Review

# Beyond the scalpel: rare and experimental nonsurgical treatments for basal cell carcinoma

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## Abstract

Basal cell carcinoma (BCC) is typically found on sun-exposed skin and is the most common form of skin cancer. Risk factors include male sex, fair skin, increased ultraviolet radiation exposure, prior history of BCC, chronic arsenic exposure, genetic predisposition, and immunosuppression. BCC is a slow-growing tumor that typically presents as a shiny and pink papule or nodule with telangiectasias. However, its presentation varies depending on the histological type, which can be confirmed by biopsy. First-line therapies for low-risk BCC include standard surgical excision and curettage and electrodesiccation, whereas the gold standard for high-risk BCC is Mohs microscopic surgery. This review summarizes the current guidelines for BCC treatment and discusses the mechanism of action and clinical implications of alternative rare, experimental, and anecdotal treatments in the literature.

## Introduction

Basal cell carcinoma (BCC) is the most common form of skin cancer, originating from the basal cell layer of the epidermis, and typically occurs on sun-exposed areas of the skin (approximately 80%).[1] Risk factors for BCC development include male sex, fair skin, increased ultraviolet (UV) radiation exposure, prior history of BCC, chronic arsenic exposure, genetic predisposition, and immunosuppression.[1] BCC is a locally aggressive but slow-growing tumor that typically presents as a shiny, pink papule or nodule with telangiectasias; however, its presentation varies depending on the histological type.[1,2] According to the World Health Organization, BCC can be classified into 10 subtypes: superficial basal cell carcinoma (sBCC), nodular basal cell carcinoma (nBCC), infundibulocystic BCC with adnexal differentiation, pigmented, infiltrative, micronodular, basosquamous, fibroepithelial, sclerosing/morphoeic, and BCC with sarcomatoid differentiation.[3]

The selection of treatment options depends on a variety of factors, including the patient's age, comorbidities, and treatment preferences, as well as the size, location, and pathology. The National Comprehensive Cancer Network categorizes treatment guidelines according to the risk of BCC recurrence, which are summarized in **Table 1**.[4] Although BCC is locally invasive, it is typically slow growing with an exceedingly low risk of metastasis, making it generally nonlethal or minimally harmful.[2] Classifications of low- versus high-risk primary BCCs are summarized in **Table 2**. Numerous rare, experimental, and anecdotal treatment options have been reported in the literature.

The purpose of this review is to summarize the current guidelines for the treatment of BCC and describe the mechanisms of action and clinical implications of unconventional but potentially effective nonsurgical treatments (**Figure 1** and **Figure 2**). This review also highlights key preclinical and clinical studies evaluating the efficacy of these treatments. Several botanical compounds, traditionally used in diverse systems of medicine, have undergone experimental investigation as potential treatments for BCC. In addition, certain previously established medications, dietary supplements, and vitamins originally designed for different medical purposes have been explored for their potential efficacy. Finally, ongoing research continues to investigate novel and unconventional therapeutic approaches. Current and emerging treatments for BCC are summarized in **Table 3**.

## Discussion

A literature search of PubMed was conducted using the common and scientific names of herbal remedies, along with MeSH terms such as *complementary*, *herbal*, *botanic*,

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**Table 1.** *BCC Treatment Indications and Contraindications.*

| Treatment | Indications | Contraindications |
|---|---|---|
| **Surgical Treatment** | | |
| Surgical excision | First-line for low-risk primary BCC; may be used for select high-risk tumors with complete margin assessment[5] | N/A |
| MMS | First-line for BCC in high-risk areas[5] | N/A |
| Deep shave removal | BCC in low-risk sites on trunk or extremities in immunocompromised patients[6] | N/A |
| **Destructive Treatment** | | |
| Cryosurgery | Small, well-defined primary low-risk BCCs less than 10 mm without sclerosing or infiltrative growth patterns[7]; useful when more effective therapies are contraindicated; good for patients with bleeding disorders or anesthesia issues[8] | High-risk sites except less than 3 mm; less than 2 cm; sclerosing/ morphoeaform, infiltrative or micronodular BCC[7]; cold intolerance; cryoglobulinemia or cryofibrinogenemia; Raynaud; platelet deficiency[9] |
| Curettage alone | Small sBCCs or nBCCs less than 10 mm[7]; nBCC less than 6 mm in high-risk areas and less than 2 cm elsewhere[10] | Malignant lesions less than 2 cm; aggressive growth; lesions greater than 3 mm in high-risk sites; very thin skin |
| Electrocautery with curettage | Low-risk primary BCCs[5] | Terminal hair-bearing or cosmetically sensitive areas (H-zone)[5,11] |
| **Energy Devices** | | |
| Radiotherapy (low-energy X-ray, brachytherapy, high-energy radiotherapy) | High-risk BCC when surgery is contraindicated or not preferred | N/A |
| Photodynamic therapy (not FDA-approved) | Small nBCC (less responsive) | N/A |
| **Topical Treatment** | | |
| Topical 5-fluorouracil 5% (twice daily, 4–6 weeks) | sBCC in low-risk locations when conventional methods are impractical[12] | Pregnancy[13] |
| Imiquimod 5% cream (5 days/week, 6 weeks) | Biopsy-confirmed primary sBCC less than 2 cm on trunk, neck, or extremities in immunocompetent adults (excluding hands and feet) when surgery is not an option[14,15] | Not indicated for other BCC subtypes[14] |
| **Systemic Treatment** | | |
| HhI (vismodegib, sonidegib) | Sonidegeib: locally advanced BCC in adults after surgery or radiation therapy, or non-candidates[16]; Vismodegib: locally advanced or metastatic BCC after surgery,[17] or non-candidates | Pregnancy[16,17] |
| Intravenous cemiplimab (350 mg over 30 minutes every 3 weeks) | Locally advanced or metastatic BCCs refractory to HhIs[18,19] | N/A |
| Platinum-based chemotherapy | Metastatic BCC refractory to HhIs and immunotherapy[5,19] | N/A |

Abbreviations: BCC, basal cell carcinoma; HhI, hedgehog pathway inhibitor; MMS, Mohs micrographic surgery; nBCC, nodular basal cell carcinoma; sBCC, superficial basal cell carcinoma.

