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Review Article

Integrative Approaches to Skin Cancer Chemoprevention and Sun Protection: Beyond Sunscreen

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Over time, ultraviolet radiation from the sun can inflict substantial damage to human skin. While traditional sun protective agents, including sunscreens and sunblocks, are generally considered safe and effective, limitations exist regarding their absolute benefit. With a growing concern for skin health related to sun damage, the use of complementary and alternative sun protection methods has become increasingly popular. Many studies have been conducted and evidence suggestive of a photoprotective benefit from a variety of alternative agents is accumulating. The aim of this paper is to review the available literature regarding the photoprotective and chemopreventive properties of a variety of these agents.

To find relevant articles and studies, a literature review was conducted across six databases including PubMed, EMBASE, Cochrane Library, PubMed Central, UpToDate, and Google Scholar, utilizing PRISMA guidelines. Randomized controlled trials, systematic reviews, as well as retrospective and prospective cohort studies were included in this review. While evidence supports the photoprotective properties of many of these agents (e.g., polypodium leucotomos, genistein, niacinamide, silymarin, and others), few long-term studies of these agents have been conducted resulting in a paucity of data regarding their chemopreventive effect in humans. Given the lack of available evidence, no consensus recommendations currently exist. However, with the photoprotective potential that many of these agents display, future trials may provide sufficient evidence to support their use in skin chemoprevention.

INTRODUCTION

By the mid-20th century, the relationship between sun exposure and skin cancer had been well established.[1,2] Early epidemiologic evidence demonstrated that skin cancers were more common in sun-exposed body sites and occurred more frequently in individuals with a greater degree of sun exposure.[1,2] Since that time, additional studies have characterized the direct role of sun exposure on the development of mutations in tumor suppressor genes leading to basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma.[2] Moreover, sun exposure is directly linked to collagen degradation, wrinkle formation, and older-appearing skin.[3]

To reduce skin cancer and minimize photoaging, it makes sense to avoid the sun as much as possible. However, in addition to driving vitamin D production, direct sunlight can contribute to psychological well-being. Some studies have even demonstrated that ultraviolet (UV) radiation results in the production of β-endorphin, a possible explanation for the feeling of euphoria many individuals describe with sun exposure.[4] These emotional benefits of time spent in the sun, juxtaposed with the known harmful effects, create a cognitive dissonance. Many of those who enjoy the sun question how they can reap the physiologic and psychological benefits while minimizing the risks.

The most common ways to protect the skin from UV radiation include avoidance of the sun at peak hours, sun protective clothing and sunglasses, and application of sunscreen. Sunscreen is widely used and has clear evidence for efficacy and safety; however, gaps exist between studies and reality, largely having to do with incorrect or inadequate sunscreen application.[1] With growing interest in skin

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care and a rise in the use of complementary and alternative medicine,[5] additional measures beyond sunscreen have gained popularity. Some of these measures, including oral supplementation and dietary changes, have been studied and may be efficacious. However, others may have no effect whatsoever, and some may even be harmful.

The aim of this paper is to outline the current proven methods of sun protection and review the available literature regarding potential benefits or harms of a variety of supplemental and alternative agents. We intend to highlight the approaches that have resulted in some reliable evidence and show how they could be useful in an integrative approach.

SECTION I: SUNSCREEN AND SUNBLOCK

Conventional sun protection, including chemical sunscreens and mineral-based sunblock, have been reviewed in great detail since their inception in the mid-20th century. Over time, regulatory agencies have developed standardized metrics to evaluate optimal sunscreen agents.[6] Ideally, these agents should be safe, chemically inert, nontoxic, hypoallergenic, photostable, and effectively block broad spectrum UV radiation (See Figure 1). Additionally, the use of sunscreen or sunblock should minimize the cumulative damage and associated health hazards from long-term sun exposure.

