Review Article

# Complementary and Alternative Approaches to Skin Cancer

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The high treatment costs and prevalence of skin cancer, paired with discrepancies in access to dermatological care, drive patients and researchers to explore complementary and alternative medicine (CAM). While current conventional dermatologic treatments such as surgery and chemotherapy are standards of care, CAM therapies continue to gain traction for patients looking for less invasive options. CAM treatments are highly diverse, ranging from plant-derived flavonoids to topical agents and dietary supplements. Applicable literature was compiled from PubMed, Scopus, and Google Scholar databases to explore their potential. Our findings suggest significant dermatological benefits such as tumor suppression, cell cycle regulation, and enhanced UV protection for some modalities. Current CAM implementation is limited by inconsistent regulation and a lack of long-term studies. CAM treatment has shown significant success in both treating and preventing skin cancer progression. Given the growing patient interest in CAM, our findings suggest adopting an evidence-based approach when considering the dermatological applications to target tumor suppression, enhanced UV protection, or cell cycle modulation. This review aims to discuss areas for clinical implementation, mechanisms, efficacy, and how CAM might complement standards of care for skin cancer. Health care practitioners must remain informed about CAM to guide patients effectively, promote informed decision-making, and ensure safe integration of CAM into dermatological care.

## INTRODUCTION

Complementary and alternative medicine (CAM) has gained increasing attention within dermatology and oncology as patients seek holistic and less invasive approaches to managing skin cancers. From 2016-2018 some 6.1 million American adults were treated for skin cancer, which resulted in $8.9 billion in cumulative treatment costs.[1] The high prevalence of skin cancer and associated medical expenditures incentivize many patients to explore alternative therapies. Despite CAM not being subjected to the same degree of regulation as conventional medications, more adults in the United States are using CAM, with usage having increased from 19.2% of adults in 2002 to 36.7% in 2022.[2]

While only around 1.2% of dermatology visits involve a conversation about CAM, it is reported that 35-69% of patients with skin disease have used CAM at least once in their lifetime.[3,4] In 2007 the most commonly used CAM was nonvitamin, nonmineral, natural products with 17.7% usage among adults.[5] CAM therapies have demonstrated varied clinical application potential with regards to efficacy, ease of application, accessibility, and low cost. The CAM treatments discussed below show promise in augmenting standards of care by preventing cutaneous UV damage, aiding in skin repair, and targeting tumor cell cycle pathways.

While not every dermatologist recommends CAM, it is important for all clinicians to be aware of commonly used CAM, given their side effects, drug interactions, or other factors that might affect diagnosis or treatment. Simultaneously, it is essential to understand that CAM usage may delay proper diagnosis and treatment and could lead to disease progression in some scenarios. Understanding the benefits, detriments, and the contraindications of CAM is essential. This review aims to provide an updated perspective on several of the most promising CAM treatments related to cutaneous malignancies. It highlights their mechanisms, potential benefits, safety, and areas requiring further clinical investigation. Table 1 summarizes the key CAM modalities explored in this review, providing an overview of their mechanisms and potential benefits.

## CAM TYPE

### PLANT-DERIVED FLAVONOIDS

#### *GOSSYPIN*

Gossypin is a pentahydroxy flavone that is found in various plants and plant products such as hibiscus (*H. esculentus, H.vitifolius,* and *G. indicum*), richly colored spices, grains, cotton, tea, wine, herbs, and reddish-purple fruits and vegetables such as berries or grapes.[6-8] Flavonoids are purported to have a multitude of bioactive properties including being antibacterial, antiviral, antioxidant, neuroprotective, anticarcinogenic, antimutagenic, and anti-inflammatory.[9]