**Table 2.** *Classification of Low-Risk Versus High-Risk Primary BCC.*

| Risk | Criteria |
|---|---|
| Low-risk primary BCC | • Well-defined, primary BCC less than 20 mm located on trunk or extremities (excluding genitalia, pretibia, hands, and feet)[5]<br>• Histopathology: nodular or superficial histopathologic growth pattern, other nonaggressive growth patterns (infundibulocystic, fibroepithelioma of Pinkus); perineural invasion<br>• No history of radiation at the site<br>• Immunocompetent patient |
| High-risk primary BCC | • Tumors location: cheeks, forehead, "mask area" of face (nose, lips, eyelids, eyebrows, periorbital skin, chin, mandible, ears, pre/postauricular areas, temples), scalp, neck, pretibia, hands, feet, genitalia[5,20]<br>• Tumor size: at least 1 cm on head/neck and at least 2 cm elsewhere<br>• Poorly defined or infiltrative borders<br>• Histopathology: aggressive features (micronodular, morpheaform, sclerosing, mixed infiltrative, basosquamous) or perineural invasion<br>• Recurrent or refractory tumors<br>• Tumors in sites of prior radiation (controversial) |

Abbreviations: BCC, basal cell carcinoma.


**Figure 1.** *Basal cell carcinoma risk stratification and potential future pathways.*

Adapted from Paul S, Knight A. *The Importance of Basal Cell Carcinoma Risk Stratification and Potential Future Pathways.* JMIR Dermatol. 2023;6:e50309. Originally published in JMIR Dermatology, 30 Oct 2023, under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/). Reproduced with permission.

or *alternative*, in combination with the keywords "nonmelanoma skin cancer" and "basal cell carcinoma."

## Unveiling Emerging Advances in Botanical Compounds

### *Black Salve*

Black salve has previously been used for the treatment of warts and moles. It contains zinc chloride and sanguinarine derived from bloodroot (*Sanguinaria canadensis*), both of which are escharotic agents that induce tissue necrosis. These ingredients, along with stibnite, were originally used in the fixation paste for Mohs micrographic surgery (MMS).[12] Preclinical studies have shown selective induction of apoptosis in human squamous cell carcinoma (SCC) cells when sanguinarine is applied at low doses, whereas higher doses cause necrosis of normal keratinocytes. The mechanism of action of sanguinarine is multifaceted. It triggers the production of reactive oxygen species (ROS), resulting in oxidative stress within cancer cells. This process involves rapid caspase activation, disruption of mitochondrial membrane potential, and apoptotic cell death. Bloodroot has also been shown to inhibit nuclear transcription factor κB (NF-κB) activity,

**Table 3.** *Current and Emerging Treatments for BCC.*

| Compound | Study Type | Key Findings | Reference |
|---|---|---|---|
| **Botanical Compounds** | | | |
| Black salve | Preclinical | Induces apoptosis in SCC and inhibits angiogenesis and migration | 21 |
| | Case reports | Complete BCC response in 8/12 reports | 12 |
| Solasodine glycosides | Preclinical | Selectively binds cancer cell lectins and induces apoptosis | 21 |
| | Case reports | Visible clearance but residual tumor on biopsy | 22 |
| | Clinical trials | 66% clearance versus 25% with vehicle; 22% recurrence at 1 year; 86 patients had complete regression at 3 months | 23,24 |
| Hypericin | Preclinical | Induces apoptosis via caspase activation and mitochondrial disruption | 25 |
| | Clinical trials | sBCC: 28% complete clinical response; nBCC: partial response | 26,27 |
| Frankincense oil | Preclinical | G1 cell cycle arrest, inhibits topoisomerase II, reduces MMP-2/9 | 28 |
| | Case report | BCC on arm resolved; BCC on chest had residual cancer | 29 |
| Ajoene | Preclinical and clinical trial | 17/21 patients showed tumor reduction via apoptosis | 30 |
| Green tea | Preclinical | Reduces tumor growth via β-catenin/Wnt pathway inhibition and induces apoptosis via endoplasmic reticulum stress pathway in SCC cells | 12,31 |
| | Case reports | 1 year of temporary arrest from new BCC development | 32 |
| | Clinical | Minimal clearance in sBCC; no effect on NMSC after 12 months | 31,33 |
| Beta-carotene | Preclinical and clinical | Reduce free radicals; no significant effect on new BCC | 34 |
| Curcumin | Preclinical | Induces apoptosis via multiple pathways | 12,35,36 |
| Gingerol | Preclinical | Reduces UV-B damage/ROS and decreases tumor formation in mice | 37,38 |
| Milk thistle | Preclinical | Inhibits BCC growth via apoptosis and reduces UV-B damage in mice | 12,39,40 |
| Genistein | Preclinical | Topical/oral application reduces UV-B–induced tumor incidence in mice | 41 |
| Calluna and vitis extracts | Preclinical | Reduces inflammation and UV-B damage in mice | 42 |
| Procyanidin | Preclinical | Dose-dependent tumor inhibition and antioxidant effects | 43 |
| Lycopene | Clinical trial | Reduces UV damage, MMP-1, and DNA damage in tomato paste group | 44 |
| **Medications, Vitamins, or Supplements** | | | |
| Diclofenac gel | Preclinical | Inhibits COX-2 and lowers B-cell lymphoma 2 and Prostaglandin $E_2$ in BCC | 45 |
| | Clinical trials | Histological regression in sBCC; limited efficacy in nBCC | 45,46 |
| Itraconazole | Case report | Significant tumor reduction after 8 months | 47 |
| | Clinical trial | Reduced cell proliferation by 45%, Hh pathway activity by 65%, tumor area by 24% in BCC at least 4 mm; stabilized HhI-resistant metastatic BCC | 48,49 |

