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EPIDEMIOLOGY (R DELLAVALLE, SECTION EDITOR)

Phytochemicals and Naturally Occurring Substances in the Chemoprevention of Skin Cancer

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Abstract
Purpose of Review Non-melanoma skin cancer outnumbers all other cancers combined by three to four-fold while melanoma is the fifth most common cancer overall, and the deadliest form of skin cancer. Despite treatment advancements in the past several decades, incidence continues to rise. Phytochemicals and other naturally occurring substances may provide sustainable chemopreventive solutions. The purpose of this study is to review the key findings from the literature and report on the level of evidence based on study design.
Recent Findings A comprehensive PubMed search was completed from 1984 to present using keywords "skin cancer chemoprevention" alone and with "phytochemicals," "alternative," "essential oils," and "vitamins." This search demonstrated that the literature strongly endorses the role of naturally occurring substances in the context of skin cancer chemoprevention, however the literature is predominantly comprised of data based on in vitro and animal based models.
Summary Prior to acceptance into mainstream practice, high quality prospective studies to evaluate the role of naturally occurring compounds in the context of skin cancer chemoprevention are indicated.

Keywords Chemoprevention · Phytochemicals · Essential oils · Nicotinamide · Non-melanoma skin cancer · Melanoma

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Introduction

One in five Americans will develop skin cancer in their lifetime [1]. Non-melanoma skin cancer (NMSC) is currently the most common cancer in the USA with over five million estimated cases per year and rates continuing to climb [2, 3]. The Global Burden of Disease Study found that patients with NMSC have disability-adjusted life-years similar to uterine cancer and substantially more than thyroid cancer, Hodgkin lymphoma, and testicular cancer [4]. In regard to melanoma, despite comprising less than one percent of total skin cancers, mortality rates are second only to lung cancer [5]. The annual cost of treating skin cancers in the USA is estimated at $8.1 billion: approximately $4.8 billion for NMSC and $3.3 billion for melanoma. This severe economic burden in addition to the significant morbidity and mortality rates has engendered a movement towards creative strategies for skin cancer chemoprevention, including incorporation of phytochemicals and naturally occurring substances, which can fall under the umbrella of complementary and alternative medicine (CAM). Complementary and alternative medicine (CAM) is loosely defined as any healing practice "that does not fall within the realm of conventional medicine" [6]. A 2010 report cited that 78% of respondents felt that physicians should incorporate CAM into their treatment plans [7, 8]. Additionally, many of the drugs developed to treat cancer are not suitable for chemoprevention due to their side effect profile, toxicity, and development of resistance over time. Natural products may provide sustainable alternatives.

To evaluate the evidence in support of these therapies, the authors conducted a comprehensive PubMed search from 1984 to present using keywords "skin cancer chemoprevention" alone and with "phytochemicals," "alternative," "essential oils," and "vitamins." Results yielded a large trove of literature strongly endorsing the role of naturally occurring substances in the context of skin cancer chemoprevention, however predominantly consisting of data based on in vitro and animal based models. Studies predominantly center on the effect of phytochemicals with mention of several additional naturally occurring compounds.

Proanthocyanidins

Phytochemicals are bioactive compounds found in plants with disease preventive properties. They are wide-ranging in type and mechanism, including polyphenols, flavonoids, isoflavenoids, phytoalexins, phenols, anthocyanidins, and carotenoids. They work via a variety of mechanisms that include stimulation of the immune response, induction of gene suppression, blocking of oxidative damage to DNA, detoxification of carcinogens, and initiation or inhibition of select signaling pathways [9]. Heightened interest in phytochemicals has been spurred by increased epidemiological and experimental evidence suggesting a protective role in development of a variety of cancers, including cutaneous malignancy.

