E enhances photoprotection in human fibroblasts when combined with other antioxidants (74). However, chemical environment can influence the antioxidant capacity of vitamin E; in the absence of sufficient co-antioxidants like vitamin C, vitamin E may exhibit prooxidant activity, underscoring the importance of a balanced antioxidant network (75, 76). Beyond the direct antioxidant effects, vitamin E may also modulate gene expression and cellular signaling pathways involved in proliferation and apoptosis, although these mechanisms are less defined in the context of skin cancer prevention. The controversy surrounding vitamin E efficacy, particularly in

human studies, underscores the need for further research, especially given the promising results from animal studies and the potential for dietary sources to offer benefits not seen with supplements (77).

Lycopene

Lycopene, a potent carotenoid antioxidant found abundantly in tomatoes and other red fruits, has been extensively studied for its potential role in skin cancer prevention and treatment due to its ability to combat oxidative stress and UV-induced damage (78). Animal studies have demonstrated the efficacy of lycopene against skin cancer, particularly in models of UV-induced carcinogenesis (79). For instance, a research showed that topical application of lycopene before UV radiation reduced photodamage *in vitro*, suggesting its protective role against UV-induced skin cancer, with a significant decrease in tumor incidence and multiplicity (80). Another study by Wang *et al.* noted that lycopene enhanced the expression of autophagy protein p62 in mice and led to the degradation of Keap1 (Kelch ECH associating protein 1), the main protein locking Nuclear factor erythroid 2-related factor 2 (Nrf2) in cytoplasm (81). A research by Rizwan *et al.* also demonstrated that daily of tomato paste for 12 weeks reduced Matrix Metalloproteinase-1 (MMP-1) expression, a key marker of skin aging, though it showed no photoprotective effect orally in some contexts (82). In humans, dietary intake of lycopene-rich foods, such as tomato paste, has been associated with reduced UV-induced erythema, indicating a potential protective effect against UV damage that can lead to skin cancer (83). For treatment, lycopene has been investigated for the ability to minimize skin toxicity in patients undergoing cancer therapy, with Moroni *et al.* finding that lycopene supplementation reduced skin toxicity in patients treated with panitumumab for metastatic colorectal cancer, highlighting the potential in managing treatment-related skin adverse effects, though not directly treating skin cancer (84).

At the cellular and molecular levels, lycopene exerts the effects through several mechanisms crucial for skin cancer prevention (85). Primarily, it has been shown to activate the Nrf2 pathway, which enhances the expression of antioxidant enzymes such as catalase, glutathione reductase, superoxide dismutase, and glutathione peroxidase (86), and upregulates mRNA levels of genes like cat, sod1, gpx1, gsr, gclc, and gclm, promoting cellular defense against oxidative damage (87). In skin cells, lycopene prevents UV-induced damage by maintaining redox homeostasis and reducing the production of ROS, which are key contributors to skin aging and cancer development, as evidenced by decreased levels of 4 Hydroxynonenal. 4-Hydroxynonenal (4-HNE), 8-OHdG, and ROS (88).

Furthermore, lycopene modulates various signaling pathways involved in cell proliferation, differentiation, and apoptosis (89). It interferes with growth factor receptor signaling and cell cycle progression in cancer cells by downregulating FOXO3a, CDK2, and CDK4, thereby inhibiting tumor growth (90, 91). Additionally, lycopene induces autophagy, increasing p62 expression and facilitating p62/Keap1 binding, leading to Keap1 degradation via the autophagy-lysosomal pathway, which stabilizes Nrf2 and potentially inhibits tumorigenesis. These multifaceted actions at the cellular level underscore the efficacy of lycopene as a chemopreventive agent for skin cancer, though the efficacy in humans remains a subject of ongoing research (92).

Lutein

Lutein, a xanthophyll carotenoid abundant in dark green leafy vegetables such as spinach and kale, and other colorful fruits and vegetables, has been investigated for its potential role in skin cancer prevention and treatment due to the potent antioxidant and anti-inflammatory properties (93). While direct evidence from trials specifically targeting skin cancer is limited, existing studies provide insights into the protective effects of lutein against UVR-induced skin damage, a primary risk factor for skin cancer (94). In a randomized, double-blind, placebo-controlled trial involving 30 healthy women, dietary supplementation with 20 mg/day of lutein for 12 weeks significantly increased the Minimal Erythema Dose (MED), indicating enhanced skin photoprotective potential by 22% (95). This suggests that lutein can bolster the skin's defense against UVR-mediated damage, potentially reducing the risk of skin cancer by improving resistance to UV-induced erythema (49).