| Compound | Study Type | Key Findings | Reference |
|---|---|---|---|
| Topical remetinostat | Clinical trial | 54.8% histological clearance; well-tolerated | 50 |
| Alpha-DFMO | Preclinical and clinical trial | Reduces UV-induced ODC activity; significant reduction in new BCC development | 51 |
| Nicotinamide | Preclinical | Prevents UV-induced ATP depletion and enhances DNA repair | 52 |
| | Clinical trials | Reduces BCC rates in general population and transplant patients | 52,53 |
| Acitretin | Preclinical | Promotes apoptosis and growth inhibition; especially effective combined with imiquimod or IFN-α | 54 |
| | Case reports | Combination with imiquimod: BCC clearance in 5 cases, tumor reduction in 2 cases | 60-62 |
| Ascorbic acid | Clinical trial | 4/7 BCCs resolved within months with 1 recurrence; 86.7% BCC clearance versus 57.1% with imiquimod; intravenous form stabilized advanced disease | 63-65 |
| Vitamin D | Clinical trial | Mixed findings: higher serum D linked to fewer recurrences but possibly higher risk of new BCC | 55,56 |
| Selenium | Clinical trial | No significant difference in BCC incidence; possible increased risk of new BCC | 57,58 |
| **Exotic or Unconventional** | | | |
| Melittin | Preclinical and case report | Induces apoptosis via Signal Transducer and Activator of Transcription 3 inhibition and cell-cycle arrest; 1 reported case of complete sBCC clearance with no recurrence | 59 |
| Cashew nut extract | Clinical trial | 100% clinical remission with no recurrence in small study; larger trial showed significant clinical clearance but no histological clearance with some recurrences | 60,61 |
| PALA | Preclinical | Reduces UV-B–induced tumor growth dose-dependently in mice | 62 |
| Sarcophine-diol | Preclinical | Topical SD decreased tumor multiplicity and area via caspase-3 and -8 induction and COX-2 suppression in mice | 63 |
| Coffee | Preclinical | Induces apoptosis in UV-damaged keratinocytes | 64 |
| | Observational study | Reduced BCC risk with intake | 65 |
| Calcium electroporation | Proof of concept | Induces apoptosis by intracellular calcium overload through electrical membrane permeabilization | 66 |

Abbreviations: ATP, adenosine triphosphate; BCC, basal cell carcinoma; COX-2, cyclooxygenase-2; DFMO, difluoromethylornithine; Hh, hedgehog; HhI, hedgehog pathway inhibitors; IFN-α, interferon-α; MMP, matrix metalloproteinases; nBCC, nodular basal cell carcinoma; NMSC, nonmelanoma skin cancer; ODC, ornithine decarboxylase; PALA, N-Phosphonacetyl-L-Aspartate; ROS, reactive oxygen species; sBCC, superficial basal cell carcinoma; SCC, squamous cell carcinoma; SD, sarcophine-diol; UV, ultraviolet.

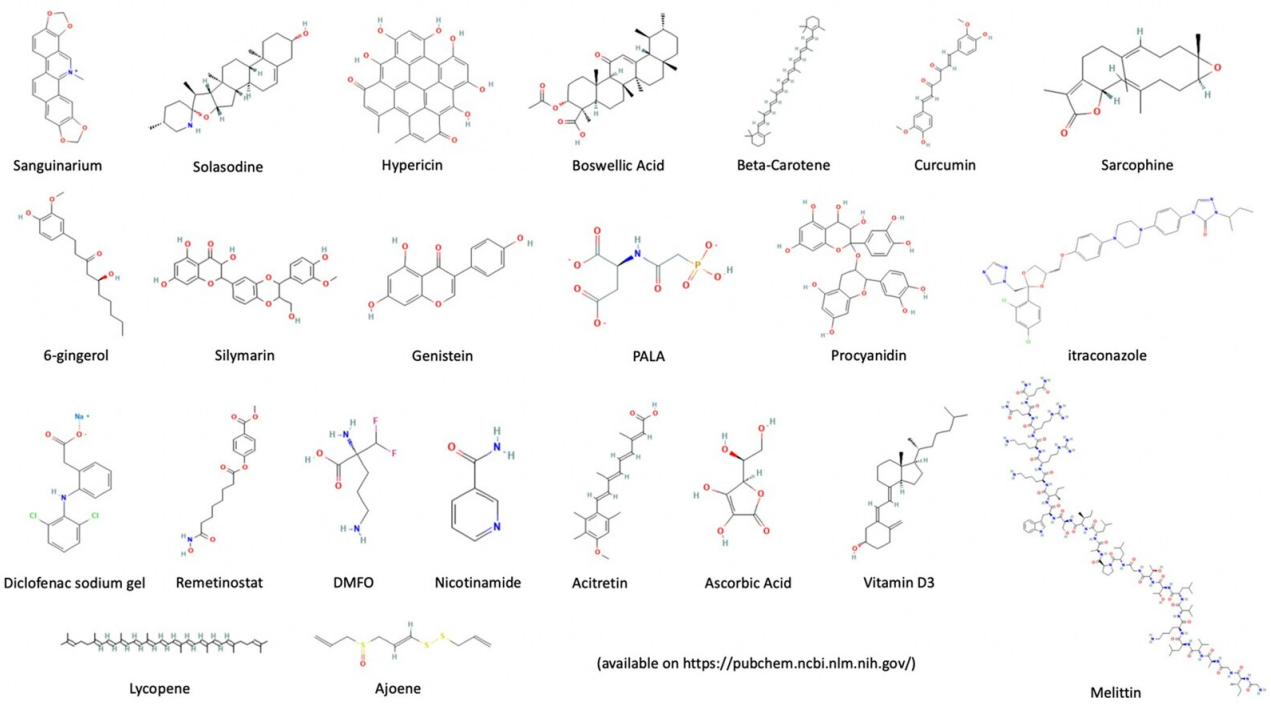


**Figure 2.** *Chemical structures of alternative treatments for basal cell carcinoma.*

which regulates the cell cycle and apoptosis. In addition, it may impede tumor angiogenesis by inhibiting vascular endothelial growth factor, thereby reducing the tumor's nutrient supply. Bloodroot may also suppress cancer cell invasion by interfering with matrix metalloproteinase (MMP)-2 and MMP-9 signaling pathways, which facilitate extracellular matrix degradation and cancer cell migration.[21]