Apigenin

Apigenin (5,7,4′-trihydroxyflavone) is a bioflavonoid found in food sources such as guava, orange, tea, onions, parsley, thyme, celery, and sweet red pepper [10] (level of evidence 5). It has been reported to exert chemopreventive effects for a variety of cancers including that of the breast, digestive tract, prostate, colon, and skin [11•]. Animal models have provided mechanistic insight into its effects on the skin, which include inhibition of angiogenesis, stabilization and enhanced expression of tumor suppressive p53, and suppression of UVB-induced increases in COX-2, an enzyme associated with inflammation, cell survival, proliferation, angiogenesis, invasion, and metastasis [10, 11•]. Apigenin has also been reported to act via the mammalian target of rapamycin (mTOR) signaling pathway, activating AMP-activated protein kinase (AMPK) in keratinocytes to inhibit baseline mTOR pathway activity, which is essential in regulation of cell growth and proliferation and also in the development of NMSC (Fig. 1) [10].

The clinical efficacy of mTOR inhibitors in skin cancer chemoprevention has been modest due in part to the multiple feedback loops that control mTOR activity. To circumvent this, several second-generation drugs are in development that target not only mTOR but also its upstream regulator, phosphoinositide 3-kinase (PI3K). This dual targeting, however, is likely to boast increased toxicity. Apigenin may serve as a naturally occurring, non-toxic alternative with dual-specificity inhibition to block both UVB-induced Akt (an upstream regulator of mTOR) and mTOR activity [10]. Oral bioavailability, however, is relatively low. Recent developmental efforts have demonstrated that solid dispersions of apigenin with carbon nanopowder can increase bioavailability in animal models [11•]. Apigenin can also be loaded into ethosomes composed of phospholipids and ethanol to enhance solubility, permeation, and deposition in the skin. Poly(lactic-*co*-glycolide) (PLGA)-loaded apigenin nanoparticles have also been used to enhance effects of apigenin [12].

Anthocyanins

Anthocyanins are bioflavonoids that, with derivatives anthocyans and anthocyanidins, are abundant in many fruits and vegetables. Chemopreventive mechanistic insight has been provided by epidemiological, in vitro, and in vivo studies [11•]. For example, in vitro work on cyanidin-3-glucoside (C3G), an anthocyanidin particularly dense in edible berries, has demonstrated its ability to significantly decrease production of UVB-induced pro-inflammatory cytokines and to

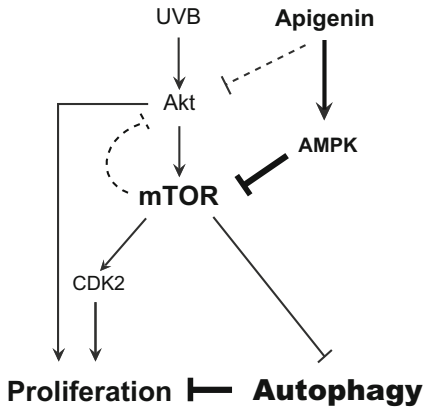

Fig. 1 Signaling pathways involved in inhibition of mTOR activation by apigenin and subsequent cellular reaction in keratinocytes. UVB activates mTOR pathway through PI3K/Akt signaling, while apigenin inhibits UVB-induced mTOR activation mainly by AMPK, which further induces autophagy and suppresses cell proliferation [10]

inhibit activation of mitogen activated protein kinases (MAPKs), extracellular signal regulated kinases (ERK) 1/2, and c-jun N-terminal kinase (JNK). The chemopreventive effects become evident when considering that ERK 1/2 enzymes are involved in uncontrolled cell growth and JNK1/2 enzymes are involved in apoptosis, cell proliferation, and inflammatory cytokine production. Dietary anthocyanidins delphinidin and peonidin were also reported to inhibit UVB-induced carcinogenesis in animal models [11•].