There is clear evidence that many of the sunscreen and sunblock products used today meet these standard expectations when applied correctly; however, controversies exist regarding their true efficacy and the reproducibility of the results in the real world.[6] Remarkably, some studies have demonstrated an increased number of BCC and melanoma among sunscreen users. Possible explanations for these findings include sunscreen users staying outside for longer periods of time due to false reassurance, sunscreens themselves acting as carcinogens, or vitamin D deficiency predisposing to cancer development.[7]

Along with concerns regarding real world efficacy, other limitations exist. In particular, oxybenzone, a common sunscreen agent, has been demonstrated to cause photosensitivity in a small percentage of people. Additionally, oxybenzone has been restricted from certain areas due to concerns about coral-reef bleaching. While sunscreen use continues to be endorsed, the following sections will review the literature on supplemental and alternative agents for sun protection.

SECTION II: COMPLEMENTARY AND ALTERNATIVE AGENTS (SEE TABLE 1)

POLYPODIUM LEUCOTOMOS

Polypodium leucotomos is a South American species of fern. For many years, extracts from this plant have been used for a variety of dermatologic conditions including: psoriasis, atopic dermatitis, vitiligo, polymorphic light eruption, and melasma.[8] In regard to photoprotection, studies indicate that the extract contains compounds which display multiple mechanisms potentially contributing to its protective effect against sun damage. Orally administered P. leucotomos extract reduces UV-mediated oxidative stress by enhancing the activity of endogenous antioxidant systems, blocking the formation of reactive oxygen species and reducing DNA damage.[9] Other cited mechanisms include inhibition of the release of inflammatory cytokines.[9,10]

Clinical data from several studies have provided evidence demonstrating a significant decrease in skin inflammation following sun exposure in treated cohorts compared to untreated.[10] For example, the photoprotective effect of oral P. leucotomos was investigated in a study of nine human participants who were exposed to doses of UV radiation with and without oral P. leucotomos pre-treatment. Results demonstrated a significant decrease in erythema ($p<.01$), sunburn cells ($p<.05$), pyrimidine dimers ($p<.001$) proliferating epidermal cells ($p<.001$), with pre-treatment compared to without.[11] Reported side effects included gastrointestinal complaints and pruritus in up to 2% of patients; other studies have reported no side effects or adverse events in the treatment group.[8,12]

Although such studies provide evidence supporting a photoprotective benefit of oral supplementation with P. leucotomos derived supplements, further standardized clinical trials are necessary before a definitive consensus is established in the dermatologic community. Regardless, these supplements are already sold over-the-counter and clinicians may recommend them as adjunctive therapy because of the evidence supporting their benefit and lack of significant side effects.

GRAPE SEED EXTRACT

Grape seed extract (GSE) is rich in polyphenolic compounds, particularly proanthocyanidins which are known for their strong antioxidant activity. These compounds have been studied as anti-inflammatory agents in a variety of conditions including autoimmune disease, allergies, and arthritis. Although the underlying mechanism has not been fully characterized, studies suggest GSE inhibits inflammation, facilitates rapid repair of DNA dimers, and stimulates the immune system to target mutated or otherwise abnormal cells.[13,14]

In more recent literature, GSE has been shown to reduce UV-induced carcinogenesis in mice.[15] Additional studies have shown that GSE provides a protective effect against UV-induced cell damage in human fibroblast cells.[16] Moreover, studies evaluating the beneficial effects of topical GSE have demonstrated improvements of age-related changes including skin elasticity, moisture, and smoothness.[16] Moreover, a study published in June 2019 evaluated the anti-aging potential of topical GSE in 20 female volunteers. Results demonstrated significant improvements in skin pH, elasticity, and moisture content, compared to placebo ($p<0.05$).[17] Few known side effects exist other than rare, mild skin irritation.

The properties of GSE and its active compounds, proanthocyanidins, may be useful in reducing UV-induced skin damage. While GSE products can be purchased over the counter and there are clear studied benefits, future large-

