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Phytochemicals for the Prevention of Photocarcinogenesis†

Mary Katherine Montes de Oca¹, Ross L. Pearlman¹, Sarah F. McClees¹, Rebecca Strickland¹, and Farrukh Afaq^{1,2,*}

¹Department of Dermatology, University of Alabama at Birmingham, Birmingham, Alabama, USA

²Comprehensive Cancer Center, University of Alabama at Birmingham, Birmingham, AL, USA

Abstract

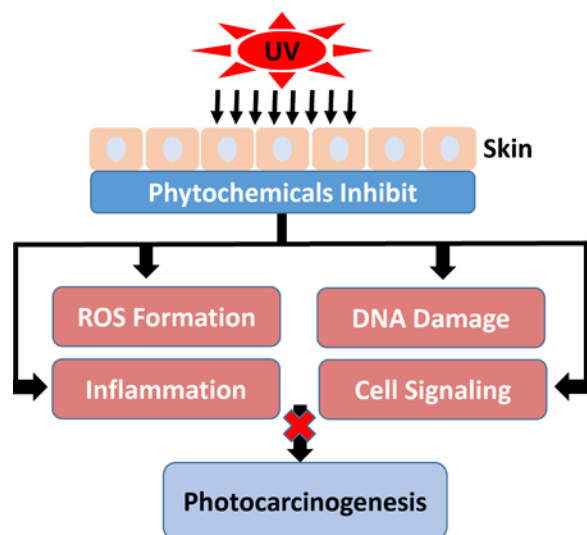
Ultraviolet (UV) exposure has an array of damaging effects and is the main cause of skin cancer in humans. Non-melanoma skin cancer (NMSC), including basal cell carcinoma and squamous cell carcinoma, is the most common type of cancer. Incidence of NMSC has increased due to greater UV radiation, increased life expectancy, and other changes in lifestyle; the annual cost of skin cancer treatment in the United States has increased concurrently to around eight billion dollars. Because of these trends, novel approaches to skin cancer prevention have become an important area of research to decrease skin cancer morbidity and defray the costs associated with treatment. Chemoprevention aims to prevent or delay the development of skin cancer through the use of phytochemicals. Use of phytochemicals as chemopreventive agents has gained attention due to their low toxicity and anti-carcinogenic properties. Phytochemicals also exhibit antioxidant, anti-inflammatory, and anti-proliferative effects which support their use as chemopreventive agents, particularly for skin cancer. Preclinical and human studies have shown that phytochemicals decrease UV-induced skin damage and photocarcinogenesis. In this review article, we discuss the selected phytochemicals that may prevent or delay UV-induced carcinogenesis and highlights their potential use for skin protection.

Graphical Abstract

Ultraviolet (UV) exposure is the main cause of human skin cancer due to its damaging effects on skin cells. Chemoprevention prevents or delays the development of skin cancer through the use of phytochemicals. Phytochemicals impede the damaging effects of UV radiation and may lead to inhibition of photocarcinogenesis.

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*Corresponding author: farrukhafaq@uabmc.edu (Farrukh Afaq).



INTRODUCTION

Skin is the largest organ in the human body and acts as an external barrier to the environment. Thus, skin is accessible to ultraviolet (UV) exposure through solar radiation or through UV-emitting tanning devices. The three main subtypes of UV radiation are UVA (320–400 nm), UVB (280–320 nm), and UVC (200–280 nm) (1). While UV radiation yields positive effects such as vitamin D production for proper bone health, UV exposure is the main cause of skin cancer development in humans due to its damaging effects (1,2). The skin is most susceptible to UV irradiation because macromolecules in the skin easily absorb UVB (3,4). UV irradiation produces damaging effects through DNA damage, reactive oxygen species (ROS) production, inflammation and activation of signal transduction pathways, and these effects comprise driving factors for skin cancer development. Because UVC is absorbed by the stratospheric ozone, it plays an insignificant role in human skin carcinogenesis. Although UVB only accounts for 5% of all UV radiation, it causes carcinogenesis to a higher magnitude than UVA. UVA accounts for 95% of all solar UV radiation but is less intense than UVB and does not induce carcinogenesis as effectively as UVB (1,5). Nonetheless, both UVA and UVB have been suggested as contributing factors to skin cancer development (6).

Non-melanoma skin cancer (NMSC) is the most common type of cancer, and its incidence exceeds breast, colon, lung, and prostate combined (7). However, NMSCs have a relatively good prognoses and low mortality rate (8,9). There are two primary types of non-melanoma skin cancer: squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), and they are both derived from the stratum basale of the epidermis. NMSC is commonly found in populations with fair skin (8). In the United States, NMSC incidence has increased with more than five million new cases each year (10). Further, those with a history of skin cancer are at an increased risk of developing other lethal types of cancer (11,12). Basal cell carcinoma accounts for 80–85% of skin cancer and is caused by intermittent UV exposure, particularly during youth (13,14). BCC rarely invades other tissues and grows slowly.

Squamous cell carcinoma results from cumulative sun exposure and makes up around 15 to 20% of all skin cancers (13). SCC is common among those who work outdoors and are exposed to substantial UV radiation (15). SCC most frequently occurs on areas of the body which are most exposed to sunlight such as the face and head, and these cancers are capable of metastasizing (13,16,17). Sunscreen and protective clothing can prevent skin cancer with limited efficacy, and patients are often noncompliant with sunscreen use (18). Increased outdoor exposure to UV radiation, changes in lifestyle, and an increased life expectancy may contribute to the increased risk of developing skin cancer [www.cancer.org/statistics]. In the United States, the average annual cost of skin cancer treatment is more than eight billion dollars [cdc.gov/cancer/skin]. Therefore, preventive approaches must be developed in order to protect from skin cancer or its precursor conditions. Various phytochemicals are known to target UV-induced cellular events involved in skin tumorigenesis. The purpose of this review is to discuss the effects of UV radiation on skin carcinogenesis and the use of phytochemicals to prevent or delay the development of skin cancer.

UV-INDUCED DNA DAMAGE

The primary intracellular target for UV radiation is DNA, and UV light absorbed by DNA forms photoproducts (8). Cyclobutane pyrimidine dimers (CPDs) are the most common type of DNA damage and are formed in mammalian cells when DNA absorbs photons from UV radiation, particularly UVB (19,20). The skin is capable of naturally repairing dimers through photoreactivation via photolyases or through nucleotide excision repair (NER), which removes dimers and seals nicks in DNA (21). If mutations are present, p53 acts as a guardian of the genome by causing cell cycle arrest and regulating NER (22). NER is a critical protective mechanism, and its significance was revealed in humans with an autosomal recessive disorder of defective NER known as xeroderma pigmentosum (XP). These individuals are unable to repair UV-induced DNA damages and are much more predisposed to skin photocarcinogenesis. If the cell is incapable of repairing DNA damage, the mutagenic dimers can lead to proliferation and ultimately carcinogenesis. Such mutations are commonly found in tumor suppressor genes and oncogenes (23). p53 is a common mutated tumor suppressor gene found in about ninety percent of individuals with non-melanoma skin cancer (24). When p53 is mutated, cells enter the cell cycle without undergoing DNA repair and become resistant to apoptosis (25).

UV-INDUCED ROS FORMATION

UV radiation also generates ROS including superoxide anion, hydrogen peroxide (H₂O₂), and singlet oxygen, which further cause oxidative damage to DNA, proteins and lipids (7,26). ROS damage the deoxyribosyl backbone of DNA and produce pyrimidine dimers, including CPDs and 6,4-pyrimidine-pyrimidones, as well as DNA cross-links or strand breaks. Free radical oxidation of proteins causes a change in protein structure and function, which may alter or activate various signaling pathways and lead to inflammation, cell proliferation, angiogenesis and tumorigenesis (27). Free radicals may also extract electrons from lipids in the process of lipid peroxidation. This may lead to membrane damage and programmed cell death (28). The skin contains endogenous antioxidant systems (enzymatic and non-enzymatic), which function to neutralize free radicals and prevent cellular damages

induced by oxidative damage (29,30). However, UV exposure overwhelms the skin's endogenous ability to neutralize ROS, leading to a state of oxidative stress in the skin.

UV-INDUCED INFLAMMATION

UV exposure activates pro-inflammatory cytokines from keratinocytes, fibroblasts, and tumor cells. Tumor initiation, promotion, and progression are all influenced by UV-induced inflammation (31). Visible signs of skin inflammation include erythema (sunburn), edema and increased skin thickness, which result from dermal vasodilation and increased vasculature permeability (31,32).

UVB induces activation of the nuclear factor kappa B (NF κ B) and mitogen-activated protein kinase (MAPK) pathways which enables transcription of lipid mediators and inflammatory genes such as inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2) and prostaglandin E₂ (PGE₂) (33,34). UV-induced iNOS activation leads to the production of nitric oxide (NO) and subsequent inflammation and photocarcinogenesis. NO may interact with superoxide to generate ROS and further upregulate the expression of COX-2 (34). UV-induced COX-2 expression is also activated by AKT, AMPK and SIRT6 (13,35–37). COX-2 is the rate-limiting enzyme involved in the synthesis of prostaglandins which facilitate inflammatory processes (38). UV-induced expression of COX-2 has been implicated in inflammation and cancer including SCC and BCC (39,40). Prostaglandins, particularly PGE₂, mediate skin inflammation in humans (41). One endogenous protective mechanism against inflammation is regulated by Nrf2, and activation of Nrf2 has been shown to protect against UV-induced inflammation in mice and humans (42).