A review of published case reports describing the use of black salve for skin cancer reported complete response in 8 of 12 cases of BCC (5 confirmed by biopsy), 2 cases of residual BCC, 2 cases of disease progression, and 1 case of metastasis.[12] Despite the potential cytotoxic activity of black salve, it is imperative to exercise caution because of its propensity to cause tissue necrosis, leading to eschar formation, erythema, and pain in surrounding tissue. Black salve may also result in significant, often permanent scarring and disfigurement. Patients, particularly those with chronic conditions such as peripheral vascular disease or uncontrolled diabetes, should be counseled to avoid use because of increased susceptibility to complications related to impaired wound healing.[67]

## *Solasodine Rhamnosyl Glycosides*

Solasodine rhamnosyl glycosides (SRGs) are derived from a variety of plants and vegetables and target glycoproteins found on cancer cells to initiate apoptosis.[12] SRGs selectively attach to endocytic lectins found exclusively on the surface of cancer cells, sparing normal tissue. Upon binding, they form complexes that enter cancer cells through receptor-mediated endocytosis. Inside the cells, SRGs induce apoptosis by disrupting lysosomes and releasing their hydrolytic enzymes, leading to tumor cell death. SRGs also trigger apoptosis through upregulation of death receptors, such as Fas and Fas-associated death domain, and downregulation of the anti-apoptotic protein Bcl-2, while increasing the pro-apoptotic protein Bax, culminating in activation of caspases-8, -9, and -3.[21] In Australia, SRGs have been formulated into a cream and licensed for the treatment of actinic keratosis (AK).[12]

A case report described a 52-year-old man with SCC in situ of the penis who did not respond to 2 courses of 5% imiquimod cream. The patient declined MMS and instead applied SRG cream with occlusion twice daily while receiving monthly cryotherapy for 10 months. This treatment resulted in complete clinical resolution with no evidence of disease at the 2-year follow-up.[12] Another case report of a 47-year-old man with BCC on the right temple who opted for SRG cream instead of surgery showed visible clearance of the growth but residual tumor on biopsy several months later.[22]

A randomized controlled trial (RCT) of 94 patients with confirmed BCC greater than 0.5 cm compared a topical mixture of solasodine glycosides versus a vehicle without SRGs applied twice daily under occlusion for 8 weeks.[23] Results showed 66% clearance in the solasodine glycosides group versus 25% in the vehicle group; however, 22% of successfully treated patients experienced recurrence during 1-year follow-up. In a study of 86 patients using SRG cream twice daily under occlusion for an average of 5.2 weeks, complete regression was observed in all BCCs at the 3-month follow-up. Reported adverse events (AEs) included itching, burning, swelling, erythema, and ulceration.[24]

### *Hypericin (St. John's Wort)*

Hypericin is a photoactive compound derived from *Hypericum perforatum* that induces cytotoxicity in tumor cells after activation by visible light (520–750 nm wavelength).[25] This effect involves dose-dependent inhibition of cell proliferation, DNA fragmentation, and activation of caspases-8 and -3, which are integral to apoptotic pathways. Apoptosis of Jurkat cells from human leukemic lymphoma was also partially mediated by the TRAIL/TRAIL-receptor system, which activates upstream caspases. Hyperforin, another component of *H. perforatum*, inhibits tumor growth in various cancer cell lines, including SCC and melanoma, via light-independent mechanisms. It induces apoptosis through activation of caspases-9 and -3 and disruption of mitochondrial membrane potential. Hyperforin also activates a mitochondria-mediated apoptosis pathway via cytochrome c release and directly affects endothelial cells, reducing proliferation and disrupting microvessel formation.[25] In a clinical study of 8 patients with BCC, treatment with hypericin injections followed by visible light irradiation resulted in clinical remission within 6 to 8 weeks (NCT03546166).[26] Another study treated 34 patients with topical *H. perforatum* extract under occlusion with weekly red-light irradiation for approximately 6 weeks. Results showed 28% complete clinical response and 11% histological clearance in patients with sBCC, whereas patients with nBCC only experienced partial remission. Reported AEs included burning, pain, and photodermatitis.[27]

### *Frankincense Oil*

Frankincense oil, derived from resins of *Boswellia* species, has been used to treat a variety of inflammatory conditions.[12] Preclinical studies demonstrated that boswellic acid acetate (BC-4) induces cell cycle arrest in the G1 phase, reducing cell division and proliferation. BC-4 also inhibits topoisomerase II activity in B16F10 melanoma cells, a key enzyme involved in DNA replication and cell division. In human fibrosarcoma HT-1080 cells, BC-4 effectively inhibits secretion of MMP-2 and -9 in a dose-dependent manner.[28] A case report described a 56-year-old man with nBCC on the arm and an infiltrative BCC on the chest who applied frankincense oil several times daily for 4 months. Complete resolution was observed for the nBCC on the arm, whereas residual BCC remained on the chest upon biopsy.[29] Allergic contact dermatitis related to the extract has also been documented.[12]

### *Ajoene*

Ajoene is a garlic-derived organosulfur compound used for cardiovascular conditions and exhibits antifungal activity. A clinical study by Tilli et al[30] treated 21 patients with nodular nBCC or sBCC using topical 0.4% ajoene cream for 6 months. Overall tumor size reduction was observed in 17 patients, and results were verified in vitro.[30] Immunohistochemical analysis examined expression of the apoptosis-suppressing protein Bcl-2 before and after treatment, revealing significantly decreased expression following therapy. Interestingly, the percentage of tumor cells expressing the proliferation marker Ki-67 remained largely unchanged, suggesting that ajoene's effects were not primarily cytostatic. In vitro studies of BCC cell cultures confirmed that ajoene induced apoptosis in a dose- and time-dependent manner, highlighting its role in activating the mitochondria-dependent apoptotic pathway.[30]