Animal studies further support this notion; for instance, mice fed a diet supplemented with lutein exhibited significant inhibition of UVB radiation-induced ear swelling and suppression of contact hypersensitivity, key indicators of UVR-induced inflammation and immunosuppression linked to skin cancer development (96). Additionally, observational studies have associated higher dietary intake of lutein and zeaxanthin with a reduced risk of SCC in individuals with a history of skin cancer, with a Relative Risk (RR) of 0.47 (95% CI: 0.25-0.89) for the highest vs. lowest tertile, indicating a significant protective effect. These findings collectively suggest that lutein may play a protective role in skin cancer prevention, particularly through its ability to mitigate

UVR-induced damage, though the efficacy of supplements versus dietary intake remains a subject of ongoing research (97).

At the cellular and molecular levels, lutein quenches singlet oxygen and scavenges free radicals (98). It protects fibroblasts from UVA-induced oxidative damage by preventing the decrease in catalase and SOD (99), and when combined with topical application, it improves skin elasticity and reduces lipid peroxidation under UV exposure (100). Lutein also modulates inflammatory responses by inhibiting proinflammatory signaling pathways such as NF-κB and activator protein 1 (AP-1), leading to reduced production of inflammatory mediators like IL-6, Cyclooxygenase-2 (COX-2), and MMP-9, which are involved in the pathogenesis of skin cancer (101). By dampening inflammation, lutein may prevent the chronic inflammatory state that promotes tumorigenesis (102). Additionally, lutein may enhance the natural antioxidant defenses of skin by activating Nrf2 pathway, which upregulates the expression of antioxidant enzymes. Further research, particularly large-scale RCTs focused on skin cancer outcomes, is needed to fully elucidate the clinical efficacy of lutein (103).

Resveratrol

Resveratrol, a naturally occurring polyphenolic compound found in grapes, red wine, and certain berries, has been extensively studied for the antioxidant, anti-inflammatory, and anti-proliferative properties. An animal study by Jang *et al.* showed that resveratrol in a two-stage mouse skin carcinogenesis model significantly inhibits tumor incidence and multiplicity, reducing the development of skin tumors induced by UV radiation or chemical carcinogens (104). Similarly, Tsai *et al.* found that dietary resveratrol suppressed 7,12-Dimethylbenz(a) anthracene (DMBA)-induced skin tumorigenesis in mice, decreasing both tumor volume and incidence, suggesting a protective role against chemically induced skin cancer (105). Preclinical studies using animal models, such as the DMBA/TPA-induced model in female CD-1 mice, showed that resveratrol significantly reduced skin tumor incidence and the number of tumors per mouse (106). In UVB-mediated photocarcinogenesis in female SKH-1 mice, resveratrol treatment decreased skin hyperplasia and modulated molecular markers such as p53, COX-2, ODC, and survivin, suggesting the role in preventing UVB-induced skin cancer (107). Another study using the DMBA/TPA model in CD-1 mice showed that resveratrol induced apoptosis through the upregulation of p53, Bax, cytochrome C, and APAF, and downregulation of Bcl-2 (108).

In terms of human studies, while there are no RCTs specifically addressing the efficacy of resveratrol in skin cancer prevention or treatment, some clinical trials on other cancers provided indirect evidence of its potential. In colorectal cancer patients with hepatic metastasis, supplementation with SRT501, a micronized resveratrol formulation, at 5 g/day for two weeks increased the amount of cleaved caspase-3 in hepatic tissue, indicating increased apoptosis of cancerous tissue compared to placebo (109). At the cellular and molecular levels, resveratrol influences cell cycle progression and can induce apoptosis in cancer cells by modulating various signaling pathways, including the activation of p53 and the inhibition of survivin, thereby controlling cell growth and promoting the death of cancerous cells (110). It also modulates inflammatory responses by inhibiting proinflammatory signaling pathways, which are involved in the pathogenesis of skin cancer (111).

Key Topical Antioxidants in Skin Cancer Prevention and Treatment

Topical antioxidants, such as vitamin C (ascorbic acid), vitamin E (alpha-tocopherol), ferulic acid, and green tea polyphenols (e.g., epigallocatechin-3-gallate, EGCG), are commonly used to neutralize free radicals, reduce inflammation, and support the natural defense mechanisms of the skin (112) (Table 3). These compounds work synergistically to enhance photoprotection, prevent UV-induced DNA damage, and lower the risk of skin cancer development, particularly in individuals with high sun exposure, such as those engaged in outdoor activities (113).

Several advanced topical formulations have been developed to optimize the delivery and efficacy of antioxidants for skin cancer prevention and treatment, leveraging nanotechnology and novel delivery systems to overcome challenges like poor solubility and limited skin penetration. For instance, curcumin, a potent antioxidant with anti-inflammatory properties, has been incorporated into nanovesicles (e.g., liposomes, ethosomes) and nanogels (e.g., carboxymethyl cellulose-casein nanogels with folic acid coating) to enhance the bioavailability and penetration into skin cancer cells, showing improved cytotoxic potential against melanoma and SCC (114, 115). Silymarin, another antioxidant, is formulated in nanostructured lipid carriers within gels, demonstrating enhanced anti-tumor activity (116). Combinations of antioxidants, such as quercetin and resveratrol in nanostructured lipid carrier gels, have shown significant efficacy in treating skin cancer by improving stability and delivery (117, 118). Additionally, ultra-flexible

Table 3: Key topical antioxidant formulations suggested for skin cancer.