UV exposure causes infiltration of activated macrophages and neutrophils (CD11b⁺ cells) which express iNOS and produce NO, a hallmark of inflammation (43). These oxidative products produced by inflammatory cells may induce tumor development at sites of chronic inflammation (44,45). Inflammatory leukocytes also produce myeloperoxidase (MPO) which is used as a marker of infiltration of inflammatory cells (46). MPO synthesis and secretion induces vasodilation during the inflammatory reaction (47). UV exposure of the skin also increases the expression of pro-inflammatory cytokines, including IL-1 β , IL-6 and TNF- α which aid in tumor promotion and carcinogenesis. TNF- α induces ROS formation and may lead tumor growth (48). IL-12 expression protects against tumorigenesis, and deficiency of IL-12 leads to increased COX-2 and PGE₂ levels as well as increased levels of IL-1 β , IL-6 and TNF- α (49,50).

UV-INDUCED CELL SIGNALING PATHWAYS

The MAPK family of serine/threonine kinases consists of ERKs, JNK, and p38 proteins (51). UV exposure leads to direct phosphorylation and activation of the MAPK pathway, or UV-induced ROS formation may indirectly activate the MAPK pathway (52). Once activated, p38, JNK, and ERK phosphorylate target proteins such as cyclic-AMP-response-element-binding protein (CREB). This results in the activation of various transcription factors including activator protein-1 (AP-1). The AP-1 complex is a dimer of c-Fos and c-Jun which mediates inflammation, cell proliferation, tumorigenesis, and extracellular matrix

damage (13). AP-1 mediates cell proliferation by controlling the expression of cell cycle regulatory proteins such as cyclins, p53 and p21 (53).

UV irradiation activates the epidermal growth factor receptor (EGFR) which subsequently phosphorylates AKT in a PI3K-dependent mechanism. Activation of the PI3K pathway regulates cell proliferation, apoptosis, and inflammation. (54–57). UV exposure also activates NF κ B which translocate to the nucleus to activate genes involved in stress, inflammation, apoptosis and growth. Epidermal proliferative cells exposed to continuous UV radiation rely on NF κ B for defense and survival (58,59). The Keap1-Nrf2-ARE pathway controls the oxidative stress response, and oxidative stress causes the transcription factor Nrf2 to dissociate from Keap1, translocate to the nucleus, and bind with the ARE (60). Activation of the Nrf2 signal pathway results in enhanced expression of antioxidant enzymes such as heme oxygenase-1 (HO-1) and glutathione reductase (GR) (61). UV irradiation significantly decreases Nrf2 mRNA expression in skin, and inhibition or deficiency of Nrf2 leads to UVB-induced skin damage and inflammation. Targeting various signal transduction pathways may reduce damage caused by UV radiation.

Studies have found that UVA and UVB exposure activates signal transducer and activator of transcription 3 (STAT3) that induces cell proliferation and inhibits apoptosis (62,63). In fact, constitutive activation of STAT3 has been found in various human cancers, and STAT3 activation is necessary for carcinogenesis in SCC (62,64,65). Studies have found that STAT3 phosphorylation at Tyr⁷⁰⁵ and subsequent activation are mediated by UV-induced ROS formation and DNA damage in human keratinocytes and fibroblasts (66,67).

As a tumor suppressor gene, p53 detects DNA damage and induces cell cycle arrest in order to allow cells to repair DNA before the cell cycle may again progress without damage or allow the cells to undergo apoptosis. In fact, the cause of most human cancers including NMSC may be due to defects in the p53 pathway involving the WAF1/p21 and Bax genes. When p53 is phosphorylated and activated by DNA damage, it upregulates gene expression of WAF1/p21 which participates in cell cycle arrest by inhibiting cyclin-CDK complexes (68). After UVB exposure, SKH-1 mouse skin express increased levels of WAF1/p21 and p53, causing cell cycle arrest and apoptosis (69).

Ornithine decarboxylase (ODC) is an enzyme involved in polyamine synthesis that regulates cell proliferation, cell transformation, and cell cycle regulation. UV irradiation activates ODC, and there is a direct relationship between increased levels of ODC and tumor growth (70). The MAPK signal pathway is involved in the activation of ODC (71). In order to verify the role of ODC in photocarcinogenesis, studies have shown that α -difluoromethylornithine, an irreversible inhibitor of ODC, blocked tumor formation (72). COX is an important enzyme in inflammation and prostaglandin synthesis. Although the isoform COX-1 is constitutively active, UV radiation induces COX-2 expression and subsequent prostaglandin formation. Increases in prostaglandin formation induce tumorigenesis through cell proliferation and angiogenesis, both of which are important events in SCC and BCC. COX-1 and COX-2 contribute to the development of BCC, while COX-2 overexpression has been found in UV-induced SCC (73). Various signaling pathways are involved in UV-induced

COX-2 expression. Activation of AKT, p38, and SIRT6 promotes COX-2 expression while inhibition of AMPK yields similar effects (13,36).

PHOTOCARCINOGENESIS AND CHEMOPREVENTION

Photocarcinogenesis is a three-step process involving initiation, promotion, and progression. As a complete carcinogen, UV radiation is capable of inducing each step of carcinogenesis (74,75). During initiation, UV radiation induces DNA damage in the form of CPDs, 6-4 pyrimidone photoproducts, DNA strand breaks, and cross-links. DNA mutations, if unrepaired, will replicate and result in signature mutations in various genes such as tumor suppressor genes or proto-oncogenes in epidermal basal cells. As a result, these cells become “initiated” (76). Because tumor initiation is an irreversible stage and may occur at any time in a person’s life, it is a difficult stage to target with chemopreventive strategies (77). Promotion occurs when the mutated, tumor-initiated cells are repeatedly exposed to UV, causing the cells to proliferate and expand into a benign tumor. UV exposure activates various signal transduction pathways resulting in clonal expansion of the initiated cells (78). Tumor promotion occurs for a longer duration of time, may involve multiple exposures of the carcinogen, and is a reversible process (76). Therefore, chemoprevention approaches are more promising when tumor promotion is targeted. Progression occurs when the benign tumor transforms into a malignant neoplasm that is able to invade and metastasize. The process of progression may be induced by gene modifications and selection and gene instability (79,80). Because tumor progression is slow and rate-limiting, this stage may be a promising target for chemoprevention as well (13).

Chemoprevention is an increasingly studied approach to preventing or delaying the development of skin cancer, particularly tumor promotion and progression, through the use of phytochemicals. Phytochemicals have shown promise by modulating cell signaling pathways, inducing cell cycle arrest, stimulating DNA repair, acting as antioxidants, and inhibiting inflammation (13,31,81–84). Phytochemicals are active compounds found in plants and include flavonoids, carotenoids, stilbenes, lignans, and many others. The active compounds are extracted from tea, fruits, vegetables, beans, seeds, cocoa, and soy and are used topically or orally to prevent or protect from skin cancer. Many phytochemicals have polyphenol groups consisting of multiple hydrophilic hydroxyl groups that act as antioxidants to scavenge free radicals or ROS. By inhibiting the formation of ROS, polyphenols inhibit oxidative damage to DNA, proteins, and lipids. Some phytochemicals act as anti-inflammatory agents by inhibiting the production of inflammatory mediators and cytokines. In addition, phytochemicals exert anti-photocarcinogenic properties by modulating cell signaling pathways and regulating the cell cycle, cell proliferation, and angiogenesis (31,81,84). We have discussed selected phytochemicals (Table 1) which have significant protective effects against UV-induced skin cancer (Figure 1).

RESVERATROL

Resveratrol, a naturally occurring polyphenolic stilbene found in red wine, grapes, peanuts, fruits, mulberries and pines, has antioxidant, anti-inflammatory, anti-proliferative, and anti-tumorigenic properties (84–86). Resveratrol is the active component found in the root of

Polygonum cuspidatum and may be produced in response to stress or infection (87). Topical application of resveratrol both before and after UVB exposure imparts protection against UVB-induced skin carcinogenesis in SKH-1 hairless mouse model (88). Resveratrol increases UVB-induced apoptosis through modulations in NF κ B, MAPK, survivin, WAF1/p21, SIRT1, p53 and cyclin-CDK (59,69,88,89). NF κ B is a transcription factor that responds to ROS-induced changes in the redox status of cells, and it plays a vital role in the chemopreventive effects of resveratrol. Human keratinocytes exposed to UVB resulted in decreased levels of inhibitory I κ B α in the cytosol and increased phosphorylation of I κ B α at Ser³², which both indicate activation of the NF κ B pathway. However, resveratrol treatment suppressed UVB-mediated activation of NF κ B by increasing the expression of I κ B α and reducing the phosphorylation of I κ B α (59). Survivin, a protein that inhibits apoptosis, acts by binding caspases and inhibiting their activation. Survivin is expressed in most aggressive human cancers, and the onset and progression of BCC and SCC may be due to induction of survivin (90,91). Studies have found a positive relationship between NF κ B levels and survivin expression, supporting the evidence that resveratrol may protect skin from UVB-induced damage by controlling the expression of survivin (58). In fact, resveratrol treatment before and after UVB exposure resulted in decreased mRNA and protein levels of survivin, and the down-regulation of survivin phosphorylation led to induced apoptosis. Smac/DIABLO directly interacts with survivin and is necessary for the antiapoptotic properties of survivin. UVB exposure both to normal human epidermal keratinocytes and to SKH-1 hairless mouse skin resulted in increased levels of survivin and decreased levels of Smac/DIABLO [88,89]. Resveratrol acts by inhibiting phosphorylation of survivin, decreasing survivin levels, and increasing Smac/DIABLO levels to induce cell death (88).