Proanthocyanidins

Closely related to anthocyanins are proanthocyanidins, a class of polyphenols chemically categorized as oligomeric flavonoids. Proanthocyanidins derived from whole grape seeds, or grape seed proanthocyanidins (GSPs), are a mixture of catechins and/or (−)-epicatechins that have antiinflammatory, antioxidant, and antimetastatic properties. They have been widely studied in cancer, although the evidence for their efficacy in prevention of skin cancer is limited [13]. In animal models, GSPs are found to inhibit UV radiation- and chemical carcinogen-induced skin carcinogenesis. In vitro data demonstrates that GSPs act in melanoma via the Wnt/beta-catenin pathway, aberrant activation of which has been observed in nearly one third of human melanoma cases [13] (level of evidence 5). It is also reported that dietary GSPs (0.2 and 0.5%, *w*/*w*) inhibit growth of melanoma cells by significantly decreasing cell viability and inducing the apoptotic cell death of human melanoma cell lines. This is accomplished by a dose-dependent decrease in levels of antiapoptotic proteins (Bcl-2, Bcl-xl) and an increase in pro-apoptotic proteins (Bax). GSPs were noted to exert these apoptotic effects on melanoma cells without any signs of toxicity to normal cells [13]. GSPs are also reported to stimulate repair of damaged DNA in UV-exposed skin with the number of cyclobutane pyrimidine dimer (CPD)-positive cells being significantly lower in groups who received dietary GSPs ($p < 0.001$) [14] (level of evidence 2).

Curcumin

Curcumin, a constituent of turmeric, is a powdered rhizome of *Curcuma longa* widely used in Ayurveda, Unani, and Siddha medicines. It has long been reported to have antiinflammatory, antioxidant, anticarcinogenic, antimutagenic, anticoagulant, and antiinfective properties [15] (level of evidence 5). It is also reported to protect against acute photodamage. Animal and in vitro work investigated the effect of topical curcumin for 3 days/week for 6 months on inflammatory cells and lipid peroxidation [15]. It noted that curcumin significantly attenuated acute UVB-induced lactate dehydrogenase (LDH) release, intracellular reactive oxygen species production, and DNA damage, and activated expression of phase II detoxifying enzymes along with promotion of DNA repair activity. Animal studies also demonstrate topical application of curcumin prior to chronic UV exposure causes delay in tumor appearance, multiplicity, and size (Table 1) [15].

Best photoprotective effects were achieved by long-term topical application, although this may be limited by risk for contact dermatitis, which occurred after weeks of topical treatment in humans [15]. Another problem with topical administration is penetration of the epidermis. Formulations have been developed that prolong contact of curcumin with skin. For example, one group used curcumin solubilized in acetone and applied as a "wet dress." Curcumin has also been emulsified in carboxymethyl cellulose (CMC)-Na for improved penetration and bioavailability [15]. A 2016 study describes the development of C3 complex, a standardized preparation (Sabinsa) of three curcuminoids: curcumin (76.07%), demethoxycurcumin (DMC; 20.28%), and bisdemethoxycurcumin (3.63%) [16] (level of evidence 5). DMC and bisdemethoxycurcumin are natural derivatives of curcumin and similarly possess antiinflammatory and antiproliferative properties. They are also more stable than curcumin in serum [16]. Oral bioavailability is also low due to rapid internal metabolism and poor aqueous solubility. There have been efforts to circumvent this issue with the development of curcumin analogs and nanomaterial based drug delivery methods. Piperine, a natural anticancer agent, has been reported to enhance bioavailability of curcumin by inhibiting curcumin glucuronidation. Co-administration of piperine (20 mg) with curcumin (2 g) resulted in a 2000% increase in bioavailability in humans [11•].