### *Green Tea*

Green tea, derived from *Camellia sinensis*, contains the active component epigallocatechin-3-gallate, which has been linked to inactivation of β-catenin signaling in the Wnt pathway, thereby reducing tumor development (NCT02029352).[31] Other preclinical studies demonstrated antitumor effects of cannabinoids on melanoma and nonmelanoma skin cancer (NMSC) through increased concentrations of anandamide, an agonist of cannabinoid receptors, which is metabolized to J-series prostamides via cyclooxygenase-2 (COX-2) overexpression. This pathway activates apoptosis via endoplasmic reticulum stress in the murine SCC JWF2 cell line.[12]

An RCT treated 39 patients with sBCC using either topical sinecatechins (green tea extract) 10% ointment or placebo twice daily for 6 weeks. Complete histological tumor clearance was observed in a small proportion of patients in both groups. Although the sinecatechins group showed slightly greater reduction in tumor size and decreased expression of Ki-67 and Bcl-2, these differences were not statistically significant. The sinecatechins group also experienced more skin-related AEs, including erythema, edema, erosions, crusting, and itching.[31]

A case study of a 47-year-old woman with Gorlin syndrome who applied a gel containing green tea extract and 4 other plant extracts for 30 minutes under a heated electric blanket demonstrated temporary arrest of new BCC development for 1 year.[32] However, a review of green tea in cancer prevention reported an RCT in which participants consuming green tea orally for 12 months showed no effect on NMSC.[33] Although green tea extract shows potential in reducing tumor size and temporarily preventing new BCC in some cases, its overall efficacy in preventing NMSC remains inconclusive based on current evidence.

### *Beta-Carotene*

Beta-carotene, derived from various colorful plants, has retinol activity and has been associated with a decreased risk of certain human cancers. The exact mechanisms underlying its protective effects are not fully understood, but several pathways have been proposed. Beta-carotene, along with other carotenoids, can inhibit the formation of free radicals generated by UV-B radiation and can quench singlet-excited oxygen, a harmful ROS involved in skin damage and carcinogenesis.[34] A clinical trial enrolled 1805 patients with new NMSC. Of these, 334 patients with 1 or more new BCCs received 50 mg of

beta-carotene capsules daily, while 317 patients received placebo. Despite good adherence, minimal side effects, and significantly elevated plasma beta-carotene levels in the treated group, results after 5 years showed no significant difference between the groups in the development of new NMSC.[34]

## *Curcumin*

Curcumin, the active component of turmeric (*Curcuma longa*), has been shown to inhibit in vitro human SCC cell growth.[12] It has been used in traditional medicine for inflammatory skin and gastrointestinal conditions, weight management, and digestion.[35] In a review of curcumin as an alternative treatment for skin cancer, it was demonstrated to hinder melanoma cell migration and invasion in laboratory studies. Curcumin also triggers apoptosis via activation of caspases-3 and -8, suppression of the JAK-2/STAT3 pathway, and inhibition of Akt/mTOR signaling.[12] Encapsulation of curcumin in cationic liposomes combined with STAT3 siRNA has been shown to restrain human SCC cell growth in vitro and inhibit growth of mouse melanoma cells both in vitro and in vivo. Preclinical studies on BCC cells demonstrated that curcumin induces apoptosis via increased p53 protein expression.[35] Another study confirmed that curcumin selectively inhibits COX-2 and induces apoptosis through p53 activation.[36] However, topical application of turmeric or curcumin can potentially lead to AEs, including allergic contact dermatitis, contact urticaria, and pruritus.[12]

## *Ginger Extract*

6-Gingerol is a naturally occurring plant phenol derived from ginger (*Zingiber officinale*) and has been used in traditional medicine for its antioxidant, anti-apoptotic, and anti-inflammatory properties, providing relief from symptoms such as nausea and vomiting.[37] Preclinical studies have investigated its effects on skin cancer. Topical ginger extract applied to mice before UV-B irradiation, as well as treatment of HaCaT cells with 6-gingerol, demonstrated suppression of ROS accumulation and inhibition of NF-κB, COX-2, and UV-B–induced caspases.[37] Another study applying topical ginger extract to mice showed reduced skin tumor incidence and multiplicity, with significant reductions in skin tumor promotion markers and COX and lipoxygenase activities.[38]

## *Milk Thistle*

Milk thistle (*Silybum marianum*) is a plant native to Europe but also found in the United States and South America. It contains silymarin, a mixture of flavonoids and flavonolignans. Silibinin, derived from milk thistle seeds, has been shown to inhibit growth of skin cancer and other cancer types, including prostate, breast, head and neck, and liver cancers.[12] Preclinical studies have explored the effects of silibinin and its oxidation product, 2,3-dehydrosilibinin (DHS), on BCC in vitro and in vivo. Both compounds inhibit BCC cell growth and clonogenicity and induce apoptosis, with DHS being more potent at lower concentrations. They reduce phosphorylation of epidermal growth factor receptor (EGFR), ERK1/2, Akt, and STAT3, and suppress activation of transcription factors NF-κB and AP-1, disrupting mitogenic signaling pathways. Oral administration of silibinin and DHS in vivo significantly inhibits BCC tumor growth and decreases expression of proliferation markers and key regulatory proteins in tumor tissues.[12,39]

Silibinin also reduces BCC cell proliferation and tumor growth in hedgehog (Hh) inhibitor–resistant BCC cells via modulation of multiple signaling pathways. It aids in repairing UV-induced DNA damage, particularly by enhancing the nucleotide excision repair pathway through involvement of the p53 tumor suppressor protein, suggesting potential as a preventive agent against BCC. In mice, silibinin reduced UV-B–induced skin inflammation. However, further research is needed to determine whether p53 is essential for silibinin's efficacy in BCC prevention in Patched1$^{+/-}$ mice, a model where the Hh pathway plays a critical role in BCC development.[40] No human clinical trials have yet confirmed the efficacy of silibinin or milk thistle for skin cancer treatment, and there are no documented clinical cases of its use in BCC management.