After UVB exposure, SKH-1 hairless mouse skin expressed increased levels of WAF1/p21 and p53, which both act to induce cell cycle arrest and apoptosis. Resveratrol further stimulated UVB-mediated increases in p53 and WAF1/p21, leading to cell cycle arrest in the G1 phase and eventually apoptosis (69). Resveratrol acts as an anti-proliferative agent by targeting various cell proliferation molecules including the CKI–cyclin–CDK network and PCNA. CDK–cyclin complexes regulate the cell cycle and lead to cell cycle progression when activated. UVB exposure resulted in increased expression of CDK-2, -4, and -6 as well as cyclins D1 and D2 which led to cell proliferation (69). CKIs are a class of proteins that inhibit cyclin–CDK complexes (69,92). Topical application of resveratrol resulted in down regulation of UVB-induced increase in cyclin D1, cyclin D2, CDK-2, CDK-4 and CDK-6. By decreasing the levels of cyclins and CDKs, resveratrol acts as an anti-proliferative agent. MAPK regulates the cell cycle by enhancing proliferation and may also play a role in increasing the expression of cyclin D1. MAPK phosphorylation is increased in response to UVB exposure, but this phosphorylation was inhibited in SKH-1 hairless mouse skin treated with resveratrol. PCNA also causes cell proliferation and is upregulated in response to UVB exposure. However, SKH-1 hairless mouse skin treated with resveratrol prior to UVB exposure resulted in downregulation of UVB-induced increase in PCNA levels (69). Thus, by modulating the CKI–cyclin–CDK network, the MAPK pathway, and PCNA, resveratrol plays an important role against UVB-induced skin carcinogenesis.

UVB-induced skin edema and hyperplasia were inhibited by topical application of resveratrol to SKH-1 hairless mice (69,85). UVB exposure also resulted in infiltration of

leukocytes which may provide an additional oxidative burst. By inhibiting UVB-induced infiltration of leukocytes and subsequent ROS formation, resveratrol may contribute antioxidant activity (69). Topical application of resveratrol to SKH-1 hairless mice inhibited UVB-induced COX-2 protein expression and ODC enzyme activity (85). Thus resveratrol acts as a chemopreventive agent by inhibiting tumor promotion. UVB-exposed mouse skin contained increased levels of H₂O₂ and lipid peroxides. Resveratrol treatment acts as an antioxidant by inhibiting UVB-induced lipid peroxidation and H₂O₂ generation in SKH-1 hairless mouse skin (85). UVB irradiation significantly decreases Nrf2 mRNA expression in skin, and inhibition or deficiency of Nrf2 leads to UVB-induced skin damage, oxidative stress, and inflammation. Therefore, resveratrol acts as a chemopreventive agent that targets Nrf2 activation, increases expression of antioxidant enzymes, and protects against UVA- and UVB-induced apoptosis. (93–95). Ethanol extract of peanut sprout, which contains resveratrol, protected against UVB-induced oxidative stress in human dermal fibroblasts by activating Nrf2 and upregulating the expression detoxifying enzymes (60). Treatment of UV-exposed human keratinocytes with resveratrol resulted in decreased levels of ROS, IL-6 and COX-2, demonstrating the anti-inflammatory and antioxidant effects of resveratrol (96). Resveratrol also acts as an anti-inflammatory agent and promotes healing by upregulating IL-10 and MMP-9 production. IL-10 is one of the primary anti-inflammatory cytokines that limits the activity of enzymes involved in respiratory burst in tissues exposed to oxidative stress. Hence, resveratrol-mediated upregulation of IL-10 induces anti-inflammatory effects. Upregulation of MMP-9 activity may allow inflammatory cells to cross the extracellular matrix after UVB irradiation in order for skin repair to occur. Therefore, resveratrol-mediated increase in MMP-9 may induce skin healing (94). Pterostilbene, the analog of resveratrol, is more potent than resveratrol in its chemopreventive and anti-inflammatory effects in UVB-exposed mice (93).

Due to its poor solubility in aqueous solution, resveratrol has limited therapeutic effectiveness and low bioavailability *in vivo* when administered orally. Nanostructured delivery systems such as the liquid-crystalline system (LCS) have been developed for proper delivery of resveratrol. LCS shelters the active molecule and sustains drug release, making it an effective delivery system for molecules in topical preparations. Hairless mice treated with resveratrol-loaded LCS were protected from UVB-induced skin damage through inhibition of skin edema, leukocyte recruitment, lipid peroxidation, superoxide anion production, and oxidative stress. MMP-9, IL-10, Nrf2, and HO-1 were upregulated following resveratrol-loaded LCS treatment. Topical treatment with resveratrol-loaded LCS maintained catalase (CAT) activity, glutathione (GSH) levels, expression of glutathione peroxidase (GPx) and GR. Delivery systems such as LCS may allow for proper topical administration of chemopreventive agents (94). Resveratrate, a stable derivative of resveratrol, is more easily absorbed into skin tissue and becomes converted to resveratrol in the skin (97). Resveratrate was applied to human volunteers after UV exposure, and treatment resulted in decreased UV-induced erythema (98). A recent study found that pretreatment with resveratrol-containing microemulsion gel inhibited UVB-induced erythema in guinea pig skin (99). Therefore, resveratrate and various emulsions may be used for effective delivery and enhanced efficacy of resveratrol in preventing photocarcinogenesis.

EGCG

Green tea is a popular beverage derived from the *Camellia sinensis* plant by steaming and drying tea leaves (100). The active ingredients of green tea are polyphenolic compounds known as catechins or flavonols which exert anti-inflammatory, antioxidant, and anti-carcinogenic properties. The primary catechins in green tea are (-)-epicatechin, (-)-epigallocatechin, (-)-epicatechin-3-gallate and (-)-epigallocatechin-3-gallate (EGCG), and EGCG is the most photoprotective agent of these (84,101,102). Studies have shown that topical application of EGCG inhibits UV-induced carcinogenesis and thus may prevent NMSC development (13,84,102,103).

EGCG acts as an antioxidant and anti-proliferative agent to prevent skin tumorigenesis (84,102). EGCG prevents tumor-promoting ligands from binding epidermal growth factor receptor (EGFR). There is evidence that activation of the EGFR activates AP-1 and initiates p38 and PI3K pathways (104,105). Thus, EGCG acts to inhibit the p38 MAPK pathway and AP-1 activation and therefore inhibits tumorigenesis (13). In order for tumors to grow, invade, and metastasize, new blood vessels must form to allow for proper oxygen supply. CD31 and VEGF are essential endothelial markers, which are expressed in order to induce angiogenesis in tumors, including UVB-induced tumors. Oral administration of green tea polyphenols (GTPs) to UVB-irradiated SKH-1 hairless mice resulted in inhibition of CD31 and VEGF, suggesting that GTPs act by inhibiting angiogenesis in UVB-induced skin tumors. Increased expression of MMP-2 and MMP-9 plays a crucial role in tumor growth and angiogenesis, and administration of GTPs in UVB irradiated mice inhibited the expression of these MMPs. In addition, TIMP1 acts by inhibiting MMPs, and oral administration of GTPs increased TIMP1 in skin tumors of SKH-1 hairless mice. Administration of GTPs in UVB irradiated mice increased the numbers of cytotoxic T cells in skin tumors that cause an inhibition or regression of tumors in SKH-1 hairless mice (106).

UVB irradiation causes an inflammatory response that recruits leukocytes to the site of irradiation. Leukocytes produce ROS that may further induce inflammation. *In vitro* studies found that pretreatment of EGCG in UVB-exposed keratinocytes decreased H₂O₂ generation and inhibited phosphorylation of MAPK (107). Pretreatment of mouse skin with EGCG was shown to inhibit UVB-mediated infiltration of leukocytes specifically CD11b⁺ cells, prevent myeloperoxidase activity, and cause less epidermal structure damage in C3H/HeN mouse skin. CD11b⁺ cells are monocytes/macrophages involved with the immune response and serve as a source of ROS in response to UVB exposure. By inhibiting the infiltration of leukocytes, EGCG reduced the production of ROS by leukocytes and ROS-induced photocarcinogenesis (43). Pretreatment of EGCG was also found to inhibit UVB-mediated nitric oxide synthase expression and the production of ROS, such as NO and H₂O₂, in mouse epidermis and dermis (43). Topical application of GTPs in hydrophilic cream to SKH-1 hairless mice was shown to inhibit UVB-mediated reduced expression of GPx, CAT, and GSH levels. The antioxidant properties of GTPs may help to reduce lipid peroxidation, protein oxidation, and UVB-mediated carcinogenesis (108). UVB-exposure induces formation of CPDs which induce inflammatory responses such as upregulation of COX-2 and PGE₂. Administration of GTPs in drinking water removed CPDs and inhibited subsequent COX-2 activity and PGE₂ formation (50). In addition, GTP treatment to

C3H/HeN mice stimulated DNA repair of UVB-induced formation of CPDs. GTP treatment removed or repaired the UVB-induced DNA damage by increasing the expression of NER genes such as XPA, XPC, and RPA1 (109). Thus, GTPs are capable of inducing DNA repair in response to UVB-induced CPD formation.