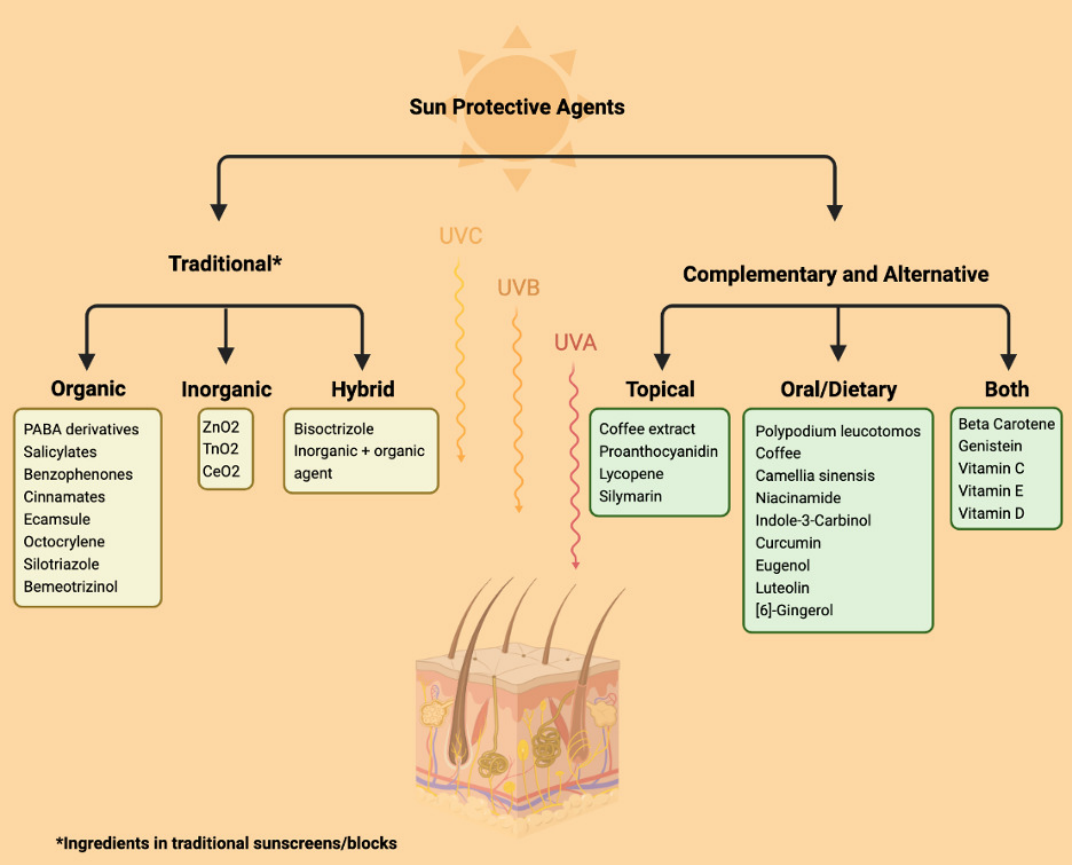

Figure 1. Overview of skin cancer chemoprevention and sun protection approaches

scale clinical trials must be performed before GSE can be truly assessed for efficacy and safety.

COFFEE

Coffee is one of the most popular beverages in the world.[18] There is evidence supporting various health benefits of coffee consumption. While some data suggests specific benefits related to sun protection and skin cancer prevention, these associations have not yet been well characterized.

A Norwegian study in 1986 explored the relationship between coffee consumption and occurrence of nonmelanoma skin cancer in 16,555 individuals. Coffee consumption was strongly associated with a lower incidence of nonmelanoma skin cancers.[19] While some later studies have supported this finding, others have found no association. In regard to melanoma, a recent systematic review found a statistically significant relative risk of 0.75 for melanoma among regular coffee drinkers compared to controls.[20]

Two studies further explored the relationship between coffee and UV radiation in hairless mice. In these studies, spent coffee ground ethanol extract (ESCG) was applied topically to mice and was found to significantly reduce UVB-induced intracellular reactive oxygen species, leading to lower levels of erythema.[21,22] Additionally, results indicated that ESCG protected mouse skin from UVB-induced photoaging by suppressing the expression of matrix metalloproteinases, leading to lower levels of wrinkle formation.[21,22]

There is some evidence to support the beneficial effects of regular coffee consumption on skin cancers. Additionally, other forms of coffee including topical ESCG may have photoprotective properties. However, more prospective cohort studies with systematic quantification of coffee use would be necessary to further elucidate this association.