## *Genistein*

Genistein is a soybean-derived isoflavone with diverse anticancer activity and has been used as an alternative treatment for menopausal symptoms, osteoporosis, and cardiovascular disease.[41] Preclinical studies in hairless mice demonstrated that both topical and oral genistein significantly inhibited UV-B–induced skin carcinogenesis. Genistein reduced tumor multiplicity and incidence in UV-B initiation and promotion studies. Topical application was more potent than oral administration. Genistein also protected against acute and chronic UV-B–induced skin damage and photoaging, including blocking acute skin burns and alleviating skin roughness and wrinkling in chronically UV-B–exposed mice.[41] Mechanistically, genistein inhibited phosphorylation of EGFR and activation of mitogen-activated protein kinases in human keratinocytes, which are steps in pathways associated with inflammation and cell proliferation. It also protected against photodamage induced by psoralen plus UVA (PUVA) therapy, reversing PUVA-induced cutaneous damage and molecular alterations in mouse skin.[41] Additional studies using 7,12-dimethylbenz[a]anthracene (DMBA)–initiated and 12-O-tetradecanoylphorbol-13-acetate (TPA)–promoted skin tumor models in mice showed that daily genistein application reduced tumor incidence and multiplicity. Two studies consistently demonstrated that genistein substantially inhibited TPA-promoted skin tumorigenesis, reducing tumor multiplicity by approximately 60% and 75%, respectively ($P < .01$), though effects on tumor incidence were less pronounced.[68]

### *Calluna vulgaris (Cv) and Vitis vinifera (BM) Extract*

Preclinical studies have explored the chemoprotective properties of *Calluna vulgaris* (Cv) extract and hydroethanolic extract from *Vitis vinifera* (BM), obtained from evergreen flowering shrubs and grapevines, respectively.[42] In an in vivo study, 40 SKH-1 mice with UV-B–induced skin damage were randomly divided into 4 groups: control, UV-B irradiated, Cv with UV-B irradiation, and BM with UV-B irradiation. BM extract significantly inhibited UV-B–induced sunburn cells and cyclobutane pyrimidine dimer formation 24 hours post-irradiation. Retreatment with both extracts significantly reduced proinflammatory cytokines, including interleukin-6 and tumor necrosis factor-α, which are involved in UV-B–induced immunosuppression and tumor growth signaling. BM extract demonstrated stronger antioxidant activity than Cv, suppressing oxidative stress caused by UV-B exposure.[42]

### *Procyanidin*

Procyanidins, found in grape seeds, possess anti-inflammatory, anti-arthritic, anti-allergic, and anti-aging properties. Using a mouse skin carcinogenesis model, a polyphenolic fraction from grape seeds (GSP) was applied after tumor initiation with TPA and DMBA. GSP demonstrated a dose-dependent anti–tumor-promoting effect, significantly reducing tumor incidence, multiplicity, and volume. Further analysis of 9 polyphenols in GSP, including catechin, epicatechin, procyanidins B1–B5, procyanidin C1, and procyanidin B5-3′-gallate, showed antioxidant activity, inhibiting epidermal lipid peroxidation to varying degrees. Procyanidin B5-3′-gallate exhibited the highest antioxidant activity.[43]

### *Lycopene*

Lycopene, a red-pigmented carotenoid derived from various plants, possesses potent antioxidant and anticancer properties in cultured cells and animal models.[44] An RCT enrolled 20 women who ingested 55 g of tomato paste in olive oil or olive oil alone daily for 12 weeks. Participants consuming tomato paste demonstrated increased resistance to UV radiation (UVR)–induced erythema compared to the control group. Skin biopsies showed that tomato paste reduced expression of MMP-1, a marker associated with skin aging, following UVR exposure. Additionally, tomato paste mitigated UVR-induced reduction in fibrillin-1 and increased procollagen I deposition. Supplementation also reduced mitochondrial DNA damage caused by UVR.[44]

## Repurposed Medications, Vitamins, or Supplements

### *Diclofenac Sodium Gel*

Diclofenac, a nonsteroidal anti-inflammatory drug approved for AK, is under investigation for potential efficacy in BCC.[69] Diclofenac 3% inhibits COX-2, an enzyme frequently overexpressed in BCC. This inhibition reduces prostaglandin $E_2$ levels, downregulates the antiapoptotic protein Bcl-2, and may influence signaling pathways activated in BCC (NCT01358045).[45] In a clinical study, 14 patients with high-risk BCC received a $CO_2$ laser session followed by topical diclofenac 3% and imiquimod 5% for 20 to 24 weeks. Significant improvement was observed in 9 patients, weak response in 5, with the greatest effect seen in the nBCC subtype.[46] Another trial evaluated topical diclofenac, vitamin $D_3$, or a combination in patients with sBCC or nBCC applied twice daily for 8 weeks.[45] Diclofenac treatment led to a decrease in Ki-67 and Bcl-2 expression and achieved complete histologic tumor regression in 64.3% of sBCC cases, while combination therapy achieved 43.8% regression. No complete regression was observed in the control group. Diclofenac did not significantly alter tumor characteristics in nBCC. Most AEs were mild, including erythema, pruritus, and erosions at the application site. A few cases required discontinuation owing to severe local reactions.