EGCG acts through various signal transduction pathways to inhibit the damaging effects of UVB exposure. Oral administration of GTPs to SKH-1 hairless mice resulted in increased UV-induced expression of p53, p21, and caspase-3, leading to apoptosis of tumor cells (106,110). EGCG treatment resulted in inhibition of UVB-induced phosphorylation of the MAPK proteins including ERK1/2, JNK, and p38 in normal human epidermal keratinocytes (107). MAPK activation mediates AP-1 activity, and inhibition of UVB-induced MAPK activation by EGCG leads to inhibition of AP-1 activation in HaCaT cells. Therefore, EGCG inhibits c-Fos, a component of AP-1, to inhibit cell proliferation and cell survival (52).

Several studies have tested the efficacy of EGCG in preventing photocarcinogenesis by enhancing its delivery through various mechanisms. The antioxidant effects of EGCG were significantly enhanced when HaCaT cells were treated with the glucosylated form of EGCG, Glc-EGCG. Treatment with Glc-EGCG inhibited ROS formation much more efficiently than EGCG, suggesting that Glc-EGCG may be used to prevent ROS production in UV-exposed skin (111). UVB-exposed SKH-1 hairless mice pretreated with EGCG in a hydrophilic cream have decreased tumor incidence, size, and multiplicity (112). Chitosan microparticles are an additional method that help improve the stability and delivery of phytochemicals (113). Studies have shown that tea catechins may be digested by skin enzymes, and green tea extract delivered in chitosan microparticles resulted in enhanced human skin permeation and decreased metabolism of the active catechins (114–116). Therefore, chitosan microparticles may be used to prevent enzymatic degradation, enhance photochemopreventive effects, and improve the delivery of EGCG. Topical application of oil-in-water emulsions containing EGCG on human skin enhanced the delivery of EGCG into the deeper stratum corneum area (117).

Treatment of human skin with EGCG protected against UVB-induced ROS formation and leukocyte infiltration. Prostaglandins play a role in the production of ROS, and human skin pretreated with EGCG and exposed to UVB irradiation resulted in prominent reduction of PGE₂ compared to human skin only exposed to UVB radiation (118). Thus, EGCG acts as an anti-inflammatory and antioxidant to prevent photocarcinogenesis. In addition, studies on human skin have demonstrated the effects of GTPs on the rapid repair of UVB-induced DNA damage. Topical application of GTPs onto human skin resulted in the inhibition of UVB-induced CPD formation in both the dermis and epidermis. In addition, this study found that topical application of GTPs resulted in inhibition of UVB-induced erythema in human skin. UVB-exposed human skin treated with GTPs resulted in decreased DNA damage and inflammation (119). Similar effects were found in UVB-exposed human skin equivalent in which the stimulation of IL-12 production decreased the formation of CPDs (120). Green tea has also been found to protect from UVA-induced DNA adduct formation (121). Topical application of green tea extract to human skin afforded protection from solar simulated UV-induced oxidative DNA damage by decreasing the levels of 8-oxo-dG (122). Therefore,

several studies on human skin have demonstrated the effects of GTP as an antioxidant, anti-inflammatory, and DNA repair agent to inhibit photocarcinogenesis.

POMEGRANATE FRUIT EXTRACT

Pomegranate is derived from the *Punica granatum* tree and contains two main polyphenols, anthocyanins and hydrolysable tannins, which are the primary antioxidant components of the fruit. Anthocyanins include cyanidin and delphinidin while the hydrolysable tannins are punicalin, pedunculagin, punicalagin, and gallagic and ellagic esters of glucose (123). Pomegranate fruit extract (PFE) exerts antioxidant and anti-inflammatory properties (123,124). PFE protects against UVB-induced oxidative stress and ROS formation in human skin fibroblasts (125). In human immortalized HaCaT keratinocytes exposed to UVB-irradiation, PFE protected cells from oxidative stress. PFE further reduced UVB-induced oxidative stress by inhibiting UVB-mediated reduction in GSH concentrations. Thus, PFE exerts its antioxidant properties by maintaining the levels of GSH (126). While UV-irradiation induces cell death and decreases the number of viable cells, PFE application inhibited UV-induced apoptosis (125). Similar effects were found when HaCaT keratinocytes were pretreated with PFE. The proposed mechanism by which PFE protected cells is through inhibition of oxidative stress (126). Oral feeding of PFE to SKH-1 hairless mice resulted in inhibition of UVB-induced increase in ODC, a rate-limiting enzyme of polyamine synthesis (127). Polyamines and ODC activity regulate cell proliferation and photocarcinogenesis, and studies have found a positive relationship between ODC activity and tumor promotion (72,128). The inhibition of ODC by PFE may prevent tumorigenesis by inhibiting cell proliferation (127,128).

PFE acts as an anti-inflammatory agent through various mechanisms. Oral feeding of PFE to SKH-1 hairless mice resulted in inhibition of UVB-induced hyperplasia, skin edema, and infiltration of leukocytes (127). Another study found that oral feeding of PFE to SKH-1 hairless mice yielded similar anti-inflammatory effects and also inhibited UVB-induced COX-2 and iNOS expression and subsequent inflammation. Thus, PFE inhibits tumorigenesis through these mechanisms (33). IL-8 is a pro-inflammatory cytokine that is upregulated in response to UVB-irradiation in human keratinocytes and *in vivo* (129). Increase in IL-8 leads to angiogenesis, chemotaxis, tumorigenesis, and cell proliferation (130,131). UVB-induced increase in IL-8 was inhibited by pretreatment of HaCaT cells with pomegranate seed oil nanoemulsions (132).

Oral feeding of PFE reduced UVB-induced CPD formation in SKH-1 hairless mice (127). UV exposure induces expression of MMPs which degrade the extracellular matrix, regulate angiogenesis, and aid in tumor invasion in metastasis (133). SKH-1 hairless mice fed with PFE exhibited inhibition of UVB-induced expression of MMPs (33). By inhibiting the expression of MMPs, PFE exerts anti-angiogenic effects and inhibits tumor growth. Several signaling pathways are targeted by topical application of PFE. Activation of the MAPK pathway leads to angiogenesis, tumorigenesis, and invasion (134,135). Pretreatment of HaCaT cells with polyphenol-rich PFE inhibited UVB-induced phosphorylation of MAPK and c-Jun (126). Treatment of PFE inhibited UVB-induced activation of the NF κ B pathway and therefore inhibits UV-induced gene transcription in SKU-1064 human skin fibroblasts

(125). Oral feeding of PFE in drinking water inhibited UVB-induced skin tumorigenesis in SKH-1 hairless mice. Several human tumors express constitutively active STAT3 and NF κ B. In response to UV irradiation, STAT3 and NF κ B become phosphorylated and activated and subsequently induce cell proliferation. Compared to a UVB irradiated alone group, mice that received oral feeding of PFE reduced UVB-induced phosphorylation of STAT3 and NF κ B and decreased iNOS and COX-2, which are downstream molecules of these signaling pathways. In addition, oral feeding of PFE decreased UVB-induced angiogenic proteins such as HIF-1 α , VEGF, and CD31 in mice tumors. Therefore, PFE prevented skin photocarcinogenesis by decreasing UV-induced inflammation and angiogenesis (136).

Pretreatment of UVB-exposed HaCaT cells with pomegranate seed oil nanoemulsions enhanced the delivery and efficacy of the polyphenol constituents of PFE. The nanoemulsions protected cells against UVB-induced DNA damage and decreased secretion of IL-8, a pro-inflammatory cytokine that enhances cell proliferation and angiogenesis. Pomegranate seed nanoemulsions may be a promising delivery method in order to enhance the anti-inflammatory and DNA repair properties of PFE (132).

Pretreatment of human reconstituted skin with pomegranate derived products resulted in a decreased expression and activity of UVB-induced MMPs. In addition, treatment with pomegranate derived products prior to UVB exposure resulted in inhibition of UVB-mediated formation of CPDs and 8-oxo-dG in human reconstituted skin (137). Furthermore, pretreatment of human reconstituted skin with pomegranate derived products inhibited UVB-induced protein oxidation, PCNA protein expression, and phosphorylation of c-Jun. Thus, PFE may be used for photochemoprevention because it exerts antioxidant, anti-proliferative, anti-angiogenic, and anti-tumorigenic properties. A clinical trial on human volunteers tested the effects of oral administration of pomegranate extract on UV-induced pigmentation. Low dose oral administration of pomegranate extract inhibited UV-induced sunburn in volunteers, suggesting the protective effect of pomegranate extract (138).