CAMELLIA SINENSIS

Along with coffee, tea has many purported health benefits. The leaf found in true teas (as opposed to other herbal "tisanes") is that of *Camellia sinensis*. This Asian species of shrub has been studied for a variety of medical benefits including prevention of skin cancer.[23]

Studies have suggested a theoretical benefit after demonstrating that patients consuming camellia tea were noted to have increased DNA repair and other cytoprotective adaptations following UV light exposure.[23] This theoretical benefit was tested in a 2007 case control study which found a statistically significant reduced risk of SCC and BCC development with regular tea consumption.[24] However, a similar study published in 2011 showed no reduction in SCC risk with regular consumption of tea.[25] It is thought that variability in tea strength, standardization of ingredients, and amount consumed limit the reproducibility of these findings, as evidenced by another study demonstrating that tea concentration (strength), brewing time, and amount consumed have major influences on the potential protective effects of tea in relation to skin cancers.[26]

Given the contrasting findings of several studies, there is no current consensus on the association of tea consumption and development of skin cancers. Large scale, long-term studies with regulated tea consumption would be necessary in order to provide sufficient evidence for the use of tea as a chemoprotective agent.

NIACINAMIDE

Niacinamide (NAM), also known as nicotinamide, is a form of niacin (vitamin B3) found in many supplements. Often, it is used to treat vitamin B3 deficiency, which may manifest clinically as pellagra. However, NAM has been marketed to provide other health benefits. For example, studies have demonstrated that NAM provides a protective effect with regards to non-melanoma skin cancers, particularly SCC.

A phase 3 randomized trial conducted in 2015 found that twice daily supplementation with oral NAM reduced the rate of new SCC and BCC by 23% compared to placebo at 1 year among patients at high risk for skin cancer.[27] Further studies have also demonstrated efficacy of NAM in transplant patients and among inhabitants of arsenic-contaminated areas.[28]

While several studies have demonstrated the chemoprotective effect of NAM, a Bayesian analysis of the previously mentioned phase 3 trial reported insufficient evidence with regard to its chemoprotective effect.[29] Additionally, patients may experience side effects including flushing, gastrointestinal symptoms, and insulin resistance.[27,30] While these side effects are often mild, it should be noted that NAM is not without its potential complications.

Based on the available literature, some dermatologists recommend NAM use, especially in high-risk patients. In these cases, patients should be counseled on the possible side effects. However, given the conflicting evidence, a definitive consensus within the dermatologic community has not been reached and official recommendations do not currently exist.

BETA CAROTENE AND LYCOPENE

Beta carotene and lycopene are pigments found in a variety of vegetables including carrots and tomatoes. Both of these compounds act as antioxidants and have been studied for their ability to protect against free radical DNA damage.

One study conducted in 1994 demonstrated that beta carotene supplementation led to lower rates of tumor development in mice after exposure to UV radiation.[31,32] Long term studies and literature analyses indicate some promising trends but have not found any statistically significant association between beta carotene and development of human skin cancer.[31] Interestingly, some argue that beta carotene can potentiate skin damage.[33]

In regard to lycopene, one randomized control trial in 2011 studied 20 healthy women and found that ingestion of lycopene-rich tomato paste reduced UV induced matrix metalloproteinases and enhanced DNA repair.[34] Similarly, a 2017 study conducted on hairless mice demonstrated a significantly lower incidence of tumor development with topical use.[35]

Despite some evidence suggestive of a photoprotective role in preventing tumorigenesis, more substantial human trials are needed for these two compounds to better elucidate their potential benefits. Topical and oral formulations of these compounds are available over the counter and, while anyone seeking their potential benefit may use them, current recommendations have not been established.

GENISTEIN

Genistein is a flavone and one of the main components of soy-based food, oregano and sage.[36] This compound has been extensively studied for its many health benefits such as anti-cancer, anti-inflammatory, and antioxidant effects.[36] Additionally, genistein has been marketed to reduce signs of skin aging and studied for its potential protective effects against skin carcinogenesis.[35]

One study performed on mice demonstrated that both topically applied and orally supplemented genistein sufficiently inhibited UVB-induced skin cancers in a dose dependent manner up to >90%.[37] Other studies have confirmed its photoprotective properties in mice.[38,39] One study also showed a reduction in UVB-induced skin damage in human skin treated with topical genistein,[37] although no long term human trials have been conducted. Side effects have not been well studied; however, some researchers have found that this compound may bind estrogen receptors, promoting growth of certain breast tissue and breast cancers.[40]

While long term studies must be conducted before any consensus is made in the dermatologic community, rodent models have shown promise in the photoprotective effects of genistein. Because of its pronounced topical effect in mice, future studies with regard to its integration in sunscreens may be beneficial. Currently, topical formulations are available over the counter; however, recommendations have not yet been established. Of note, it should be avoided in individuals with breast cancer due to its potential breast tissue agonist properties.