Curcumin is "Generally Recognized as Safe" by the US Food and Drug Administration and the Joint Food and Agriculture Organization/World Health Organization (FAO/WHO) Expert Committee on Food Additives approved daily intake of curcumin level of 0.1–3 mg/kg body weight. In a

Table 1 Several natural products as skin cancer chemopreventive and therapeutic agents by targeting AA cascade and its associated signaling pathways [11•]

Natural product	Experimental model	Anticancer/anticarcinogenic effects	Mechanisms
Cyanidin-3-glucoside (anthocyanin)	In vivo	Suppressed UVB-induced skin damage and inflammation in SKH-1 hairless mice	↓ERK 1/2, ↓JNK1/2, ↓p38, MKK4, ↓COX-2, ↓iNOS, ↓NF-κB
Delphinidin (anthocyanin)	In vitro	Exhibited protective role against UVB-mediated skin carcinogenesis	↓MAPKK4, ↓JNK, ↓p38, ↓AP-1, ↓NF-κB, ↓COX-2
Berberine	In vitro	Suppressed melanoma cell migration	↓COX-2, ↓PGE2, ↓EP2, ↓EP4
Curcumin	In vitro	Caused apoptosis in melanoma cells	↑Caspase-3, ↓cyclin D1, ↓COX-2, ↓NF-κB
Diallyl sulfides	In vivo	Exhibited protective effect of DAS in UVB light-induced skin lesion in SKH-1 hairless mice	↓COX-2, ↓PGE2, ↓NF-κB
Epigallocatechin-3-gallate	In vitro	Suppression of cell migration or invasion of A375 and Hs294t melanoma cells	↓COX-2, ↓PGE2, ↓NF-κB, ↓EP2, ↓EP4
Eugenol	In vitro	Protected against chemically induced skin cancer	↓COX-2, ↓iNOS, ↓NF-κB, ↓PGE2, ↓TNF-alpha, ↓IL-6

phase I clinical trial, curcumin oral administration up to 3.6 g/day for 4 months was tolerated by patients with colorectal cancer.

Resveratrol

Resveratrol, *trans*-3,5,4′-trihydroxystilbene, is a stilbene found in grapes, berries, peanuts, red wine, and many other plants. It has been shown to possess various medicinal properties; however, its effect on skin cancer has only recently been studied [17, 18] (level of evidence 5). In animal models, it was found that resveratrol treatment at a dose of 1 or 2 mg/kg caused a significant reduction in DMBA-induced tumor occurrence, tumor volume, and tumor weight when compared to a DMBA control group [18]. Reported mechanisms include an increase in cell-cycle and apoptosis genes such as p53, p21, caspase-3, bax, survivin, cyclin-B, and cdc-2 [18]. Pterostilbene, 3,5-dimethoxy-4′-hydroxy-*trans*-stilbene, a natural analog of resveratrol, was also reported to prevent DMBA/TPA-induced tumor formation in mice by blocking MAPK/NF-κB/AP-1/COX-2 pathways. A 2015 study demonstrated that topical treatment with pterostilbene in an animal model protected against UVB radiation-induced skin damage and carcinogenesis via reduction of chronic UVB radiation-induced oxidative damage and maintenance of the skin's antioxidant defenses (i.e., glutathione, catalase, superoxide, and GSH peroxidase activities) and potential modulation of the Nrf2-dependent antioxidant response [19] (level of evidence 5). Additional studies report resveratrol suppresses metabolic activation of pro-carcinogens to carcinogens by modulating the metabolic enzymes responsible for their activation [20] (level of evidence 2). RCTs, however, have been unable to substantiate an impact of supplementation with resveratrol [21].

Obstacles in the clinical development of resveratrol include the rapid internal metabolism and poor pharmacokinetic parameters [11•]. Pterostilbene is noted to have a more favorable pharmacokinetic profile by way of a chemical structure containing one less methoxy group compared to resveratrol. It is thus less susceptible to conjugation metabolism and is characterized by a relatively longer half-life [19]. Of note, pterostilbene is reported to possess enhanced chemopreventive properties when combined with another phytochemical, lupeol, an active triterpenoid [22] (level of evidence 5). These two compounds can commonly be found in blueberries, grapes, white cabbage, green pepper, olive, and mangos. This synergistic relationship demonstrates that combinations of phytochemicals often have better efficacy than individual components. It is important to note, however, that possible interactions may counter the benefits, and thus, it is important to utilize the appropriate dose combinations [22].