**Table 1. Overview**

| CAM Type | Compound | Mechanism of Action | Notable Effects | Citations |
|---|---|---|---|---|
| Plant-Derived Flavonoids | Gossypin | Dual inhibitor of CDK4 and BRAFV600E kinase; suppresses G1-S cell cycle transition and melanoma cell growth | Reduces melanoma tumor size and improves survival rates in vivo without noticeable toxicity. | 6-9 |
| | Gossypetin | Inhibits PBK/TOPK signaling and prevents UV-induced activation of proliferation proteins | Protects against UV radiation; effectively prevents basal cell carcinoma (BCC) in mouse models. | 7, 8, 10-12 |
| | Genistein | Binds to estrogen receptors; enhances DNA repair; protects against UV damage | Improves skin repair in ovariectomized rats; reduces UV-induced erythema and photodamage in human trials. | 8, 13-21 |
| | Green Tea Polyphenols | Namely EGCG inhibits UV-induced inflammatory and oxidative stress pathways and accelerates DNA repair via IL-12-dependent nucleotide excision repair | Topical application reduces UV-induced inflammation, oxidative stress, DNA damage, and promotes antitumor immune responses | 22-25 |
| | Proanthocyanidins | Antioxidant; inhibits cancer progression and promotes DNA repair | Potential photothermal agent; promotes melanoma cell death and enhances wound healing in hydrogel scaffolds. | 8, 26-32 |
| | Silymarin | Antioxidant; inhibits tumor proliferation; enhances membrane stability | Effective in UVB-induced skin cancer prevention; promising as a sunscreen additive with nanotechnology delivery. | 8, 33-39 |
| Topical Treatments | **Ingenol Mebutate** | Induces cell death via Hedgehog pathway; disrupts mitochondrial function | Initially FDA-approved for actinic keratosis but withdrawn from EU market in 2020 for high risk profile; showed potential for non-melanoma skin cancer treatment but may also increase malignancy risk. | 8, 40-48 |
| | **Curaderm BEC5** | Targets cancer cell lectins; induces apoptosis through Fas/FasL pathway | Promising results in treating non-melanoma cancers (BCC, SCC); need further clinical validation. | 8, 49-56 |
| | Hypericum perforatum (St. John's Wort) | Photodynamic effects: induces apoptosis via reactive oxygen species | Effective against melanoma cells in vitro; potential application in esophageal carcinoma and melanoma treatment. | 8, 57-65 |
| | **Black Salve** | Corrosive escharotic agent that causes nonspecific necrosis of malignant and normal tissue | High risk of scarring, disfigurement, and cancer progression outweighs benefits; not recommended for use. | 8, 66-76 |
| Dietary Supplements | Curcumin | Modulates inflammatory and apoptotic pathways; selectively targets cancer cells | Effective in head and neck squamous cell carcinoma; nanoparticle formulations improve bioavailability. | 8, 77-84 |
| | **Niacinamide (Vitamin B3)** | Enhances DNA repair; reduces UV-induced immunosuppression | Reduces non-melanoma skin cancer incidence in human clinical trials; requires consistent long-term intake. | 8, 85-91 |
| | Coenzyme Q10 | Antioxidant; protects against free radical damage; regulates inflammatory response | Potential adjuvant in melanoma treatment; enhances photoprotection and is a potentially beneficial sunscreen additive. | 8, 92-98 |
| | Lycopene | Antioxidant; modulates tumor cell apoptosis and inhibits angiogenesis | Demonstrates anti-melanoma potential; synergistic effects when combined with other compounds like resveratrol. | 8, 99-104 |
| | Beta Carotene | Antioxidant; enhances cell defense by neutralizing UV-induced free radicals | Promising for UV protection and cancer prevention; mixed results in other cancer types, requires further study. | 8, 105-111 |
| | **Polypodium leucotomos** | Antioxidant; reduces UV-induced erythema and DNA damage | Improves sunscreen efficacy; successfully prevents actinic keratosis and non-melanoma skin cancers. | 8, 112-124 |

Note: Bolded compounds indicate CAM therapies commonly self-utilized by patients (erroneously or not) or well-established in clinical dermatology practice.

Their bioactive properties, low cost, and high availability make flavonoids an ideal candidate for CAM research.[9]

Gossypin is most promising in treating BRAFV600E mutations, which exist in almost 70% of all human melanomas.[7,8] These mutations cause the B-Raf protein,

which controls cell growth, to malfunction. Molecular docking studies have shown that gossypin acts as a dual inhibitor of cyclin-dependent kinase 4 and BRAFV600E kinase, thereby suppressing the G1-S transition of the cell cycle and proliferation of melanoma cells both in vitro and in vivo with mouse models.[7]

In vivo mice studies indicated that gossypin treatment significantly reduced melanoma tumor size and improved survival rates without noticeable toxicity.[7] Gossypin's dual inhibition of CDK4 and BRAFV600E kinase, paired with its ability to reduce melanoma tumor size and improve in vivo survival, positions it as a highly promising natural compound for targeted melanoma treatment, particularly for BRAFV600E mutations, though much more work must be done before consideration in humans.

*GOSSYPETIN*

A similar compound of interest is gossypetin, a hexahydroxylated flavonoid. Gossypetin is derived from many of the same sources but lacks the same glycosylation as gossypin.[10] Gossypetin has shown promise for its protective quality against UV radiation and is being studied as a potential treatment and prevention of solar-UV-induced cutaneous basal cell carcinoma (BCC).[10] Gossypetin was shown to bind with and block PBK/TOPK signaling via in vitro kinase assay studies.[10]

In vivo studies on SKH-1 hairless mice demonstrated that gossypetin effectively suppressed the UV-induced activation of cell proliferation proteins (PBK/TOPK, phosphor-p38 MAPK, phosphor-ERK1/2 and phosphor- H2AX0) helping to prevent BCC.[10] Additionally, gossypetin has been shown to be useful in preventing and treating osteosarcoma and esophageal cancers.[11,12]

One study developed patient-derived xenograft tumors by implanting human esophageal cancer tissue into the necks of severe combined immunodeficiency (SCID) female mice.[12] Gossypetin was tested against these tumors and successfully repressed esophageal tumor growth by causing G2 cell cycle arrest and activating apoptosis.[12] Gossypetin triggered apoptotic pathways by activating caspase 3, caspase 7, BAX, and cytochrome c.[12]

These apoptotic qualities led one study to name gossypetin as the most potent compound they tested against human osteosarcoma (OS) cell lines.[11] It was noted that gossypetin significantly decreased the self-stimulated production of proinflammatory cytokines in human OS cell lines.[11] Both gossypin and gossypetin have promising initial research that will motivate further study within the clinical realm.