SILYMARIN

Silymarin is a flavonoid derived from the milk thistle *Silybum marianum* plant, and the major active component is silibinin, also known as silybin. Several studies demonstrate that silymarin acts as an antioxidative agent and protects against UVB-induced carcinogenesis (139). The protective effects of silibinin are demonstrated in JB6 mouse epithelial cells treated with silibinin before or immediately after UVB-exposure. Silibinin caused downregulation of UVB-induced phosphorylation of ERK1/2 and AKT. By decreasing phosphorylation of ERK1/2 and AKT, silibinin protects against tumor promotion (140). UVB-induced activation of AP-1 and NF κ B leads to cell survival, but silibinin treatment before or immediately after UVB exposure in JB6 cells inhibited UVB-induced activation of these transcription factors. Thus, inhibition of various cell survival signal pathways by silibinin suggests its use as an anti-proliferative agent against skin tumor promotion (141). Topical application or dietary feeding of silibinin to SKH-1 hairless mice afforded protection against photocarcinogenesis by decreasing tumor multiplicity and tumor volume (142). Silibinin also exerted anti-apoptotic effects by inhibiting UVB-induced caspase 9 activation in HaCaT cells. In addition, silibinin protects against UVB-induced apoptosis by increasing

the number of cells in the S phase to allow for DNA repair. However, at higher doses of UVB exposure, silibinin was not effective in protecting the cells against UVB-induced apoptosis (143). Treatment with silibinin enhanced UVA-induced apoptosis in HaCaT cells. UVA exposure induced ROS production in HaCaT cells, and cells treated with silibinin prior to UVA exposure showed increased ROS production and increased apoptosis due to oxidative stress (144). Silibinin was also shown to decrease survivin levels and increase activated caspase-3 levels to induce apoptosis in SKH-1 hairless mouse skin. Silibinin treatment also increased p53 and CDKI expression while down-regulating CDK-cyclin expression levels, leading to inhibition of cell growth (142).

Silibinin protects against UVB-induced DNA damage by inducing DNA repair and suppressing apoptosis. E2F transcription factors mediate DNA repair and apoptosis, and E2F1 expression decreases in SKH-1 hairless mouse skin after exposure to UVB radiation. Silibinin reversed the effects of UVB-induced E2F downregulation, and the increased expression of E2F1 inhibited apoptosis and enhanced the repair of UVB-mediated DNA damage (145,146). Treatment with silibinin prior to UVB radiation resulted in increased repair of CPDs through upregulation of p53 in JB6 cells and SKH-1 hairless mouse skin. By increasing p53 expression, silibinin inhibited UVB-induced apoptosis and repaired DNA damage (147). Topical application of silibinin reduced UVB-induced CPD formation in mouse epidermis (148). In addition, silymarin treatment repaired UVB-induced DNA damage by increasing the expression of NER genes in normal human epidermal keratinocytes (149).

Inflammatory responses are mediated through UVB-induced increased expression in COX-2 and iNOS (150). Studies have suggested that photocarcinogenesis may result from increased COX-2 expression in mouse and human skin (39,57). Silibinin exerts anti-inflammatory effects in SKH-1 hairless mouse skin by down regulating COX-2 and iNOS expression, highlighting its potential use as a protective agent against photocarcinogenesis (150). Silymarin exerts significant inhibitory effects on ODC activity in SKH-1 hairless mouse skin, reflecting its ability to inhibit tumor promotion (74). C3H/HeN mice treated with silymarin exhibited decreased levels of UV-induced oxidative stress by inhibiting CD11b⁺ cell and inflammatory leukocyte infiltration, thereby decreasing levels of MPO in the dermis and epidermis (46). By decreasing induction of these inflammatory factors, silymarin prevents the harmful effects of UVB radiation and may be a promising agent to prevent photocarcinogenesis.

Topical or dietary treatment with silibinin inhibited angiogenesis by regulating levels of STAT3, VEGF, and HIF-1 α (150). STAT3 and HIF-1 α activation leads to increased expression of VEGF and subsequent angiogenesis and tumor invasion (151). Silibinin treatment decreased protein levels of STAT3, HIF-1 α and VEGF, suggesting its use as an antiangiogenic and anti-carcinogenic agent (150). Silymarin oil-in-water microemulsions enhance the stability and solubility of silymarin in pig skin. Thus, microemulsions showed prolonged release compared to silymarin solution, suggesting the use of microemulsion delivery systems to enhance the chemoprevention effects of silymarin (152).

GENISTEIN

Genistein is an isoflavone derived from soybeans that inhibits cellular signaling pathways, inflammation, DNA damage, and skin damage (153–157). While UVB exposure induces the activation of ERK1/2, p38, and JNK, treatment with isoflavone extract inhibited UVB-induced activation of MAPK in HaCaT cells (153). In addition, treatment with soybean isoflavone extract resulted in inhibition of UVB-induced epidermal proliferation and expression of COX-2 (153). In UV-exposed Skh:HR-1 mice, treatment with topical isoflavone extract from soybean resulted in decreased skinfold thickness (154). Therefore, genistein may be used as an anti-inflammatory agent to reduce the effects of UV on skin inflammation.

Genistein inhibited UV-induced DNA damage by inhibiting the formation of 8-oxo-dG in calf thymus DNA. Genistein treatment also exerted antioxidant properties by scavenging H₂O₂ and inhibiting the formation of superoxide anion (155). These antioxidant effects of genistein may be associated with decreased DNA damage in UV-exposed cells. In addition, genistein treatment inhibited UV-induced DNA damage by inhibiting pyrimidine dimer formation in human reconstituted skin (156). PCNA is vital for DNA replication and nucleotide excision repair. UV irradiation down-regulates PCNA expression and may lead to CPD formation, DNA mutation, and ultimately tumor initiation. Human reconstituted skin samples treated with genistein exhibited increased levels of PCNA activity which inhibited UV-induced DNA damage (156). While UVB exposure induced DNA damage in BJ-5ta human skin cells, genistein treatment significantly reduced UVB-induced DNA damage and rapidly increased DNA repair. Therefore, genistein may be used as a protective agent against UVB-induced DNA damage. A study on human skin biopsies treated with genistein prior to UV exposure demonstrated inhibitory effects on EGFR, ERK1/2, JNK, and c-Jun. Genistein decreased UV-induced skin damage in human by down-regulating c-Jun and subsequent collagenase activation (157).

Several studies have developed a liquid chromatography method in order to accurately determine if genistein has successfully permeated the skin in order to exert its effects. Genistein showed high affinity for porcine skin samples *in vitro*, and genistein was found in deeper layers of the skin when the amount was increased (158). Liquid chromatography was also used to determine the delivery of genistein from nanoemulsions before and after their incorporation in hydrogels. Results showed that higher amounts of genistein were found in the outer epidermal skin layers rather than the inner layers. In addition, higher amounts of genistein were present in porcine ear skin after incorporation in hydrogels (159). Therefore, liquid chromatography may be used in order to determine the permeation of genistein into the skin, and nanoemulsions incorporated into hydrogels may have promising effects against photocarcinogenesis.

APIGENIN

Apigenin is a flavonoid found in the leaves and stems of various fruits and vegetables including guava, orange, parsley, onion, and chili peppers from *Lycopodium clavatum* (160). Apigenin is used for its anti-oxidant, anti-inflammatory, and anti-proliferative effects in

addition to its ability to activate NER (161). Apigenin exerts anti-tumor effects by inhibiting cellular transformation, angiogenesis, and tumorigenesis and by stimulating gap junctional and intercellular communication (162–164). Various signaling pathways are targeted by apigenin, including AP-1, MAPK, and NF- κ B.

Pretreatment of HaCaT cells with apigenin reduced UVA-induced expression of MMP-1 and collagenase production. Apigenin reduced the production of MMP-1 by inhibiting expression of c-Jun and c-Fos, thereby inhibiting the activation of AP-1. Apigenin also interfered with MMP-1 production by inhibiting UVA-induced calcium influx and calcium dependent MAPK and AP-1 signaling (165). Large amounts of MMP-1 are found in UV-exposed skin and basal cell carcinomas, and MMPs mediate collagen degradation to cause skin damage (166,167). Similar effects were found in which treatment with apigenin decreased the UVA-induced expression of MMP-1 at the mRNA and protein levels in human dermal fibroblasts. In addition, apigenin acted as an antioxidant by reducing the production of ROS. Because UV-induced ROS production activates NF κ B and enhances MMP gene expression, apigenin may decrease ROS production and subsequent MMP expression (168). A recent *in vitro* study found that apigenin treatment increased the nuclear translocation and protein expression of Nrf2, and Nrf2 further regulated expression of the downstream antioxidant gene NQO1 (169).

Apigenin treatment induces expression and stability of p53 in mouse 308 keratinocytes, causing reversible G2/M checkpoint arrest during the cell cycle (170). In another study, apigenin was found to bind and suppress Src kinase and subsequently reduce UVB-induced skin inflammation and COX-2 formation in JB6 P⁺ mouse epidermal cells, HaCaT keratinocytes and SKH-1 hairless mouse skin (171). Another studies also found that apigenin blocked UVB-induced COX-2 expression in mouse keratinocytes (172,173). By inhibiting UVB-induced skin inflammation, apigenin exerted potent photochemoprotective effects. Apigenin also prevents photocarcinogenesis through DNA repair mechanisms. In order to protect DNA from UVB-induced damage, apigenin stimulated NER gene expression and reduced the formation of CPDs in human keratinocytes and mouse skin (161).