### *Itraconazole*

Itraconazole is an antifungal agent used for onychomycosis.[70] Case reports and clinical studies have evaluated itraconazole as monotherapy or in combination for BCC. One case report described an 87-year-old man with inoperable advanced BCC of the sinuses and brain treated with itraconazole and a Hh pathway inhibitor (Sonidegib) for 2 weeks after relapse. Magnetic resonance imaging after 8 months showed significant tumor regression.[47] A clinical study of 29 patients with 1 or more BCC greater than 4 mm treated with oral itraconazole 200 mg twice daily for 1 to 2.3 months showed a 45% reduction in cell proliferation, 65% reduction in Hh pathway activity, and 24% reduction in tumor area. Patients with multiple tumors demonstrated partial responses or stable disease.[48] Itraconazole has also been combined with arsenic trioxide, which antagonizes the Hh pathway at distinct sites from Hh inhibitors. In a clinical trial of 5 men with refractory metastatic BCC, 3 patients completed treatment with stable disease and reduced GLI1 mRNA levels.[49]

### *Topical Remetinostat*

Remetinostat is a histone deacetylase inhibitor approved for cutaneous T-cell lymphoma.[71] In a clinical trial, 25 participants with at least 1 BCC applied 1% topical remetinostat gel 3 times daily for 6 weeks (NCT03180528).[50] Tumor diameter decreased by more than 30% in 69.7% of lesions, and histological resolution was observed in 54.8%. The treatment was well tolerated, with only localized skin reactions. Immunohistochemistry showed increased histone H3 phosphorylation, decreased Ki-67 staining, and reduced GLI1 expression, indicating suppression of cellular proliferation.

### *Difluoromethylornithine*

Difluoromethylornithine (DFMO) inhibits ornithine decarboxylase (ODC), reducing polyamine concentrations and preventing neoplasms. UV irradiation induces ODC activity, promoting epithelial tumorigenesis. In a trial of 291 patients with prior NMSC, oral DFMO (0.5 g/m$^2$ daily) for 4 to 5 years significantly reduced new BCC development, although overall NMSC incidence was unchanged. AEs included nausea, diarrhea, and hearing loss.[51]

### *Nicotinamide (Vitamin B3)*

Nicotinamide is a precursor of nicotinamide adenine dinucleotide, a cofactor for ATP production. It prevents UV-induced ATP depletion, enhances DNA repair, and reduces immunosuppression, preserving the skin's antitumor immune response.[52] In an RCT of 386 participants with at least 2 prior NMSC, nicotinamide 500 mg twice daily for 12 months reduced new NMSC by 23% and new BCC by 20%, with no significant AEs.[52] Another RCT in renal transplant patients (n = 22) showed that nicotinamide 500 mg twice daily reduced the 6-month BCC rate (0.6 versus 1.9 in placebo) without major safety concerns (ACTRN12612000628842).[53]

### *Acitretin (Vitamin A)*

Acitretin is a retinoid used for various skin disorders, including anogenital warts, HPV-associated lesions, and skin carcinomas such as BCC.[72] Retinoids modulate gene expression via retinoic acid receptors and retinoid X receptors, which function as dimers binding to specific DNA sequences (retinoid response elements) in gene promoters, thereby directly affecting transcription.[54] In a summary of 4 case reports of patients with BCC who refused surgery, combination therapy with topical retinoic acid 0.1% cream twice daily and oral acitretin 0.4 to 1 mg/kg daily resulted in successful outcomes with no severe AEs and no BCC recurrence on follow-up.[72] Acitretin has demonstrated synergistic effects when combined with imiquimod or interferon-α (IFN-α). These combinations enhance induction of IFN-α–stimulated genes, including 2′-5′-oligoadenylate synthetase and protein kinase R, which regulate the transformed phenotype of cancer cells. Co-administration with IFN-α also upregulates STAT1, a cytoplasmic transcription factor in IFN signaling, triggering anti-proliferative and pro-apoptotic responses in tumor cells.[54] Case reports support these findings: a 48-year-old woman with 4 clusters of sBCC on the scalp treated with topical imiquimod 5% cream plus oral acitretin 25 mg daily for 16 weeks achieved complete histological clearance. Subsequent monotherapy with imiquimod alone resulted in residual BCC. Another report described 2 patients with BCC greater than 5 cm treated with oral acitretin and topical imiquimod, demonstrating tumor mass reduction.[73]

### *Ascorbic Acid (Vitamin C)*

Ascorbic acid is primarily recognized as an antioxidant. At high doses, it can generate intracellular hydrogen peroxide, selectively inducing cytotoxicity in cancer cells while sparing normal cells.[74] In 1 study, 6 patients with 7 BCC lesions (1 nBCC and 6 sBCC) applied a topical solution of saturated ascorbic acid once daily. One sBCC resolved after 13 weeks, while 1 nBCC and 2 sBCC resolved after 22 weeks. One patient who was histologically tumor-free post-treatment experienced tumor recurrence within an 18-month follow-up period.[74] Another study treated 25 patients with 29 biopsy-confirmed BCC lesions using either topical ascorbic acid twice daily or topical imiquimod for 8 weeks. Complete resolution was observed in 86.7% of lesions in the ascorbic acid group versus 57.1% in the imiquimod group.[75] A pilot study of 4 patients with locally advanced BCC received intravenous ascorbic acid 1 to 3 times per week, resulting in partial or stable response in 83% of lesions, while 17% showed progression.[76]

### *Vitamin D*

Vitamin D has been investigated for its potential protective effects against various cancers, but its role in skin cancer prevention remains inconclusive and sometimes conflicting. Its mechanisms involve interactions with the vitamin D receptor and peroxisome proliferator-activated receptor signaling pathways, which influence apoptosis, tumor promotion, and other cellular functions.[77] A recent meta-analysis found that each 30 nmol/L increase in serum 25(OH)-$D_3$ was associated with a 41% higher risk of developing BCC, although these results may have been confounded by sun exposure.[55] A prospective study of patients with BCC suggested that lower serum vitamin D levels correlated with higher initial BCC frequency and increased recurrence risk. Replacement therapy to increase vitamin D levels was associated with a significant reduction in recurrence. Maintaining serum vitamin D above 25 ng/mL also correlated with decreased BCC recurrence rates.[56]

### *Selenium*

Selenium is a trace element incorporated into the enzyme glutathione peroxidase. This enzyme, in conjunction with reduced glutathione, neutralizes reactive peroxides and helps prevent UV-induced cellular damage.[78] RCTs have evaluated selenium supplementation for BCC prevention. One RCT of 1312 patients with a history of BCC or SCC compared oral selenium 200 µg daily with placebo. No significant difference was observed in BCC incidence, although there was a noted association with the risk of developing new BCC.[57] Another RCT of 424 patients randomized to selenium 400 µg/day or placebo also found no significant effect on BCC prevention.[58]