*GENISTEIN*

Genistein is another flavonoids of interest, derived mainly from soybeans and other legumes.[8,13] It has the unique ability to promote skin health by assisting with healing and protecting against harmful exogenous factors such as ultraviolet (UV) rays. Genistein is structurally similar to human estrogen, allowing it to be classified as a phytoestrogen with the special ability to bind to estrogen receptors without altering the host's internal hormonal balance.[14] This makes genistein especially relevant to studies on menopausal symptom relief and hormone-related cancers such as breast and prostate cancer.[8,14]

Low estrogen is a common symptom of menopause which can notably affect the functional and structural integrity of the skin resulting in worse outcomes for wound healing and skin cancer development.[15,16] To understand the effect of genistein in those with low estrogen levels, it was found that topical genistein application significantly improved skin repair mechanisms in ovariectomized rats.[15] In this animal study, genistein application lowered inflammation and improved collagen deposition, angiogenesis, keratinocyte migration, and re-epithelialization via insulin growth factor 1 receptor.[15,17]

It is important to note that genistein's ability to bind to estrogen receptors could have undesirable effects in postmenopausal women who have estrogen-dependent breast cancer.[18,19] Breast cancers that co-express ER and erB-2 are particularly sensitive to the cell proliferative effects of genistein, thus making consumption and usage of products with genistein in these patients contraindicated.[8,18,19]

Genistein is also considered an isoflavone for its photoprotective, antioxidant, anti-inflammatory, collagen synthesis, and anticancer properties.[13,20] It is these properties that are largely studied within the realm of cutaneous oncology. Topical application of genistein utilizes its antioxidant qualities to downregulate single transduction cascades activated by UV rays, thereby protecting against DNA oxidative damage.[20] Genistein application successfully prevented both psoralen plus ultraviolet A (PUVA) therapy- and UVB-induced acute and chronic photodamage in hairless mice.[21] Additionally, it was found that in human trials, topical application of genistein prior to UVB exposure significantly inhibited cutaneous erythema and reduced photodamage.[21]

The properties of genistein limit its widespread use, making it too unstable for cosmetic products.[20] However, recent nanotechnological advances have shown that these drug delivery limitations can be addressed using genistein-loaded nanosized delivery, opening the door for further pharmaceutical development.[20]

*GREEN TEA POLYPHENOLS*

Flavonoids found in green tea (*Camellia sinensis*) contain bioactive compounds, namely catechins, that are recognized for their beneficial photo/chemoprotective effects against non-melanoma skin cancer.[22,23] The four main types of catechins found in *C. sinensis* are epigallocatechin gallate (EGCG), epigallocatechin (EGC), epicatechin gallate (ECG), and epicatechin (EC).[22] EGCG is the primary catechin constituting up to 80% of green tea polyphenols.[22] While *C. sinensis* is the source of green, black, and oolong tea, green tea undergoes the least amount of oxidation during processing thereby preserving the highest amount of bioactive compounds.[23] Consequently, green tea is the main focus of photo/chemoprotective research and the subject of this discussion. While tea is the most consumed beverage worldwide after water, its benefits within clinical

dermatological research generally involve topical or concentrated application.[22,24]

Green tea polyphenols, especially EGCG, exert photoprotective effects and reduce skin cancer risk when applied topically by inhibiting the UV-induced inflammatory and oxidative stress pathways in both animal and human studies.[22] EGCG application not only helps prevent DNA damage, specifically cyclobutane pyrimidine dimers, but also accelerates damage repair via IL-12 dependent nucleotide excision repair (tested and confirmed via diminished effects in IL-12 knockout mice).[24] With regards to inhibiting melanoma development, EGCG is able to suppress the JAK/STAT signaling pathway which decreases PD-L1 expression and promotes anti-tumor T-cell responses.[25] EGCG exhibits other antioxidant effects through its inhibition of inflammatory mediators such as COX-2 and prostaglandins as well as preserving antioxidant enzymes such as catalase, glutathione peroxidase, and superoxide dismutase when exposed to UVB.[22]

With these effects in consideration, it is clear to see how green tea polyphenols might enhance sunscreen efficacy. However, it is important to note that topical delivery of green tea polyphenols, like other flavonoids discussed, requires specific formulations such as lipid-based vehicles or hydrophilic creams to increase EGCG penetration and efficacy.[24]

### *PROANTHOCYANIDINS*

Proanthocyanidins, a class of flavonoids known for their potent antioxidant properties, are also gaining attention due to their ability to limit oxidative stress and inhibit the progression of cancerous cells. Proanthocyanidins, or condensed tannins, are oligo/polymers of monomeric flavonoids mainly derived from grape seeds but also found in nuts, flowers, fruits, and more.[8,26] Plants harness their antioxidant abilities to protect against environmental stressors.[26] Some studies have shown that when compared with vitamins C and E, grape seed polyphenols have better UVC protection via oxygen free radical scavenging.[27] Proanthocyanidins also possess antibacterial, anticarcinogenic, anti-allergic, anti-inflammatory, and antiarthritic effects.[26,27]

Proanthocyanidins are widely available via waste produced from agricultural and food processing industries.[26] Interestingly, proanthocyanidins are also being studied as a photothermal agent within 3D-printed hydrogel scaffolds for melanoma treatment.[28] Melanomas are challenging to treat with radio/chemotherapy and therefore are commonly surgically excised, often resulting in large, hard-to-heal wounds.[28] These wound healing problems would benefit from a material that could both assist in healing and treat remaining melanoma cells that have not been successfully excised. Proanthocyanidin-infused hydrogels under NIR laser irradiation were successful in killing melanoma cells, promoting fibroblast and umbilical endothelial cell migration, and skin regeneration thanks to proanthocyanidins' easily controllable photothermal properties.[28]

Proanthocyanidin can also be orally administered and is generally well-tolerated and safe for both human and mouse consumption.[8,29,30] Oral administration of proanthocyanidin in mice may prevent the evolution of papillomas to malignant carcinomas via lipid peroxidation and photocarcinogenesis.[30,31] Furthermore, the anticarcinogenic properties of proanthocyanidins are linked to DNA repair processes that activate antigen-presenting cells and enhance the activity of CD8+ effector T cells.[31]