Sulforaphane

Sulforaphane [1-isothiocyanato-4-(methylsulfinyl)butane], an isothiocyanate found in cruciferous vegetables such as broccoli, has been known to possess antiinflammatory and anticancer activity against a variety of cancers including the breast, prostate, colon, skin, lung, stomach, or bladder. Preclinical studies have focused mainly on the sulforaphane compound itself, while clinical studies have focused on broccoli sprout preparations rich in either sulforaphane or its biogenic precursor, glucoraphanin (Fig. 2) [23]. One of the key molecular mechanisms of action includes its activation of the

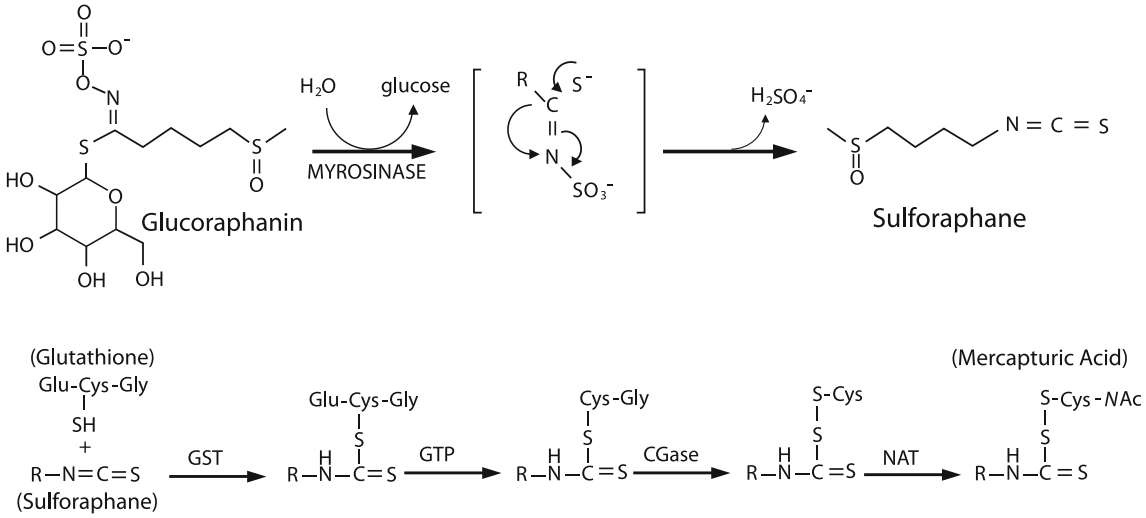

Fig. 2 Glucoraphanin in broccoli is converted to sulforaphane either by plant myrosinases or, if the plant myrosinases have been denatured by cooking, by bacterial β-thioglucosidases in the human colon [23]

nuclear factor erythroid 2-kelch-like ECH-associated protein 1 (Nrf2-Keap1) signaling pathway. Nrf2 is a transcription factor considered to be a master regulator of the environmental stress response. Under quiescent conditions, Nrf2 is held in the cytoplasm by Keap1, which facilitates its degradation via ubiquitination then proteolysis. Under oxidative and inflammatory stresses, this proteolysis is interrupted and Nrf2 can translocate into the nucleus and bind the antioxidant response element (ARE) sequences present in enhancer regions of various cytoprotective genes (Fig. 3). These genes encode enzymes and other proteins that balance redox homeostasis, detoxify electrophiles and oxidants, and repair or remove damaged proteins and nucleic acids [23]. Sulforaphane is among the most potent naturally occurring inducers of the Nrf2 signaling pathway, exhibiting efficacy in the high nanomolar range in cell cultures [23].

In preclinical studies, the most dramatic effect of sulforaphane is exhibited at the level of tumor initiation, markedly reducing the multiplicity of tumors in a murine model. Clinical studies characterize the pharmacokinetics and safety in humans and have established the safety of both glucoraphanin-rich (GRR) and sulforaphane-rich foods (SFR). Dose-limiting factors include taste, gastric irritation, and flatulence. Evidence indicates that sulforaphane is rapidly absorbed resulting in high bioavailability with oral doses although bioavailability of SFR is substantially better than GRR [23].