Due to its lipophilic characteristics, apigenin is not significantly soluble and becomes trapped in the phospholipid bilayer plasma membrane. Thus, apigenin is loaded in ethosomes containing mainly phospholipids and ethanol in order to enhance its solubility, permeation, and deposition in skin. Increased levels of phospholipid short-chain alcohols improve apigenin's transdermal absorption and efficacy. By enhancing the delivery of apigenin, ethosomes consequently enhance the anti-inflammatory effects of apigenin. *In vitro* and *in vivo* studies demonstrated that apigenin delivery via ethosomes suppressed UVB induced COX-2 levels and thus reduced inflammation. By inhibiting UVB-induced skin inflammation, apigenin may be used to prevent damage from UV radiation (174). Poly (lactic-co-glycolide) (PLGA)-loaded apigenin nanoparticles have also been used to enhance the effects of apigenin against photocarcinogenesis due to their small size and fast movement into the tissues. Treatment of UVB-exposed Swiss albino mice with oral and topical PLGA-loaded apigenin nanoparticles resulted in decreased epidermal hyperplasia, decreased PCNA expression, increased active caspase-9 expression, and increased apoptosis.

Therefore, nanoparticles containing apigenin may be used to inhibit skin carcinogenesis with more efficacy than apigenin alone (175).

SULFORAPHANE

Sulforaphane, found in cruciferous vegetables such as broccoli, is a naturally occurring isothiocyanate known for its chemopreventive and antioxidative effects (176). Studies demonstrated sulforaphane's protective effects against UV-induced skin damage and carcinogenesis in mice through several mechanisms. Sulforaphane acts by inducing the Keap1-Nrf2-ARE pathway, inducing cytoprotective phase II detoxification enzymes, inhibiting inflammation, and acting as a pro-apoptotic agent (42,176,177).

Sulforaphane activates a major transcription factor, Nrf2, which determines the cell's ability to survive and adapt under oxidative stress by inducing the expression of phase II enzymes (42,178). Keap1 is a protein that binds and negatively regulates Nrf2 through proteasomal degradation (179). Under stress Nrf2 releases from Keap1, translocates to the nucleus, and binds to the ARE site in the promoter of many genes involved in cytoprotection such as phase II enzymes and antioxidants (177,179). Nrf2 deficiency is related to accelerated disease progression and increased sensitivity to carcinogens. Further, in SKH-1 hairless mice with constitutively active Nrf2, UV-induced cutaneous tumors were lower in incidence and multiplicity compared to wild-type mice. In addition, topical application of sulforaphane resulted in increased activation of Nrf2, which reduced UV-induced skin erythema in healthy human subjects (178). Therefore, preventive techniques have been used in mice and human models which activate Nrf2 and protect against UV-induced skin erythema, inflammation and carcinogenesis. Sulforaphane acts as an indirect antioxidant by upregulating the gene expression of antioxidants CAT, superoxide dismutase (SOD), quinone oxidoreductase-1 (QO-1), and glutathione S-transferase (GST) via Nrf2 activation (180). UV exposure also leads to activation of AP-1, a transcription factor that mediates skin photocarcinogenesis. Keratinocytes express increased levels of AP-1 when exposed to UVB irradiation (177). Sulforaphane has been found to inhibit UVB-induced activation of AP-1 in human keratinocytes. Treatment of keratinocytes with sulforaphane was found to inhibit AP-1 activation by blocking AP-1 from binding DNA (181). Topical application of sulforaphane exerted cytoprotective effects by significantly elevating NAD(P)H: quinone oxidoreductase 1 (NQO1) levels in both mice and human subjects (182,183). NQO1 is a phase 2 enzyme which binds and stabilizes p53, and NQO1-deficient mice are unable to induce p53 and initiate apoptosis, leading to skin tumor formation (184). Sulforaphane application elevated NQO1 expression in mouse skin, which may protect against damaging effects of UV by stabilizing p53 and detoxifying UV-induced ROS. In addition, GSH is a phase 2 enzyme which detoxifies free radicals through several mechanisms. In SKH-1 mouse skin and human keratinocytes, UV exposure has been found to decrease the expression of GSH, and application of sulforaphane inhibited UV-induced depletion of GSH (183). Based on these findings, sulforaphane may be used to protect against the damaging effects of UV irradiation.

Sulforaphane is not chemically stable in aqueous, protic, and polar aprotic environments and becomes rapidly degraded in these solvents. However, sulforaphane exhibited increased

stability in organic formulations such as polyethylene glycol (PEG) ointment bases and organic oleaginous bases. In addition, topical application of PEG formulations of sulforaphane significantly decreased AP-1 activation in SKH-1 hairless mouse skin. Proper delivery of sulforaphane in organic preparations may enhance the anti-carcinogenic effects of sulforaphane (177).

HONOKIOL

Honokiol is a natural lignin component from the bark and leaves of *Magnolia* species with anti-inflammatory and chemopreventive properties (185,186). A study found that treatment with honokiol decreased UVB-induced skin tumor multiplicity and induced intrinsic and extrinsic apoptosis pathways in SKH-1 hairless mice (187). Honokiol treatment decreased UVB-induced skin tumor multiplicity and tumor volume as well as inhibited the transformation of papillomas to carcinomas in SKH-1 hairless mice (185,186). Treatment with honokiol inhibited several inflammatory mediators including COX-2, PGE₂, TNF- α , IL-1 β , and IL-6 expression in skin and skin tumors of UVB-exposed SKH-1 hairless mice. Honokiol also inhibited photocarcinogenesis by inhibiting cell cycle regulators including cyclins, and CDKs, as well as by increasing expression of p21 and p27. In addition, UVB-mediated activation of PI3K and AKT were attenuated in SKH-1 hairless mouse skin treated with honokiol (186). Treatment with honokiol before or after UVB exposure may inhibit skin photocarcinogenesis through these chemopreventive mechanisms.

LUTEOLIN

Luteolin is a flavonoid found in onions, broccoli, chili, carrot, and celery which exhibits anti-carcinogenic and anti-inflammatory effects (165–191). Studies using HaCaT cells found that luteolin inhibits UVA-induced AP-1 activation as well as c-Fos, c-Jun, and MMP-1 expression (165). Luteolin also inhibited UVB-induced MMP expression by suppressing JNK1 and p90RSK2 activity in HaCaT cells (188). Similar effects were observed when UVA-exposed dermal fibroblasts were treated with luteolin. By inhibiting the MAPK pathway, luteolin decreased UVA-induced MMP-1 expression, which may suggest the protective effects of luteolin (189). Because MMPs play a role in degradation of ECM, angiogenesis, and tumor invasion, luteolin may be used as a protective agent against photocarcinogenesis (192,193). Treatment of UVB-exposed normal human keratinocytes with luteolin resulted in increased levels of Bcl2 and decreased UVB-induced cell death (190). Through this mechanism, luteolin increases the survival of normal human keratinocytes. In SKH-1 hairless mouse skin luteolin treatment inhibited UVB-induced PKC ϵ and Src activation which consequently downregulated MAPK and AKT signaling pathways (191). Studies have shown that PKC ϵ and Src activation participate in angiogenesis, tumor invasion, and the development of NMSC (194,195). Therefore, by inhibiting PKC ϵ and Src pathways, luteolin may inhibit photocarcinogenesis. Treatment of normal human keratinocytes with luteolin reduced UVB-induced release of inflammatory mediators including IL-1 α and PGE₂ (190). Luteolin also acts as an anti-inflammatory agent by inhibiting UVB-mediated activation of AP-1 and NF κ B transcription factors leading to decreased COX-2 expression in JB6P⁺ cells and SKH-1 hairless mouse skin (191).

QUERCETIN

Quercetin is a natural flavonol found in grapes, berries, apples, onions, tomatoes, seeds, nuts, and tea (196). Various studies have found that quercetin inhibits DNA damage, acts as an antioxidant, and targets various signaling pathways which suggest its use as a chemopreventive agent (197–199). Because quercetin is not easily absorbed, one study determined the effects of a glycosylated form of quercetin known as quercitrin (199). Pretreatment of JB6 mouse epidermal cells and SKH-1 hairless mice with quercitrin resulted in a decrease in UVB-induced ROS production, DNA damage, and apoptosis. While UVB irradiation resulted in increased expression of active caspase 3 and cleaved PARP, pretreatment of quercitrin inhibited these effects, proposing its role in attenuating apoptosis. Quercitrin exerted antioxidant effects by decreasing UVB-induced ROS generation, inhibiting UV-induced decrease in CAT and SOD, and decreasing the ratio of GSH/GSSG (199). Quercetin and ascorbic acid treatment has also been found to inhibit UVB-induced p38, CREB, and PI3K activation as well as c-Fos activity in HaCaT cells (198). UV-induced MMP-1 and TNF- α expression were also inhibited by quercetin treatment in EpidermTM. In addition, quercetin inhibited DNA damage by blocking UV-mediated formation of CPDs (197). Through these mechanisms, quercetin may be used to provide protection against skin photocarcinogenesis.

Although quercetin demonstrates protection against UV-induced DNA damage, oxidative damage, and modulates cell signal transduction pathways, the efficacy of quercetin is limited by its poor penetration and deposition in the skin (200). A recent *in vivo* study used quercetin-loaded Poly (D,L-lactide-co-glycolide) tocopheryl polyethylene glycol 1000 succinate (PLGA-TPGS) nanoparticles to enhance the delivery and bioavailability of quercetin in HaCaT cells and NIH mice. The quercetin-loaded PLGA-TPGS nanoparticles inhibited UVB-induced COX-2 expression and NF κ B activation in the HaCaT cells. Quercetin-loaded PLGA-TPGS nanoparticles permeated and deposited in mice skin and decreased UVB-induced skin damage (201). A recent study on human volunteers found that treatment with quercetin phospholipids 1% cream resulted in decreased UV-induced skin inflammation by reducing erythema and wheal diameter. This study demonstrates the anti-inflammatory activity of quercetin and the efficacious delivery of quercetin by using a phospholipids-based delivery system cream of quercetin (202).