SILYMARIN

Silymarin is a flavonoid that can be isolated from the seeds of milk thistle, an herb native to the Mediterranean region.[41] It has been used as an herbal remedy to treat liver-associated illness for centuries; but over the last two decades, it has been studied for its anticarcinogenic properties and intrinsic antioxidant activity.[39]

A 2017 study used a mouse model to establish that silibin, a water soluble form of silymarin, provides protective effects through its antioxidant properties and its ability to activate p53, a tumor suppressor and cell-cycle regulator.[42] This study further demonstrated a significant reduction in photodamage, tumor number, as well as multiplicity in mice treated with topical silibin.[40] Other studies have confirmed a dose-dependent protective effect of silymarin with reductions of up to 96% in tumor volume and 74% in tumor incidence in treated mice.[43] Side effects have not been well studied.

Overall, many reports, including literature reviews and meta-analyses, suggest the potential use of silymarin in the prevention of NMSCs. However, to date, no significant human trials have been conducted and no established recommendations exist for the use of silymarin. Currently it is available over the counter and may benefit from trials with its integration in sunscreen.

VITAMIN C

Vitamin C has been studied for its potential as a photoprotective agent due to its antioxidant properties. So far, there is little evidence suggestive for a significant effect in protection against photodamage or carcinogenesis. One study found that 500mg/day vitamin C supplementation significantly raises vitamin C plasma and skin content but found no reduction in UV-induced inflammation.[44] As a topical agent however, many studies have found that vitamin C can increase collagen production and protect against UV damage.[44] Murray and colleagues, for example, demonstrated a reduction in UV-induced photodamage in humans with 10% topical Vitamin C pretreatment. While this suggests a photoprotective effect, no long-term studies have associated its use with a reduction in carcinogenesis.[44-46]

As a topical agent, vitamin C shows promise in its benefit to skin. The evidence to support the photoprotective properties of Vitamin C, coupled with its lack of side effects, make it a potentially useful complementary agent. As such, it is commonly found as an added ingredient to sunscreens. However, no evidence to suggest a reduction in skin cancers exists and there are no current guidelines for its use.

VITAMIN E

Vitamin E has been shown to provide protection against UV-induced skin photodamage through a combination of antioxidant and UV absorptive properties.

One study found that topical application of vitamin E on mouse skin inhibits the formation of DNA damage, such as cyclobutane pyrimidine photoproducts.[44] Other studies have shown a direct benefit of topical vitamin E demonstrating a decrease in the incidence of skin cancers in treated mice.[47,48] Of note, topical Vitamin E is rapidly depleted by UVB radiation in a dose dependent manner and several studies have failed to show a reduction in UVB-induced photodamage and no studies have demonstrated a reduction in carcinogenesis in humans.[44,45]

Vitamin E is an example of a topical agent which shows some theoretical promise as a photoprotective agent but the evidence lacks reproducibility and human-based efficacy. Further studies must be conducted to definitively characterize this vitamin's role in sun protection, but it is not currently described as an efficacious agent.

VITAMIN D

Multiple studies have demonstrated a photoprotective effect of vitamin D in keratinocytes exposed to UV radiation.[49] One such study found a 112% increase in mouse keratinocyte survival 24 hours post-UV radiation in cells treated with 10^{-8} M $1,25(OH)_2D_3$. This study also demonstrated a 40% decrease of sunburn cells in mouse skin exposed to UV radiation after treatment with $1,25(OH)_2D_3$ at a concentration of 22.8 pmol/cm^2. Other benefits included a reduction in thymine dimers and nitric oxide free radicals as well as an increase in p53 expression.[49]

These results have been replicated in humans. A study of 10 human subjects published in 2010 demonstrated a 92% decrease in thymine dimers in skin exposed to UV with pretreatment of topical 0.1 ug/cm^2 $1,25(OH)_2D_3$ compared to skin with no pretreatment.[50] Other studies have proposed a variety of mechanisms which support the photoprotective and chemoprotective potential of vitamin D used as an oral or topical supplement.[51] However, no large scale human trials have been conducted to better elucidates the role of vitamin D in photoprotection and cutaneous cancer chemoprevention.