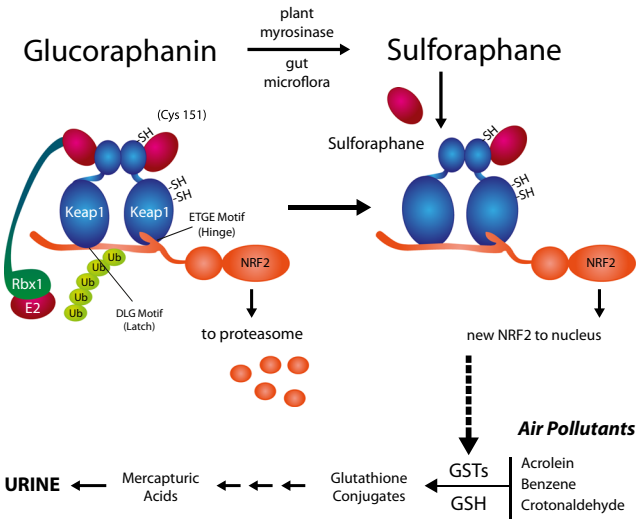

Fig. 3 Scheme of Keap1-Nrf2 interactions. Under homeostatic conditions, Nrf2 is bound by Keap1. Upon association, Nrf2 is ubiquitinated (Ub) by the Cul3 ubiquitin ligase complex, marking it for proteasomal degradation. Induction of Nrf2 signaling by sulforaphane may lead to disruption of the Cul3 association with Keap1 and interruption of Nrf2 ubiquitination. Nrf2 can therefore translocate to the nucleus to activate transcription of its target genes [23]

Lycopene

Lycopene has also been implicated in photo- and thus chemoprevention. It is a powerful antioxidant, protecting against the oxidation of proteins, lipids, and DNA. It acts as one of the most potent scavengers of singlet species of oxygen free radicals. It acts as a selective inducer of apoptosis in transformed cells. Of note, study of cellular photoprotection by antioxidants may be challenging due to the high chemical instability (particularly to air and light) and strong lipophilicity. Thus, it is important to be cognizant of storage and vehicle of delivery. Special precautions should be taken to protect lycopene from light, air, and variations in temperature. Doses above 20 μmol were reported to be toxic to human cells [24].

Nicotinamide

Nicotinamide has been utilized for chemoprevention in the context of organ transplantation, as immunosuppressed organ transplant patients are reported to have an 80-fold increased risk of squamous cell carcinoma (SCC) and a 16-fold