DELPHINIDIN

Delphinidin is an anthocyanidin found in berries, grapes, eggplant, tomatoes, carrots, and red onion with antioxidant, anti-proliferative, and anti-inflammatory properties (203). Pretreatment of HaCaT cells with delphinidin inhibited UVB-mediated decrease in cell viability and induction of apoptosis. In addition, pretreatment of HaCaT cells with delphinidin inhibited UVB-induced decrease in PCNA, increase in lipid peroxidation, formation of DNA damage, activation of caspases, increases in pro-apoptotic proteins (Bax, Bid and Bak), as well as decreases in anti-apoptotic proteins (Bcl-2 and Bcl-xL). By inhibiting UVB-mediated decrease in PCNA, delphinidin restored the expression of PCNA, which is a protein involved in DNA replication and repair. These effects suggest that delphinidin inhibits UVB-induced DNA damage and subsequent apoptosis. Similar effects

were observed in SKH-1 hairless mouse skin in which delphinidin treatment decreased the formation of CPDs and 8-oxo-dG (203). Delphinidin also significantly inhibited UV-induced ROS formation and NADPH oxidase (NOX) enzyme activity in human dermal fibroblasts. In addition, delphinidin treatment inhibited UVB-induced expression of MMP-1 in a NOX-dependent mechanism. By targeting NOX and suppressing UVB-induced MMP-1 expression, delphinidin inhibited UVB-induced skin damage (204). Delphinidin exhibits anti-inflammatory properties by suppressing UVB-induced COX-2 expression and by inhibiting the MAPK and PI3K pathways (205). Thus, delphinidin exerts photochemopreventive effects by inhibiting UVB-induced ROS formation, inflammation, DNA damage, and apoptosis.

FISETIN

Another promising chemopreventive flavonol found in strawberries, apples, grapes, peaches, mangoes, tomatoes, cucumbers, and onions is fisetin, which possesses antioxidant, anti-proliferative, and anti-inflammatory properties (206,207). Treatment of human fibroblasts with fisetin inhibited UVB-induced COX-2 and MMPs expression. Fisetin treatment also downregulated MAPK and NF κ B signaling pathways in UVB exposed human fibroblasts (207). Fisetin treatment in UVB-exposed SKH-1 hairless mouse skin inhibited inflammation by decreasing UVB-induced hyperplasia and infiltration of leukocytes as well as suppressed UVB-induced expression of pro-inflammatory molecules such as MPO, COX-2, PGE₂, TNF α , IL-1 β , and IL-6. Topical application of fisetin further induced UVB-mediated upregulation of p53 and p21 expression. In addition, fisetin treatment enhanced CPD repair in UVB-exposed SKH-1 hairless mouse skin. Fisetin also downregulated UVB-mediated increase in PI3K/AKT and NF κ B pathways (206). By inhibiting these pathways, fisetin treatment inhibited UVB-induced cutaneous inflammation.

LYCOPENE

Lycopene is a carotenoid found in tomatoes with significant antioxidant and anticancer properties (208,209). Topical application of lycopene to SKH-1 hairless mouse skin has been shown to reduce UVB-mediated apoptosis by inhibiting activation of caspase-3. Lycopene exerted anticancer activity by inhibiting UVB-induced ODC activity. Because expression of ODC is induced by UVB and associated with photocarcinogenesis, lycopene may prevent skin cancer by inhibiting ODC. Lycopene also inhibited UVB-induced MPO activity that plays an important role in inflammation. Lycopene inhibited this inflammatory response and may thus inhibit the progression to skin photocarcinogenesis (209). This study suggests that lycopene exerts anti-inflammatory, anti-apoptotic, and anticancer effects. A recent study found that treatment of HaCaT cells with lycopene prior to UVB exposure resulted in a decrease of cells in the G₀/G₁ phase followed by delay at the S phase of the cell cycle. In addition, lycopene pretreatment increased the expression of Bax in UVB irradiated cells. By modulating these cell cycle events, lycopene may protect cells from photodamage (208). Decylglucoside-based microemulsions of lycopene and ascorbic acid mixed with isopropyl myristate and monocaprylin enhanced the penetration ability of lycopene eightfold compared to a solution of the drug. In addition, the microemulsion exhibited significantly

increased antioxidant effects (210). Enhancing the delivery of lycopene through microemulsions may further increase the antiphotocarcinogenic effects of lycopene.

CONCLUSIONS AND FUTURE DIRECTIONS

UV exposure has negative effects on human health and is the main cause of NMSC. Skin is readily accessible to UV exposure and is susceptible to the damaging cellular and molecular changes induced by UV radiation. As the incidence of NMSC continues to increase, the need for effective strategies of reducing population disease burden and containing rising costs of treatment become more urgent. Chemopreventive strategies may be used in order to prevent UV-induced skin carcinogenesis, reducing incidence and decreasing the high costs of treatment. Studies have unequivocally demonstrated that exposure of skin to UV radiation results in inflammation, DNA damage, oxidative stress, immunosuppression, and activation of cell survival pathways leading to development of skin cancer. Phytochemicals have demonstrated promising effects against these adverse effects of UVB radiation, which may lead to inhibition of photocarcinogenesis. Reducing photocarcinogenesis using phytochemicals to target these effects may be a promising approach to reducing NMSC disease burden. Recently, various nanoemulsion techniques have been used to enhance the delivery and effectiveness of phytochemicals. Ongoing research is needed to evaluate the effectiveness of phytochemical nanoemulsions to inhibit UV-induced skin carcinogenesis. Due to the availability and low cost, phytochemicals may be used in creams and other topical products in order to prevent the damaging effects of UV-induced NMSC.

Acknowledgments

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Biographies



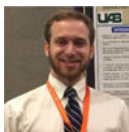
Farrukh Afaq is an Assistant Professor in the Department of Dermatology at the University of Alabama at Birmingham, Alabama, USA. He obtained his M.Phil. and Ph.D. degrees in Biochemistry from A.M.U., Aligarh, India. He worked as a Scientist at the University of Wisconsin, Madison, Wisconsin, USA. Dr. Afaq's research interests are identifying critical cellular and molecular targets in ultraviolet radiation-induced skin carcinogenesis and exploring the molecular basis for its prevention through the use of commonly consumed dietary phytochemicals. He is also investigating the effects of phytochemicals in combination with BRAF and MEK inhibitors for the treatment of melanoma by utilizing melanoma cells of different genetic backgrounds, tissue-engineered three-dimensional human melanoma skin equivalents, and genetically engineered mouse models. He has published 98 scientific articles in peer-reviewed journals and 14 book chapters.



Sarah F. McClees received her B.S. in Biology with a minor in Chemistry from the University of Alabama, Tuscaloosa, Alabama, in 2015, where she was a member of Dr. Stephen Woski's research team examining the use of cyanocarbazole derivatives as universal DNA base candidates. Sarah is currently a second year medical student at the University of Alabama School of Medicine in Birmingham, Alabama. After developing an interest in dermatology and skin cancer during her first year of medical school, she became a research intern through the UAB Cancer Research Experiences for Students (CaRES) program under Farrukh Afaq, Ph.D., investigating the efficacy and mechanism of action of certain phytochemicals against skin cancer. Her area of research focuses on the chemotherapeutic potential of phytochemicals on melanoma cells from different genetic backgrounds.



Mary Katherine Montes de Oca received her B.S. degree in Biology at Samford University in Birmingham, Alabama, in 2015. She is currently a second year medical student at University of South Carolina Greenville School of Medicine in Greenville, South Carolina. Her area of research interest is the chemoprevention of skin cancer by phytochemicals. She gained working experience in the laboratory of Dr. Farrukh Afaq.



Ross L. Pearlman obtained his B.S. at Birmingham Southern College, a private liberal arts school in Birmingham, Alabama. While there, he studied membrane trafficking using *Schizosaccharomyces pombe* (fission yeast) models. As an undergraduate, he received recognition from the Southeastern Regional Yeast Meeting for his work, winning a first-place prize in undergraduate platform presentation. He joined the University of Alabama School of Medicine, in the fall of 2014 and began working in Dr. Farrukh Afaq's laboratory through the UAB Cancer Research Experiences for Students (CaRES) program. He currently focuses on melanoma and the potential use of phytochemicals as chemotherapeutic and chemopreventive agents. He recently received the CaRES program "Best Research Project" scholarship to support his work.



Rebecca Strickland obtained a Bachelor of Science in Biology from the University of Montevallo in 2015. In 2016 she joined the laboratory of Dr. Afaq to assist with research on chemoprevention of skin cancer, gaining experience in cell culture, western blotting and immunohistochemistry techniques. Her current research is skin cancer chemoprevention.