SECTION III: DIET

Certain dietary compounds, especially those present in plant-based foods, can provide medicinal value and promote health.[52] These plant-produced compounds, called phytochemicals, encompass various classes of nutrients including those previously reviewed: polyphenols, phenolic acids, flavonoids, and carotenoids.[52] Although they cannot replace modern drugs, nor are they targeted or specific for treating diseases, research indicates that their intake is correlated with numerous positive health outcomes including reduced risk of cancer.[52,53]

In this review we have highlighted some alternative agents known for their photoprotective properties and potential chemopreventive effects. While many of these benefits are seen with topical application, the aim of this last section is to briefly introduce other dietary phytochemicals and their role in photoprotection. These include: ursolic acid, eugenol, [6]-gingerol, capsaicin, indole-3-carbinol, epigallocatechin-3-gallate, curcumin, and luteolin; all of which have been found, *in vitro*, to regulate a variety of enzymes allowing for enhanced DNA repair, regulation of cell growth, and reduced DNA mutations.[42,45,53] While they have demonstrated some evidence of photoprotection, substantial human trials and conclusive data are lacking.[45]

Of note, one of the many challenges faced when measuring the true benefit of dietary changes is the lack of bioavailability of these compounds, as they are rapidly eliminated and have a short-lived pharmacologic window.[52] Regardless of this obstacle, table 2 is meant to serve as a guide for those interested in the potential benefits of a diet rich in antioxidants and phytochemicals studied for their photoprotective properties.

CONCLUSION

Skin endures substantial oxidative stress when exposed to UV radiation, leading to mutations that may result in skin cancer. Our endogenous antioxidant system has its limits, especially as we age[44]; thus the exogenous supplementa-

Table 1. Summary of complementary and alternative agents that may promote sun protection

Agents	Experimental Design	Route Administered	Mechanism of Action	Findings
Polypodium Leucotomos	*In vivo* (mouse and human models)	Oral	Enhances activity of endogenous antioxidant systems, inhibits release of cytokines	Reduces inflammation following sun exposure, fewer measured sunburn cells, pyrimidine dimers[9-12]
Grape seeds extract	*In vitro* and *in vivo* (mouse and human models)	Topical	Antioxidant, facilitates repair of DNA dimers, stimulates immune system to target mutated cells	Reduce UV-induced carcinogenesis in mice; improve skin elasticity, moisture, and smoothness in humans[13-16]
Coffee (caffeic acid)	*In vivo* (mouse and human models)	Oral, topical	Potent antioxidant, suppresses metalloproteases, reduces tumor cell angiogenesis	Inconsistent data regarding protective effect of coffee consumption; reduces UV-induced intracellular reactive oxygen species, leading to lower levels of inflammation in mice[19-22]
Camellia Sinensis	*In vivo* (mouse and human models)	Oral, topical	Potent antioxidant, enhancement of DNA repair	Cytoprotective adaptations in vitro; inconsistent data regarding the protective effect of tea consumption in humans[23-25]
Niacinamide	*In vivo* (human models)	Oral	Possible enhancement of surveillance proteins p53 and ADP ribose polymerase	Several studies demonstrate a significantly reduced rate of new SCC and BCC; one study refutes this finding[27-30]
Beta Carotene	*In vivo* (mouse models)	Oral, topical	Antioxidant, enhances DNA repair	Lower rates of tumor development in mice after exposure to UV radiation[31-33]
Lycopene	*In vivo* (mouse models)	Topical	Antioxidant, reduces UV induced matrix metalloproteinases, enhances DNA repair	Significantly reduced incidence of skin cancer development in mice[34,35]
Genistein	*In vivo* (mouse and human models)	Topical	Antioxidant, potent anti-inflammatory, inhibits cytokine release	In mice, inhibited UVB-induced skin cancers by >90%; in humans, reduced UVB-induced skin damage[37-40]
Silymarin	*In vivo* (mouse models)	Topical	Antioxidant, activation of p53	Significant reduction in tumor incidence in mice[42,43]
Vitamin C	*In vivo* (mouse and human models)	Oral, topical	Antioxidant, collagen stimulation	Little evidence suggestive for a significant effect in protection against photodamage or carcinogenesis[44-46]
Vitamin E	*In vivo* (mouse and human models)	Oral, topical	Antioxidant, inhibits DNA damage, such as cyclobutane pyrimidine photoproducts	In mice, reduced incidence of skin cancers; in humans, several studies have failed to show a reduction in photodamage[45,47,48]
Vitamin D	*In vivo* (mouse and human models)	Topical	Inhibits DNA damage, increase p53 expression	In humans, reduced thymine dimer formation, increased cell survival after UV exposure[50]