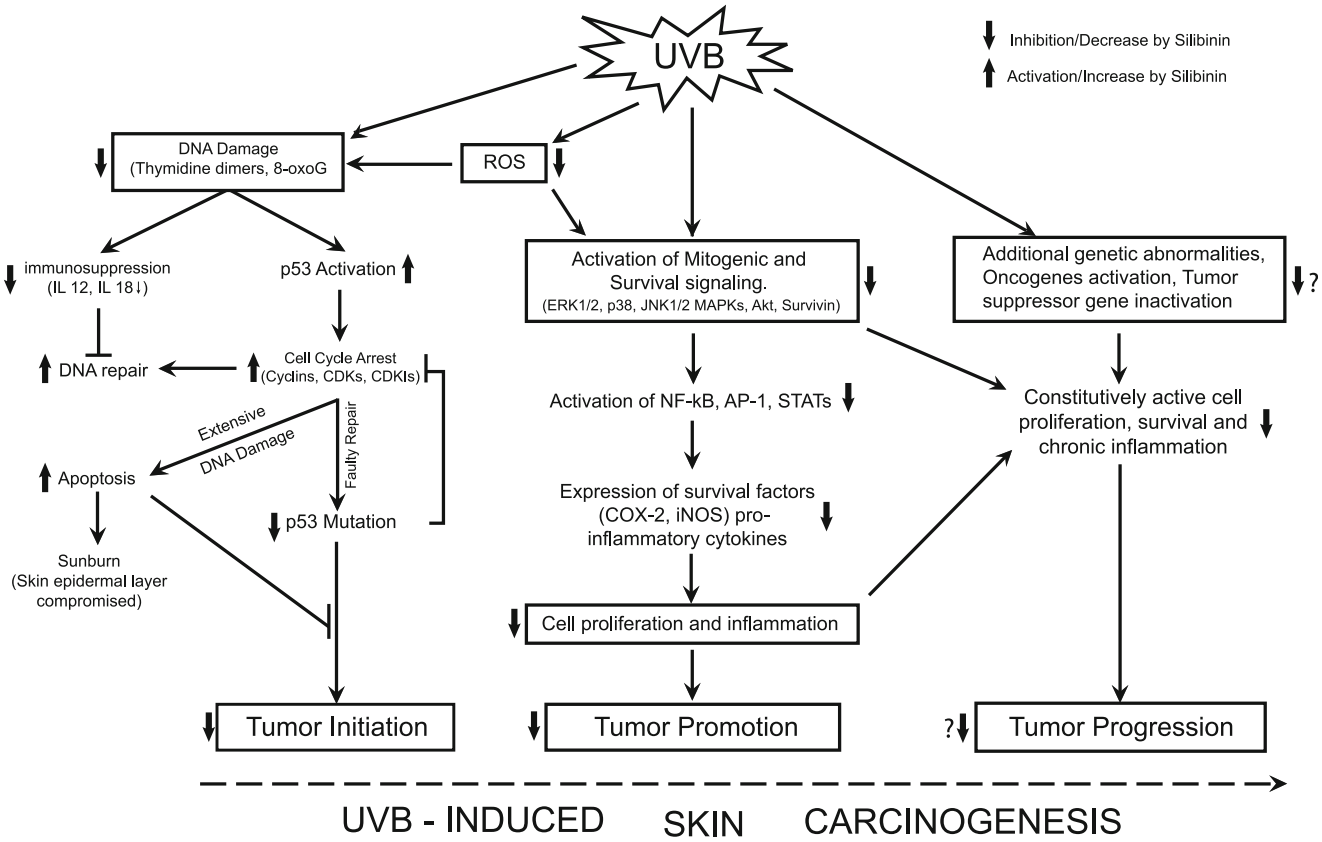

Fig. 4 Effect of silibinin on UVB-induced skin damage and carcinogenesis [28]

increased risk of BCC [25•] (level of evidence 1). As SCCs are more aggressive and likely to metastasize, chemoprevention in this regard is high yield in terms of decreasing morbidity and mortality. The current mainstay therapy for NMSC in post-transplant patients is oral retinoids, which have a number of side effects including liver and lipid abnormalities, mucocutaneous dryness, and teratogenicity. Nicotinamide (vitamin B3) enhances repair of photodamaged DNA and prevents the inhibitory effects of ultraviolet radiation on the immune system without altering baseline immune responses. In one study involving 386 immunocompetent participants at high risk of having cancer, nicotinamide 500 mg twice daily reduced new NMSC by 23% ($p = 0.02$), with 20% fewer BCCs and 30% fewer SCCs compared with placebo. Actinic keratoses (AKs) were also significantly reduced by nicotinamide in the same phase III randomized controlled trial. No safety concerns were noted, and it was reported that nicotinamide has an excellent safety profile at doses less than or equal to 3 g/day [26•].

Essential Oils

Sesamol, a component of sesame seeds and sesame oil, is a water-soluble lignin that has potent antioxidant and anticancer activities. A recent 2016 study reports that sesamol administration in a murine model (both in free and encapsulated form) significantly decreased tumor burden and lipid peroxidation level and increased antioxidant levels, thereby interfering with the development and promotion of skin tumors. Apoptosis of tumor cells was also noted to occur via down-regulation of bcl-2 and stimulation of bax protein. The compound's small size and easy permeability, however, results in excessive systemic loss compromising its local availability. Its irritant nature also limits its application on the skin. Encapsulating sesamol into solid lipid nanoparticles (SLN) reduces irritation and improves local targeting to the skin [27] (level of evidence 5).