Another study encapsulated proanthocyanidins and poly(lactic-co-glycolic acid) using emulsion solvent evaporation with chitosan and sodium tripolyphosphate as carriers and cross-linking agents, forming a cationic nanosystem.[32] This proanthocyanidin-encapsulated nanosystem successfully inhibited the proliferation of oral squamous cell carcinoma drug-resistant cell lines, possibly by the nanosystem's downregulatory effects on matrix metalloproteinase-2 and 9 expression.[32]

### *SILYMARIN*

Silymarin is a flavonoid in the milk thistle plant (*Silybum marianum*). Silybin, the primary active constituent of silymarin, is a flavanol compound derived from the milk thistle fruit.[8] Milk thistle fruit has been used for many centuries as liver support, and in liver cells, silybin is effective in conserving glutathione and fortifying membranes against oxidation.[33] Silybin's liver-protective qualities correlate with the observation that silybin can help neutralize the effects of deathcap mushroom consumption.[33]

Silymarin is also thought to have anticarcinogenic properties against breast, prostate, cervical, and UVB-induced skin cancers.[8,34] Hairless mice trials have shown promise with topical silymarin application inhibiting tumor proliferation, primarily stage 1 tumors, suggesting it could be a beneficial additive to sunscreen products.[34-36] The properties are likely thanks to silymarin's antioxidant properties and ability to inhibit carcinogenesis from tumor promoters such as merzerin, benzoyl peroxide, and okadaic acid.[37]

Silymarin has also been shown to benefit burn-induced oxidative damage in rats, improving skin morphological symptoms and thromboplastin activity.[38] Like other flavonoids, silymarin is an unstable compound, making it challenging to implement into widespread use. However, it was found that silymarin can successfully be dispensed via a nanostructured lipoidal carrier system, thereby overcoming silymarin's low water solubility, photosensitivity, and instability due to air exposure.[39] Application of this method in rats successfully improved UV-induced wrinkle score and decreased epidermal thickness.[39] The preclinical data regarding silymarin is promising and prompts further clinical research with human subjects.

### *FLAVONOIDS SUMMARY*

Of the polyphenols/flavonoids discussed, Gossypin stands out as the most promising due to its targeted efficacy against BRAFV600E-mutant melanoma, a common origin of melanoma, as well as its ability to suppress tumor growth and improve survival rates in preclinical models with minimal toxicity. Gossypetin also demonstrates significant potential with its UV-protective qualities and ability to inhibit

basal cell carcinoma and other cancer types, though further research is necessary to establish its clinical applicability. While genistein, green tea polyphenols, proanthocyanidins, and silymarin all exhibit potent antioxidant, photoprotective, and anti-inflammatory properties, their limitations in stability or delivery mechanisms demand alternative approaches through nanotechnology formulations. Advancements in delivery systems will aid the integration of safer, targeted, and effective therapies for skin cancer and beyond.

## ASSORTED TOPICAL TREATMENTS

### *INGENOL MEBUTATE*

Ingenol Mebutate (IM) is a compound derived from Australian milkweed sap (*Euphorbia peplus*). IM was FDA-approved in 2012 as a topical gel for treating actinic keratosis (a precancerous skin condition).[8] When used for 2-3 consecutive days to treat actinic keratosis, IM has been shown to produce long-term clearance and lesion reduction of over 86% (face, scalp, trunk, extremities).[40] However, in 2015 the FDA issued a warning of risks associated with IM including triggering herpes zoster and severe hypersensitivity reactions.[41] Additionally, in 2020 IM was identified as having an increased risk of skin cancer which led the European Medicines Agency (EMA) to suspend its authorization for IM use in the European Union.[42] Consequently, usage of IM for the treatment of actinic keratosis and non-melanoma skin cancer has become less recommended as risks may outweigh potential benefits.[43]

The primary concern associated with IM usage stems from an increased risk of inducing skin malignancies, discovered through studies that showed higher incidences of skin cancer development compared to patients receiving other treatments.[43] A three-year study by the EMA involving 484 patients found a 2.9% higher skin malignancy rate in the IM treatment group versus the comparison group being treated with imiquimod.[42] Similar to black salve, while IM confers some clinical benefits, its high risk profile leaves its usage not recommended pending further clinical trials. However, the descriptions of potential benefits of IM are included below as they may still be worthwhile to understand in order to inform further clinical trials.

Potential benefits of IM for treatment of dermatologic diseases are grounded in their ability to induce cell death via the Hedgehog pathway, disrupting cell membranes and mitochondrial function.[44,45] Basal cell carcinomas (BCC) can arise from mutations that over-express this pathway, illustrating a potential application for IM.[45] Studies have explored IM treatment of BCC with generally successful results; one study found histological clearance of superficial BCC (sBCC) in 63% of patients (n=8) treated with IM (0.05%) gel after two applications.[46] A case report detailed a similar treatment of confirmed sBCC in a large actinic keratoses plaque in a 64-year-old male with repeated UV exposure who desired the shortest possible treatment.[47] He was treated with two overnight IM applications (gel, 0.05%), which were successful, resulting in good cosmetic outcome and placing him in remission for 18 months.[47]

IM has also been studied to treat actinic cheilitis, which can precede the development of squamous cell carcinoma on the lips.[48] In a study of 7 people with actinic cheilitis treated with topical IM gel (0.015%), three showed full clearance, and the other four showed significant improvement after completing treatment.[48]

This treatment may be ideal for patients with adherence difficulties as it is typically dispensed as a short 3-day cycle. Treatment usually results in favorable cosmetic outcomes following healing from local skin reactions, including erythema, scales, dryness, crusts, and pruritus. Its short posology, ease of application, rapid clinical effects, good cosmetic outcome, and reassuring safety profile are positive aspects of IM. However, despite these benefits, providers and patients must be aware of IM's high risk profile in potentially inducing skin malignancies.