Antioxidant	Formulation type	Skin cancer type	Key findings
Curcumin	Nanovesicles, Nanogels (e.g., liposomes, ethosomes)	Melanoma, SCC	Enhanced bioavailability, improved cytotoxic potential
Silymarin	Nanostructured lipid carriers in gels	General skin cancer	Improved anti-tumor activity
Quercetin, Resveratrol	Nanostructured lipid carrier gels	Skin cancer	Enhanced stability and delivery, significant efficacy in treatment
Carvedilol	Ultra-flexible nanocarriers	UV-induced skin cancer	Prevents UV-induced cancer with negligible systemic absorption
Mentha spicata L. oil	Nanogels	Skin cancer	Antioxidative, anticancer, antibacterial activities
Vitamin C, E, Ferulic acid	Topical solution (15% C, 1% E, 0.5% Ferulic)	General skin cancer	Reduces erythema, sunburn cells, DNA damage
Green tea polyphenols	Topical application	UVB-induced damage	Protects against immune suppression, oxidative damage
Chitosan-gelatin	Thermosensitive hydrogels with 5FU-alginate nanoparticles	Melanoma	Enhances transdermal delivery
Carboxymethyl cellulose	Doxorubicin prodrug hydrogels	Melanoma	Improves topical chemotherapy efficacy

Abbreviations: SCC: Squamous Cell Carcinoma; UVB-induced: Ultraviolet B radiation-induced.

nanocarriers have been used to deliver highly lipophilic antioxidative molecules like carvedilol, preventing UV-induced skin cancer with negligible systemic absorption (119). Nanogels containing *Mentha Spicata* L. essential oil have also exhibited antioxidative, anticancer, and antibacterial activities, offering a multifaceted approach to skin cancer management. These formulations highlight the potential of topical antioxidants as adjunctive therapies, particularly for preventing recurrence and managing precancerous lesions (120).

In clinical practice, the application of these topical antioxidant formulations is increasingly recognized for their role in skin cancer chemoprevention, especially for high-risk populations. For example, a topical formulation containing 15% vitamin C, 1% vitamin E, and 0.5% ferulic acid has been shown to provide significant protection against solar-simulated UV radiation, reducing erythema, sunburn cells, and DNA damage (121). Similarly, green tea polyphenols, when applied topically, have been demonstrated to protect against UVB-induced immune suppression and oxidative damage in animal models, suggesting a preventive role in skin cancer (122, 123). Ongoing research continues to explore novel delivery systems, such as chitosan-gelatin thermosensitive hydrogels containing 5FU-alginate nanoparticles and carboxymethyl cellulose-doxorubicin prodrug hydrogels, to enhance transdermal delivery and efficacy against melanoma (124). Future directions include optimizing formulations for better stability, bioavailability, and targeted delivery, as well as conducting large-scale clinical trials to validate their efficacy in diverse populations. These advancements underscore the importance of topical antioxidants in comprehensive skin cancer management strategies, particularly for clinicians and researchers aiming to integrate them into dermatological care.

Key Antioxidants in Skin Cancer Survivors

Antioxidants are vital for skin cancer survivors as they help combat oxidative stress and protect cells from damage that can lead to cancer recurrence (125). The evidence for antioxidants use as a treatment or supplement for skin cancer survivors is limited and sometimes contradictory, however, incorporating a variety of antioxidant-rich foods into the diet is crucial for maximizing benefits. Colorful fruits and vegetables, nuts, seeds, and whole grains should be prioritized (126). Additionally, using skincare products containing antioxidants like vitamins C and E can help protect the skin from environmental damage (127). It is essential to consult healthcare providers before starting any supplements to ensure they are appropriate for individual health needs. By integrating antioxidants into daily life, skin cancer survivors can support their skin health and potentially reduce the risk of recurrence.

Conclusion

Dietary and topical antioxidants play a crucial role in the prevention and management of skin cancer, offering protective benefits against oxidative stress and enhancing skin health. This narrative review highlighted the significance of key antioxidants in skin cancer patients and survivors. Evidence suggests that antioxidants not only aid in reducing the risk of recurrence but also support overall

dermatological care by promoting healing and mitigating skin damage. Future researches should focus on elucidating the mechanisms of action and establishing standardized guidelines for the effective use of antioxidants in clinical practice.

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Authors' Contribution

AS: Conceptualization, Literature search, Data extraction, and writing; Original draft of the narrative review. MAM: Supervision, Methodological guidance, Critical revision, and final approval of the manuscript.

Conflict of Interest

None of the authors had a conflict of interest.

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