Silibinin is the main bioactive flavonolignan present in milk thistle extract. It has been reported to have antiinflammatory and antitumorigenic properties conferred at least in part by terpene and hydrocarbon content. Its mechanism of action is occasionally mediated by p53 and includes suppression of various inflammatory and angiogenic mediators, including COX-2, transcriptional factors nuclear factor (NF)-κB, hypoxia inducible factor (HIF)-1α, and inducible nitric oxide synthase (iNOS) (Fig. 4) [11•]. Silibinin has also been noted to exert chemopreventive effects via IL-12, an immunomodulatory cytokine with well-evidenced roles in reversal of UVB-induced DNA damage, immunosuppression, and apoptosis. Of note, it is reported that silibinin protects normal epidermal cells from apoptosis, while following severe damage, silibinin potentiates apoptotic death [28]. Both

silibinin and IL-12 were also reported in in vitro and animal-based models to accelerate repair of UVB-induced cyclobutane-pyrimidine dimers. IL-12 has thus long been utilized for these chemopreventive properties; however, concerns exist regarding epidermal delivery in addition to cost of large-scale production. Silibinin could provide a sustainable alternative by enhancing IL-12 levels in keratinocytes exposed to UVB with no effect on unexposed skin [29].

Poor bioavailability of silibinin has limited its chemopreventive potential at tumor sites, and complexes have thus been developed to improve absorption. Commercially available silibinin complexes include IdB 1016 (silipide) and silibinin-phytosome (siliphos), both of which are formulated with phosphatidylcholine. Both demonstrate improved bioavailability compared to silibinin alone. Silibinin-loaded nanoparticles may also be utilized for effective drug delivery [11•]. In vivo animal and human studies have shown that silibinin is free of serious adverse effects [28].

Additional essential oils with reported chemopreventive properties include sandalwood oil, geraniol, myrrh, and frankincense [30–32] (level of evidence 5, 5, 5). Both myrrh and frankincense were identified as containing chemopreventive monoterpenes and sesquiterpenes. Results attained in an in vitro model demonstrate, however, that a significantly larger inhibitory effect was noted in cell lines treated with myrrh essential oil as compared to treatment with frankincense and a mixture of both oils [32]. Melaleuca oil, carrot oil, rose hip (*Rosa canina* L.), colchicum oil, flaxseed oil, and caraway oil are also reported to have benefit [33–37] (level of evidence 5, 5, 5, 5, 5, 5).

Conclusion

The literature provides theoretical and mechanistic insight into the potential benefit of a variety of natural therapies in the context of skin cancer prevention with the majority of the literature focusing on effects of phytochemicals. These include apigenin, anthocyanins, proanthocyanidins, curcumin, resveratrol, sulforaphane, lycopene, and essential oils. Mechanisms of action include effects on cell apoptosis, cell proliferation, inflammation, angiogenesis, antioxidant capacity, and repair of UV-induced DNA damage. Nicotinamide also works to enhance repair of photodamaged DNA and prevent the inhibitory effects of UV radiation on the immune system. These molecular effects have clinically translated into decreased tumor occurrence, volume, and tumor weight predominantly in animal models. Thus, it becomes evident that there is an abundance of data derived from in vitro and animal models, and prior to these compounds becoming accepted into mainstream practice, additional targeted and high-quality prospective studies are indicated.

Compliance with Ethical Standards

Conflict of Interest Shauna Higgins, Kimberly Miller, Katherine Wojcik, Omeed Ahadiat, Loraine Escobedo, Ashley Wysong, and Myles Cockburn have no conflicts of interest to declare.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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