### *CURADERM BEC5*

Curaderm BEC5 is a topical cream preparation with the active ingredient solasodine rhamnosyl glycosides (BEC). BEC is derived from plants in the nightshade family (*Solanaceae*), such as eggplant (*Solanum melongena*) and Devil's apple (*Solanum linnaeanum*). Curaderm BEC5 is formulated to treat non-melanoma skin cancers like basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). By targeting and binding endogenous endocytic lectins on cancer cell surfaces, BEC can selectively destroy cancerous cells without harming normal tissues, arresting cells in the G2-M phase.[8,49-51] BEC can initiate apoptosis via the Fas/FasL pathway by releasing lysosomal enzymes, upregulating Bax, and downregulating Bcl-2.[50] The anti-cancer binding ability of solasodine glycosides is also typically dependent on rhamnose sugar presence to bind with rhamnose receptors on the surface of cancer cells.[51]

Curaderm BEC5 is not FDA-approved within the US but is available in many countries, primarily within Europe and Australia.[8] It is normally applied at least twice daily under occlusion, and the treatment process is repeated until the desired results are achieved.[52] A 2012 clinical study on BCC found that 0.005% formulations of solasodine glycosides achieved a 66% cure rate after 8 weeks of treatment.[53] From 90% of patients successfully cured, 78% had no BCC recurrence 1 year later.[53] More recent clinical studies have been sparse, however.

Clinical safety studies have confirmed a relatively favorable safety profile with negligible cutaneous irritation or sensitivity changes noticed when tested on rabbit models.[54] Interestingly, Curaderm BEC5 contains 0.05 BEC/mL, which, when applied, is less than 300 times the amount of BEC naturally found in a standard-sized eggplant (roughly 300 g).[55] It was also found that a person weighing 60 kg (~132 lbs) can withstand as much as 60 mg of BEC in their blood (1 mg BEC/kg).[55]

Although it is not indicated for treatment of melanoma, one study found that solamargine (a type of solasodine rhamnosyl glycoside) was an effective growth inhibitor of metastatic and primary melanoma cell lines (WM239 and WM115, respectively) via the extrinsic mitochondrial death

pathway.[56] Although the safety profile and successful initial studies are promising, more clinical testing is called for.

### *HYPERICUM PERFORATUM (ST. JOHN'S WORT)*

Despite its experimental status, the topical use of *Hypericum perforatum* (St. John's Wort) extract continues to be investigated for its use in treating skin cancers. *Hypericum perforatum* (HP) is a well-established plant within the world of CAM. The two main active ingredients identified in HP are hyperforin, the main compound responsible for antidepressant effects, and hypericin, known for its photodynamic effects.[8,57] Topical side effects include irritation, itching, and photosensitivity.[58]

Photodynamic therapy of melanoma lesions with hypericin successfully eradicated both pigmented and non-pigmented melanoma cells.[59,60] Hypericin was found to be successfully uptaken by melanoma cells after 4 hours of exposure and can absorb both UVA and visible light.[59,60] 3 μM of light-activated hypericin led to photodestruction of organelles and eventual apoptosis.[59,60] In pigmented cells, the predicted mechanism of cell death is via the increased permeability of melanosomes once exposed to reactive oxygen species generated by activated hypericin.[59] Thus, the anticancer effects of HP extracts on human melanoma cells differ in normoxic and hypoxic conditions.[61]

Hyperforin has also shown broad antitumor activities against melanoma cells by downregulating cyclin and CDK protein expression and upregulating proteins linked to cell cycle arrest, such as p53 and p21/waf1.[62] Additionally, it was found that hyperforin acts through downregulating melanoma progression markers and triggering lipid peroxidation.[62,63]

Hypericum perforatum has demonstrated antiproliferative and chemopreventative effects against esophageal squamous cell carcinomas (ESCC).[64,65] Hypericum perforatum nanoparticles were shown to successfully decrease expression of cyclin D1, thereby inhibiting growth of ESCC cells.[65] Hypericum perforatum extract shows promising potential in photodynamic therapy and anticancer applications, particularly against melanoma and esophageal squamous cell carcinomas.

### *BLACK SALVE*

Escharotic agents, commonly called "black salve," are often marketed as anti-cancer ointments despite questions on the trade-off between efficacy and associated risks. Escharotics are corrosive and are typically used as a topical directly on cancerous lesions. Components in black salve frequently include bloodroot (*Sanguinaria candensis*) and zinc chloride.[66] Both compounds can cause cytotoxicity and necrosis, which inspired their initial use in skin cancer treatment by Dr. Frederic Mohs.[67,68] Initially, Mohs' chemosurgery with a fixed-tissue technique involved using a paste with zinc chloride and bloodroot before surgery.[69] While Mohs found zinc chloride to be successful in destroying cancerous tissue, it would also cause cell death of healthy tissue.[67,70] It was found that the fixed-tissue technique and general use of escharotics had adverse results including increased surgical time, loss of non-cancerous tissue, secondary infection, and increased pain levels and they were abandoned.[69,71-73]

Although the fixed-tissue technique is no longer used, escharotics are still marketed for at-home treatment of skin cancers. Corrosive substances like the escharotics are dangerous and can even result in mistreating non-cancerous skin conditions resulting in harm.[8,74] Escharotic-induced necrosis can leave users with permanent scarring, disfigurement, and abnormal skin pigmentation.[8,75,76]

While black salve might confer some therapeutic effect, it comes with a host of adverse side effects. From 2015-2020, the FDA identified 15 cases of adverse side effects from black salve use including cases of cancer progression and disfigurement.[70] The uncertainty around efficacy and possible recurrence along with the risk of scarring and disfigurement makes escharotics unfavorable when compared with other CAM or allopathic treatments and they should be avoided.