tion of antioxidants may help protect against cumulative sun damage. Evidence continues to accumulate that is suggestive of special nutrients, dietary changes, and alternative agents that may help to reduce oxidative stress and free radical formation, thereby slowing down the skin damage process.[44] In our review of the literature, we highlight the potential integrative role of complementary and alternative sun protective agents.

For many of these agents, animal and human models have convincingly demonstrated a measurable photoprotective effect. This effect is mostly observed when applied topically before radiation exposure. While many of these agents show promise, studies either lack sufficient length

Table 2. Dietary items with corresponding active ingredient and regulation of enzymes and cellular pathways.

Dietary Items	Active Ingredient	Regulation of Enzymes and Cellular Pathways
Brussel sprouts, Broccoli, Cauliflower	Indole-3-Carbinol	↓Bcl-2, MITF, ↑Apoptosis
Green tea	Epigallocatechin-3-Gallate	↓COX-2, NFkB, IL-1
Soybeans	Genistein	↓H_2O_2, MDA, ↑p53, p21
Basil, Rosemary, Thyme, Apples, Berries, Oregano, Peppermint, Prunes	Ursolic acid	↓COX-2, NFκB, Bcl-2, ↑p53
Turmeric	Curcumin	↓VGEF, JNK
Cinnamon, Basil, Bay leaves, Cloves, Nutmeg	Eugenol	↓COX-2, TNF-α, c-Myc, IL-6
Celery, Olives, Carrots, Peppers	Luteolin	↓COX-2, NFκB, Bcl-3
Ginger plant	[6]-Gingerol	↓COX-2, NFκB, Bcl-2, ↑p53

Abbreviations: Bcl-2 (B-Cell Lymphoma 2 gene); MITF (microphthalmia-associated transcription factor); COX-2 (cyclooxygenase 2), NFκB (nuclear factor kappa-B); IL-1 (interleukin 1) H_2O_2 (hydrogen peroxide); MDA (3,4-mehtyle dioxy amphetamine); VGEF (vascular endothelial growth factor); JNK (c-Jun N-terminal kinase); TNF-α (tumor necrosis factor alpha); c-Myc (c myelocytomatosis oncogene)

or have otherwise been unable to show a definitive reduction in skin cancer incidence in humans. Real world application of these agents may also be hindered by dose-dependent responses. For example, products may only be commercially available at a lower concentration than those used in the studies.[44] Additionally, many of the studies noted a time-dependent response, as the photoprotective effect was most pronounced only directly after application. Lastly, other variables such as patients' baseline risk factors may have influenced some of the results.

In sum, while evidence supports the photoprotective properties of many of these agents, there is conflicting evidence regarding the direct role of these agents in the reduction of skin carcinogenesis in humans. This suggests a potential chemoprotective benefit with their use, but need for further investigation. Currently the most important strategies to reduce photodamage and risk of skin cancer are sun protective clothing, sun avoidance, and the use of sunscreens and sunblocks (when applied correctly). When these measures fail or have shortcomings, however, the complementary use of alternative agents should certainly be considered. Nonetheless, until evidence from long-term, randomized, placebo-controlled trials on human subjects becomes available, there will be no official consensus or definitive recommendations.

LIMITATIONS

Although there are no specific agents we chose not to include, it is possible that our search missed certain photoprotective agents. Additionally, studies published in journals that are not indexed in the searched databases may not have been captured. This means that there may be peer-reviewed data that could further support or refute certain conclusions that were made.

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