## Exotic or Unconventional Potential Treatments

### *Melittin*

Melittin, a peptide derived from honeybee (Apis florea) venom, exhibits anticoagulant activity, lowers blood pressure, and triggers histamine release. Bee venom also contains enzymes, including phospholipase A, hyaluronidase, and lecithinase, and peptides such as apamin and peptide 401, which have anti-inflammatory properties. Melittin has demonstrated anticancer activity through multiple mechanisms, including cell-cycle arrest, inhibition of neovascularization, downregulation of cholesterol pathways disrupting cell membrane synthesis, and induction of apoptosis via death receptor regulation and STAT3 pathway inhibition.[59] A case report described a 65-year-old woman with recurrent sBCC treated with 0.3 mL honeybee venom injection and 2% topical bee venom ointment. Complete clearance of malignant lesions was observed 1 month after the first injection, with no recurrence over a 3-year follow-up.[59]

### *Cashew Nut Extract*

Cashew nut extracts contain bioactive compounds, including cardanol, anacardic acid, and methylcardol, which inhibit mitosis via spindle disruption, thereby suppressing cell proliferation.[60,61] In an RCT of 16 patients with 36 facial BCC lesions, topical cashew nut extract applied 7 times over 1–2 weeks achieved 100% clinical remission, with no recurrences detected over a 5-year follow-up.[60] Another clinical study involving 919 patients treated with either cashew nut extract cream or vehicle for 8 weeks showed significant clinical clearance but no histological clearance with the extract. Localized cutaneous reactions were more frequent in the experimental group, and 2 patients experienced recurrence despite initial clinical response.[60]

### *N-Phosphonacetyl-L-Aspartate*

N-Phosphonacetyl-L-Aspartate (PALA) is a potent and specific inhibitor of the enzyme complex carbamoyl phosphate synthetase II/aspartate transcarbamylase/dihydroorotase, which catalyzes early steps in pyrimidine nucleotide biosynthesis. Acting as a transition-state analog inhibitor of aspartate transcarbamylase, PALA effectively deprives cells of pyrimidine nucleotides, leading to cell death. A preclinical study in mice demonstrated that topical PALA reduced UV-B–induced tumor growth in a dose-dependent manner, with no observed toxicity at concentrations up to 5%. PALA was better tolerated than standard topical NMSC treatments, such as imiquimod and 5-fluorouracil.[62]

### *Sarcophine-Diol*

Sarcophine-diol (SD) is a structural derivative of sarcophine, a toxin released by certain marine organisms as a chemical defense. SD treatment during the promotion phase increased expression of caspase-3 and -8, suggesting induction of apoptosis via the extrinsic pathway. Treatment during both initiation and promotion phases significantly decreased COX-2 expression, which regulates prostaglandin $E_2$ production, a promoter of tumorigenesis, angiogenesis, and immune modulation.[79] In a preclinical study, 27 mice with UV-B–induced skin tumors were treated topically with SD, while 27 control mice received acetone. SD treatment increased caspase-3 and caspase-8 expression and reduced tumor multiplicity by 36% and tumor area by 72% compared with controls.[63]

### *Coffee*

Coffee, derived from the *Coffea* plant, has been shown in experimental studies to induce apoptosis in UV-damaged keratinocytes through multiple mechanisms.[65] Caffeine enhances UV-B–induced apoptosis via both p53-dependent and p53-independent pathways. The p53-independent pathway involves ataxia telangiectasia and Rad3-related (ATR) kinase–mediated phosphorylation of checkpoint kinase 1 (Chk1), which normally decreases cyclin B1 to regulate mitosis. Caffeine inhibits ATR, preventing Chk1 phosphorylation and causing premature, lethal mitosis in damaged skin cells.[64] A meta-analysis of 37 627 NMSC cases across 13 studies found that caffeinated coffee consumption was associated with a reduced risk of NMSC (summary relative risk [SRR] 0.82; 95% CI, 0.75–0.89), as was caffeine intake alone (SRR 0.86; 95% CI, 0.80–0.91). These protective effects were primarily observed for BCC. No significant association was found for decaffeinated coffee or tea intake. Although these findings suggest that caffeine-containing coffee may offer moderate protection against BCC development, they are based on observational studies. RCTs are needed to confirm these results.[65]

### *Calcium Electroporation*

Calcium electroporation is an experimental anticancer therapy in which brief electrical pulses are applied to the cell membrane, increasing permeability and allowing high concentrations of calcium to enter the cell, ultimately inducing apoptosis.[66] In vitro studies demonstrate that calcium electroporation effectively induces cell death, while in vivo studies show tumor necrosis. Currently, only a proof-of-concept study has investigated calcium electroporation for the treatment of BCC. Further research, including clinical trials, is needed to establish safety, efficacy, and optimal treatment parameters.

## Conclusion

A variety of rare and experimental nonsurgical treatments have been explored for BCC. Dermatologists should consider patient-specific factors, such as contraindications to standard therapies or BCCs in cosmetically sensitive areas, when selecting the most appropri-

ate treatment. This review summarizes the mechanisms of action, potential efficacy, and AEs of alternative remedies for BCC. Although preclinical studies, case reports, and clinical trials have demonstrated some clinical responses or markers of reduced photodamage, the evidence is generally inconsistent and insufficient to replace established standard therapies. Some treatments also carry the risk of unintended tissue damage. Certain compounds show particular promise. SRGs selectively target glycoproteins on cancer cells to induce apoptosis. Studies involving topical formulations containing these glycosides have demonstrated efficacy in treating AK and some cases of BCC. However, additional clinical trials are necessary to confirm efficacy in humans and to establish evidence-based guidelines for the safe and effective use of alternative treatments for BCC.

## Potential conflicts of interest

The authors declare no conflicts of interest.

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