### *TOPICALS SUMMARY*

Topical treatments for skin cancer vary in efficacy, safety, and optimal cancer target type. Of the CAMs reviewed, Curaderm BEC5 shows the most promise for selectively targeting and destroying cancerous cells in non-melanoma cancers (BCC and SCC), though it requires further clinical validation. Hypericum perforatum has shown potential in playing a role in the treatment of melanoma and ESCC via its photodynamic and antiproliferative effects. Ingenol mebutate's initial FDA approval for high actinic keratosis clearance rates may be overshadowed by recent discoveries with regards to a high risk for malignancy development. Despite the historical use of black salve, it poses significant risks, including scarring, disfigurement, and cancer progression, making it an unsafe and unfavorable option when compared with other CAM or allopathic treatments.

## DIETARY SUPPLEMENTS

### *CURCUMIN*

Curcumin is a compound found in turmeric plants (*Curcuma longa*) that has long been recognized for its anti-inflammatory properties used to treat cancer, Alzheimer's, and coronary artery disease.[8] It has been shown to aid in managing many skin disorders, including atopic dermatitis, psoriasis, chronic wounds, skin infractions, and skin cancers such as melanoma and squamous cell carcinoma.[77-79]

Remarkably, curcumin demonstrates the ability to selectively target cancer cells and interfere with expression of cyclin D1, Bcl-2, Bcl-xl, caspases, death receptor and protein kinase pathways, and tumor suppressors such as p53.[77,80] Both in vivo mouse xenograft and in vitro studies of curcumin found anticancer activities against head and neck squamous cell carcinoma.[79,81] In vitro studies demonstrated antiproliferative effects via modulation of stat-3 and downregulation of Bax/Bcl-2, and the in vivo xenograft study noticed significant apoptotic effects via administra-

tion of curcumin with nanoparticle technology, thereby overcoming solubility and bioavailability issues.[79,81]

Another study on nasal squamous cell carcinoma found potential antiproliferative effects of curcumin nanoparticle therapy.[82] A possible mechanism is targeting the PI3K/Akt/mTOR signaling pathway, which is frequently altered in various cancers.[83] Photodynamic therapy with curcumin as a photosensitizer irradiated with 410 nm light was shown to increase apoptotic and necrotic cells when compared with curcumin without light radiation in both melanotic melanoma (A375) and amelanotic melanoma (C32) cell lines.[84]

A semisynthetic derivative related to curcumin, MePip-SF5, was found to have 5 times the antiproliferative effects on metastatic melanoma than curcumin itself.[78] This study illustrates the value of research into CAM, where exploring natural compounds can lead to important discoveries. Curcumin has broad therapeutic potential via its ability to target cancer cells and modulate key molecular pathways selectively. Initial results underscore the importance of continued research into enhancing its bioavailability and therapeutic efficacy via compound alteration or nanoparticle delivery systems.

### *NIACINAMIDE*

Niacinamide (or nicotinamide) is a water-soluble form of vitamin B3 (niacin) that can be derived from various animal and plant food sources and can also be synthesized endogenously from tryptophan.[8,85] Niacinamide is a precursor to NAD+, a coenzyme vital for ATP production and regulating pathways critical to metabolism and survival success.[85] Niacinamide has been shown to enhance DNA repair, reduce inflammation, and aid in antigen-presenting cell function to reduce UV-induced immunosuppression.[85,86]

Human clinical trials have shown skin cancer preventative benefits with twice daily 500 mg oral dosing of niacinamide.[8,85-87] Oral niacinamide supplementation has specifically demonstrated the ability to reduce instances of non-melanoma skin cancers and presented mixed results on preventing actinic keratosis.[8,85,86,88-91] One study found that after 12 months of dietary nicotinamide supplementation, the rate of new non-melanoma skin cancers was reduced by 23%, with significant decreases in actinic keratoses observed throughout the intervention period (11% to 20% reduction).[88] Studies note that beneficial effects quickly cease after discontinuing supplementation, revealing long-term, consistent use for sustained treatment, however.[85,86,88]

Additionally, niacinamide has been studied concerning skin cancer prevention in organ transplant recipients, related to their immunosuppression.[85,86,90] Results in these populations are mixed, but niacinamide's ability to stimulate antigen-presenting cells holds promise for further research into treating immunosuppression-induced carcinogenesis.

### *COENZYME Q10*

Coenzyme Q10 (CoQ10) is a lipophilic compound associated with the electron transport chain in mitochondria with known antioxidant effects, protecting membranes from free radical damage.[8,92] CoQ10 is commonly sold as a food supplement, and despite not being FDA-approved, in 2013, it was the third most consumed supplement in the U.S., following multivitamins and fish oil.[93]

CoQ10 acts as a natural and effective antioxidant against reactive oxygen species within the electron transport chain, thereby supporting the maintenance of physiological homeostasis.[94] Levels of CoQ10 in the body are reported to decrease with age, as well as various medical conditions, namely diabetes, AIDS/HIV, heart disease, some prescription drug use, and cancer, including melanoma.[8,93,95] One study found significantly lower plasma CoQ10 levels not only in patients diagnosed with melanoma but also within that population, levels were lower in metastatic patients than the metastasis-free subgroup.[95] This suggests plasma CoQ10 concentration as a prognostic factor for melanoma risk, with low CoQ10 levels (>0.60-1.00 mg/L) increasing melanoma risk by eightfold when compared with patients with above average CoQ10 levels.[8,92,95]