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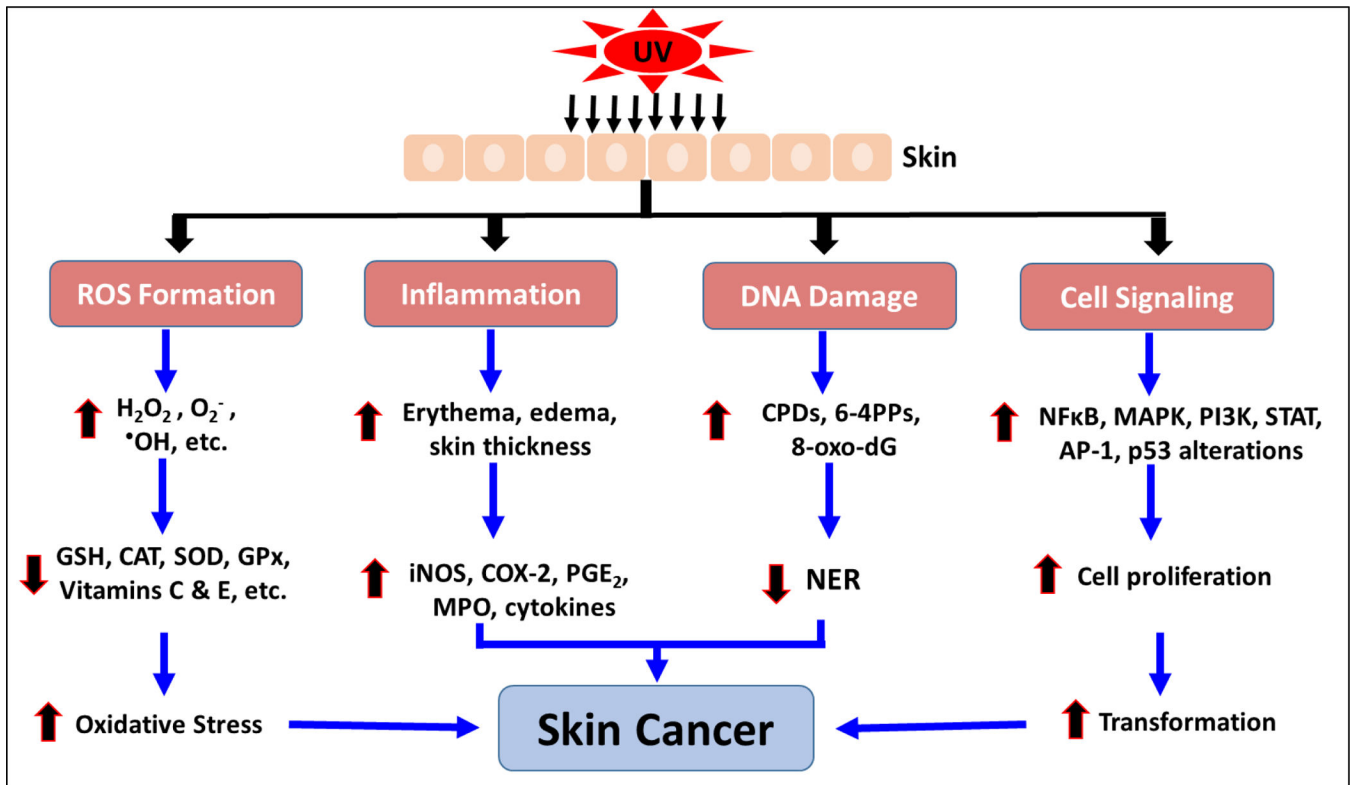


Fig. 1. Schematic diagram depicting the adverse biological effects of UV radiation leading to skin cancer

			phosphorylation ↓ODC, ↓leukocyte infiltration, ↓CPD ↑DNA repair ↓COX2, ↓iNOS, ↓MMPs ↓IL-8 ↓STAT3, ↓NFκB, ↓iNOS, ↓COX2, ↓VEGF, ↓CD31 ↓MMPs, ↓c-Fos, ↓c-Jun, ↓CPD, ↓8-oxo-dG	HaCaT cells	SKH-1 hairless mice (127) SKH-1 hairless mice (33) SKH-1 hairless mice (132) SKH-1 hairless mice (136) EpiDerm (137)
Silymarin	Milk thistle	Flavonoid	↓caspase 9, ↑NFκB, ↑ERK1/2 ↓PCNA, ↓CDK-2,-4, ↓cyclins A, E, D1, ↑p53, ↑ERK1/2, ↑p38, ↑JNK1/2, ↑caspase, ↓survivin, ↓AKT ↑E2F1, ↑DNA repair ↓CPD, ↑p53 ↓thymine dimers ↑NER ↓COX-2, ↓iNOS, ↓NO, ↓STAT3, ↓HIF-1α, ↓VEGF ↓ODC ↓CD11b+ cell infiltration, ↓MPO	HaCaT cells JB6 P+ cells NHEK	SKH-1 hairless mice (143) SKH-1 hairless mice (142) SKH-1 hairless mice (145,148) SKH-1 hairless mice (147) SKH-1 hairless mice (149) SKH-1 hairless mice (150) SKH-1 hairless mice (74) C3H/HeN mice (46)
Genistein	Soybeans	Isoflavone	↑PCNA, ↓CPDs ↓8-oxo-dG, ↓H ₂ O ₂ ↓ERK1/2, ↓p38, ↓JNK ↓EGFR, ↓ERK1/2, ↓JNK, ↓cJun, ↓collagenase	EpiDerm Calf thymus DNA HaCaT cells	Human skin (156) (155) (153) (157)
Apigenin	Guava, orange, parsley, onion, and chili peppers	Flavonoid	↓MMPs, ↓c-Jun, ↓c-fos, ↓AP-1, ↓Ca ²⁺ influx, ↓MAPK and AP-1 ↓ROS, ↓MMPs ↑p53 ↓Src kinase, ↓COX-2 ↓COX-2	HaCaT cells Human dermal fibroblasts Mouse 308 keratinocytes JB6 P+ cells, HaCaT cells Mouse 308 keratinocytes	(165) (168) (170) SKH-1 hairless mice (171) (172,173)

			↑NER, ↓CPDs ↓PCNA, ↑caspase-9	HaCaT cells	Swiss albino mice	(161) (175)
Sulforaphane	Broccoli	Isothiocyanate	↑Nrf2, ↑phase II enzymes ↑Nrf2, ↓COX-2, ↓IL-6, ↓IL-8, ↑catalase, ↑SOD, ↑QO-1, ↑GST ↓AP-1 ↑NQO1, ↑GST, ↑HO-1, ↑p53, ↑GSH ↓AP-1	keratinocytes keratinocytes	Human skin, SKH-1 mice Human volunteers, SKH-1 hairless mice	(42) (178) (180) (181) (182,183)
Honokiol	Bark and leaves of <i>Magnolia</i> species	Lignin	↓COX-2, ↓PGE ₂ , ↓TNF-α, ↓IL-1β, ↓IL-6, ↓cyclin D1, D2, E, ↓CDK-2,-4,-6, ↑p21, ↑p27, ↓PI3K, ↓AKT ↑p53, ↑caspase		SKH-1 hairless mice	(177) (186)
Luteolin	Onions, broccoli, chilli, carrot, and celery	Flavonoid	↓MMP-1, ↓c-jun, ↓c-fos, ↓JNK1, ↓p90RSK2 ↓PKCε, ↓Src, ↓MAPK, ↓Akt, ↓AP-1, ↓NFκB, ↓COX-2 ↑Bcl2, ↓IL-1α, ↓PGE ₂	HaCaT cells JB6 P+ cells NHEK	SKH-1 hairless mice	(165,188) (191) (190)
Quercetin	Grapes, berries, apples, onions, tomatoes, seeds, nuts, and tea	Flavonol	↓CPDs, ↓MMP-1, ↓TNF-α ↓p38, ↓CREB, ↓PI3K, ↓c-fos ↓ROS, ↓caspase 3, ↓c-PARP, ↑catalase, ↑SOD, ↑GSH ↓COX-2, ↓NFκB	HaCaT cells JB6 mouse epidermal cells HaCaT cells	EpiDerm SKH-1 hairless mice	(197) (198) (199) (201)
Delphinidin	Berries, grapes, eggplant, tomatoes, carrots, and red onion	Anthocyanidin	↑PCNA, ↓LPO, ↓CPDs, ↓8-oxo-dG, ↓caspases, ↓Bax, ↓Bid, ↓Bak, ↑Bcl-2, ↑Bcl-xL ↓ROS, ↓NADPH oxidase, ↓MMP-1 ↓COX-2, ↓MAPK, ↓PI3K	HaCaT cells Human dermal fibroblasts JB6 P+ cells	SKH-1 hairless mice	(203) (204) (205)
Fisetin	Strawberries, apples, grapes, peaches, mangoes, tomatoes, cucumbers, and	Flavonol	↓COX-2, ↓MMPs, ↓ERK, ↓JNK, ↓p38, ↓NFκB, ↓CREB, ↓PI3K/AKT, ↓ROS, ↓PGE ₂ , ↓NO	Human skin fibroblasts		(207)
	onions		↓PI3K/AKT/NFκB, ↓COX-2, ↓MPO, ↓PGE ₂ , ↓TNF-α, ↓IL-1β, ↓IL-6, ↑p53, ↑p21		SKH-1 hairless mice	(206)
Lycopene	Tomatoes	Carotenoid	↓ODC, ↓MPO, ↓caspase-3, ↑PCNA ↑Bax	HaCaT cells	SKH-1 hairless mice	(209) (208)