Additionally, plasma CoQ10 levels can predict the disease-free interval duration with higher concentrations associated with longer disease-free intervals.[92] CoQ10 has been shown to decrease expression of α-MSH signaling, which is usually upregulated with UV exposure, thereby inhibiting UV-induced melanin production.[92,96] One study developed a non-invasive nanoparticle hydrogel for CoQ10 and paclitaxel delivery to deep but localized melanoma tissues, improving drug bioavailability and minimizing toxicity.[97] This transdermal delivery system demonstrated protective effects against UV radiation, preventing potential carcinogenic processes by downregulating inflammatory factors and preserving collagen integrity.[97]

CoQ10's photoprotective effects are also being researched for potential as sunscreen additives. It was found that combined topical application of strawberry extract and CoQ10 significantly enhanced UV photoprotection, likely via antioxidant and anti-inflammatory properties.[98] In C57Bl/6 mice, CoQ10 analogs such as decylubiquinone have also shown suppressive qualities for pulmonary metastatic melanoma.[94] CoQ10 shows potential as a therapeutic agent, offering antioxidant, anti-inflammatory, and photoprotective benefits for melanoma prevention and treatment.

### *LYCOPENE*

Lycopene is a carotenoid nutraceutical found in many red-orange fruits and vegetables, such as watermelon and papayas, but it is particularly associated with tomatoes.[8,99] Tomato lycopene concentration ranges with ripeness or tomato type but is typically between 0.88-7.74 mg/100 g of tomato.[100,101] Lycopene is a natural antioxidant with protective qualities against various cancer types and inflammatory, cardiac, and neurological diseases.[100] It has been reported that lycopene has a dual function of prevent-

ing carcinogenesis while being able to induce apoptosis of pathological cells.[100] Furthermore, lycopene affects cancer cell migration and vessel formation, as demonstrated via in vitro studies.[100,102]

Lycopene has applications in nanoformulations as an antioxidant to protect certain compounds against oxidation, such as epigallocatechin gallate (from green tea) in one study on melanoma inhibition.[103] It was found that lycopene with epigallocatechin gallate demonstrated inhibition of melanoma proliferation and tumor angiogenesis.[103] Another study analyzed the combination of lycopene with resveratrol (from grapes) for treatment of laryngeal carcinoma cell lines (HEp-2) where, together, the two extracts demonstrated cytotoxic abilities against HEp-2 cells, the extent to which was dependent on both dosage and treatment duration.[99] It was noted that the combination of resveratrol and lycopene was more effective than individual effects.[99]

A 2022 study highlighted the potential role of lycopene in mitigating Programmed Death-Ligand 1 (PD-L1) knockdown of tongue squamous cell carcinoma in cell death signaling with T- cells.[104] Lycopene treatment inhibits cancerous PD-L1 knockdown, thereby inhibiting tumor growth and promoting apoptosis.[104] Lycopene's multifaceted bioactivities, including its antioxidant, anti-inflammatory, and anticancer properties, along with its synergistic potential when combined with other compounds, highlight its potential therapeutic uses.

### *BETA CAROTENE*

Beta carotene is part of the hydrocarbon class of carotenoids responsible for the red-orange pigmentation of plants, namely carrots, pumpkin, and even spinach and other dark green vegetables.[8,105] Beta carotene is a precursor in vitamin A synthesis, underscoring its important role in nutrition.[105] Vitamin A is critical in tissue growth, differentiation, and repair in addition to maintaining eye and immune health.[105,106]

Dietary beta carotene has been found to help prevent skin cancer via potent antioxidant effects, effectively neutralizing UV-induced free radicals and preventing structural damage.[8,107] When sequestered in cell membranes, beta carotene enhances cell defense and can work synergistically with other antioxidants.[107] A cross-sectional analysis spanning 1999-2018 found that increased dietary beta carotene reduced the severity of sunburns by mitigating UV-induced oxidative stress and lowered the risk of both skin and non-skin cancers by inhibiting DNA damage and inflammation.[108]

To optimize efficacy, It was found that thiolated chitosan-lithocholic acid nanomicelles could enhance delivery of beta carotene for skin cancer treatment.[109] The nanomicelle delivery system demonstrated delayed mouse skin cancer progression with minimal side effects.[109] While there is promising literature regarding beta carotene, there are some human cohort and interventional studies that suggest higher incidences of cancer, specifically squamous cell carcinoma and lung cancer, with dietary beta carotene supplementation.[110,111] While beta carotene shows promise in skin cancer prevention and treatment, its complex role in other cancers underscores the importance of tailored applications and further research.

### *POLYPODIUM LEUCOTOMOS*

*Polypodium leucotomos* (PL) is a fern found commonly in Central and South America that has long been traditionally used to treat asthma, diabetes, cardiac disease, and recently is being evaluated for applications in dermatology.[8,112] PL plants are incredibly resistant to environmental stress factors such as extreme temperatures and salinity, with polyphenols being their main antioxidant component.[113]

PL is administered either topically or orally and demonstrates potent photoprotective abilities shown to inhibit lipid peroxidation, UV-induced keratinocyte death, free radical damage, and release of inflammatory cytokines in both in vivo and in vitro studies.[8,113,114] PL is sold within the United States and Europe as dietary supplements and topical sunscreen products.[112] Empirical studies on PL have demonstrated success in treating many dermatological diseases, including skin cancer, photoaging, vitiligo, porphyria cutanea tarda, psoriasis, melasma, and atopic dermatitis.[8,113,115-117] Notably, PL appears to provide therapeutic benefits primarily in conditions characterized by postinflammatory hyperpigmentation and/or hyperproliferation of skin cells.[113,116]

One study found sunscreen formulated with 1% PL extract significantly improved defensive capabilities against UV-induced erythema, DNA damage, and photoimmunosuppression.[118] PL-infused sunscreen had an average booster effect of 10% when measured against metrics such as SPF and UVA protection factor.[118] Another 2023 study on PL corroborated those claims, finding that it enhanced sunscreen efficacy and showed promise for inhibiting tumor-promoting factors and lowering recurrence rates in people genetically predisposed to melanoma.[119]

PL has also been effective against oral squamous cell carcinoma, successfully inhibiting cell proliferation, migration, and inflammation.[120] Other studies have paired PL with other treatment methods, such as one 2015 study on bald patients that combined photodynamic therapy with PL extract supplementation and found that it significantly improved actinic keratosis clearance and recurrence after 6 months when compared to just photodynamic therapy alone ($p=0.040$).[121,122]

Overall, PL has a reassuring safety profile without notable side effects and appears safe for children.[122-124] PL's vast array of potential applications within dermatology makes it an interesting subject for further research.

### *SUMMARY OF DIETARY SUPPLEMENTS*

While all the above dietary supplements have favorable traits for treating or preventing skin cancer, curcumin and niacinamide appear to hold the most promise for future research and application. Curcumin's ability to selectively target cancer cells, alter key molecular pathways, and be deliverable through nanoparticles enhance its effectiveness against both melanoma and non-melanoma skin cancers.

Niacinamide stands out for its established safety profile and effectiveness in promoting DNA repair and preventing UV-induced immunosuppression, underscoring its potential for long-term skin cancer prevention, although consistent intake is required.

Dietary supplementation is an easy, accessible, and generally inexpensive option for many people. However, despite the high usage of these therapies, FDA regulation of dietary supplements is highly limited.[125] This classification of dietary supplements can be detrimental to consumers as it withholds information about potentially negative drug interactions or toxicities.[126] Further research and regulation are required to safely implement these supplements for skin cancer prevention and treatment.

## CONCLUSION

CAM offers promising avenues for the future development of skin cancer therapies with diverse applications and sources spanning plant-derived flavonoids, topical therapies, and dietary supplements. Among the flavonoids discussed, Gossypin emerges as highly promising for its ability to target BRAFV600E-mutant melanoma, reduce tumor size, and improve survival rates. Gossypin hints at the potential to incorporate genetic factors into CAM consideration, such as BRAFV600E mutations, where individual patient profiles could guide the choice and efficacy of specific CAM interventions. Curaderm BEC5 stands out among topical therapies for its promising results for targeting and killing BCC and SCC cells. Within dietary supplementation, curcumin and niacinamide demonstrate the greatest potential, with curcumin showing selective anticancer activity and niacinamide excelling in UV damage prevention and DNA repair.

Skin cancer presents with an array of diverse considerations: type and severity of cancer, patient demographics, medicinal belief systems, patient preferences, past medical experiences, access to medical care, and much more. This complex matrix of considerations may prompt the necessity for unique, more individualized options. Promising outcomes of CAM therapies suggest their potential integration one day with conventional methods such as surgery, chemotherapy, and radiation.

A lack of standardized research protocols limits CAM research and necessitates greater collaboration between CAM and conventional medical research to foster credibility and utilization. Furthermore, inconsistent regulation, lack of FDA oversight for dietary supplements, and variable quality of compounds affect both research and clinical use. These factors contribute to the lack of large-scale, long-term human clinical trials, which effectively inhibit the broader adoption of CAM into practice.

Understanding current research and common usage of CAM is important not just for the clinicians who recommend its use but for all providers as many patients use CAM independently. It is important to note that undirected CAM usage may delay diagnosis or worsen disease severity. Dermatologists must discern between evidence-supported CAM and unfounded claims to provide patients with informed recommendations, such as in the case of dangerous CAMs like escharotics and potentially IM. Open discussion that includes CAM improves trust and satisfaction in care and aligns with the broader trends in integrative medicine, where conventional and alternative approaches are combined for optimal health outcomes.

## DISCLOSURES

Dr. Lio reports being on the speaker's bureau for AbbVie, Arcutis, Eli Lilly, Galderma, Hyphens Pharma, Incyte, La Roche-Posay/L'Oréal, Pfizer, Pierre-Fabre Dermatologie, Regeneron/Sanofi Genzyme, Verrica; reports consulting/advisory boards for Alphyn Biologics (stock options), AbbVie, Almirall, Amyris, Arcutis, ASLAN, Bristol-Myers Squibb, Burt's Bees, Castle Biosciences, Codex Labs (stock options), Concerto Biosci (stock options), Dermavant, Eli Lilly, Galderma, Janssen, LEO Pharma, Lipidor, L'Oréal, Merck, Micreos, MyOR Diagnostics, Regeneron/Sanofi Genzyme, Sibel Health, Skinfix, Suneco Technologies (stock options), Theraplex, UCB, Unilever, Verdant Scientific (stock options), Verrica, Yobee Care (stock options). In addition, Dr. Lio has a patent pending for a Theraplex product with royalties paid and is a Board member and Scientific Advisory Committee Member emeritus of the National Eczema Association.

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