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Review Article

# Molecular Mechanisms of Polyphenols in Skin Cancer Therapy: Advances and Future Perspectives

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## ABSTRACT

Globally, skin cancer, including melanoma, basal cell carcinoma, and squamous cell carcinoma, is a significant health concern that requires the development of novel therapeutic strategies. Natural remedies and polyphenols are being studied as potential therapeutics for skin cancer. The chemopreventive properties of phytocompounds and polyphenols against skin cancer metastasis are discussed in this study. Polyphenols such as anthocyanins, EGCG, punicalagin, quercetin, resveratrol, and theaflavin have chemopreventive properties and are primarily studied for their treatment of melanoma. This review also discusses recent advancements in understanding the molecular mechanisms behind the anticancer properties of natural compounds, specifically polyphenols. These effects are caused by changes in pathways such as EGFR/MAPK, mTOR/PI3K/Akt, JAK/STAT, FAK/RTK2, PGE-2/VEGF, and PGE-1/ERK/HIF-1α. These changes are also influenced by signals such as NF-κB, Bim, Bax, Bcl-2, Bcl-x, Bim, Puma, Noxa, ILs, and MMPs. This study focuses on how these factors can impact crucial signaling pathways such as oxidative stress, proliferation, apoptosis, and inflammation linked to cancer development. The study explores the potential of polyphenols in conjunction with traditional treatments to enhance patient outcomes and minimize side effects. Polyphenols' chemopreventive actions against skin carcinogenesis and metastasis, involving numerous signaling pathways, indicate their potential for developing new anti-skin cancer therapeutic approaches. Future research should focus on preclinical and clinical studies to validate the efficacy and safety of natural remedies and polyphenols in combating skin cancer.



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## Table of Content

## 1. Introduction

Skin cancer is a fatal disease and a significant global public health concern that has caused considerable economic and human devastation worldwide [1]. A variety of environmental and internal factors can trigger the development of skin cancer and exacerbate the condition [2]. Skin cancer arises from several mutations in genes associated with cancer, such as proto-oncogenes and tumor suppressors, within skin cells. These mutations disrupt the normal balance of cell regulation and lead to the abnormal growth of skin cells [3]. Melanoma and keratinocyte skin cancer are prevalent in white-skinned cultures, with global prevalence increasing due to increased UV radiation exposure, particularly in basal and squamous cell carcinomas. Melanoma incidence is rising among white populations, with a 3-7% annual growth rate. Mortality rates have stabilized in the US, Australia, and European countries, with a decline in deaths in the US. However, occurrence rates continue to increase in most European countries and the US [4]. Malignant

melanoma is the most aggressive skin cancer, responsible for 65% of skin cancer-related deaths, affecting one in 56 males and one in 37 females globally. Melanoma can occur in various locations, but is responsible for over 90% of diagnoses. There is variation in incidence worldwide, with Australian patients having the highest rates. The highest incidence occurs in fair-skinned individuals and areas with intense sun exposure. European populations have a lower incidence, but geographical location favors southern Europeans [5]. Melanoma is a skin cancer caused by the interaction between melanocytes, keratinocytes, and the surrounding environment. Melanocytes secrete growth factors and are regulated by keratinocytes. They are facilitated by integrin proteins in the microenvironment. Melanoma tumors often involve local lymph nodes and lymphatic arteries, with blood vascular metastases having a worse prognosis. Early identification and excision of affected lymph nodes are crucial for melanoma management. Melanocytic nevi, benign collections of melanocytes, can be categorized as common or dysplastic [6]. Keratinocytes in the skin produce vitamin D and convert it into active metabolites, specifically 1,25(OH)2D. They have the vitamin D receptor (VDR) to respond to this. Vitamin D affects skin functions such as cell growth prevention, cell specialization, defense mechanisms, hair growth, and tumor development. Coregulator complexes, including DRIP, SRC, Hairless, and β-catenin, regulate these actions [7]. Skin inflammation is triggered by various factors, involving cells, molecules, and immune responses, which can interfere with homeostatic processes such as immune response, angiogenesis, and apoptosis. Inflammatory skin disorders often arise from the overexpression of pro-inflammatory cytokines such as interferons and interleukins, activating T helper cells and potentially leading to a chronic condition [8]. The nuclear factor kappa B (NF-κB), a light-chain enhancer of activated B cells, induces inflammation and activates signaling pathways in the formation of skin cancer [9,10]. Research on inflammation-causing substances *in in vivo* and *in vitro* organisms has identified tumor necrosis factor-alpha (TNF-α), transforming growth factor-beta (TGF-β), interleukins 6, 17, and 23, matrix metalloproteinases (MMPs) 2 and 9, furin, and cathepsin in skin cancer cell growth, survival, and metastasis [11,12]. Studies on animals reveal that suppressing the inflammatory response, specifically lowering cyclooxygenase-2 (COX-2) levels, can reduce the rate of UVB-induced cancer development [13]. Skin cancer prevention can be obtained through various strategies, including primary and secondary approaches. The primary prevention technique's purpose is to alter individual behavior and mindset to minimize sun exposure and discourage excessive sun tanning. Secondary prevention strategies focus on early diagnosis and identification [14,15]. Thus, the natural remedies and polyphenols used for treating skin cancer are discussed.

## 2. Pathophysiology of Skin Cancer

The causes of skin cancer (**Figure 1**) are complex. UVR from sunlight is the main cause of the etiology of malignant melanoma and NMSC [16]. UVA and UVB are primary forms of ultraviolet radiation, with UVA rays deeper into the skin, making them more susceptible to serious skin conditions like elastosis [17]. UVB radiation frequently causes erythema or sunburn. UVR exposure dramatically accelerates the development of skin cancer and photoaging by causing DNA damage, gene alterations, immune suppression, oxidative stress (OS), and inflammatory responses [16,18]. DNA is damaged directly by UVB radiation. Through the generation of free radicals and harm to cellular membranes, UVA rays indirectly damage DNA [16,18]. Researchers suggest a relationship between UVR-induced immunosuppression and skin cancer development, as UVR promotes tumor growth and induces mutations in tumor suppressor genes [19]. While UVA photons play a substantial role in the carcinogenesis of epidermal stem cells, UVB rays damage DNA through tumorigenesis and inflammatory

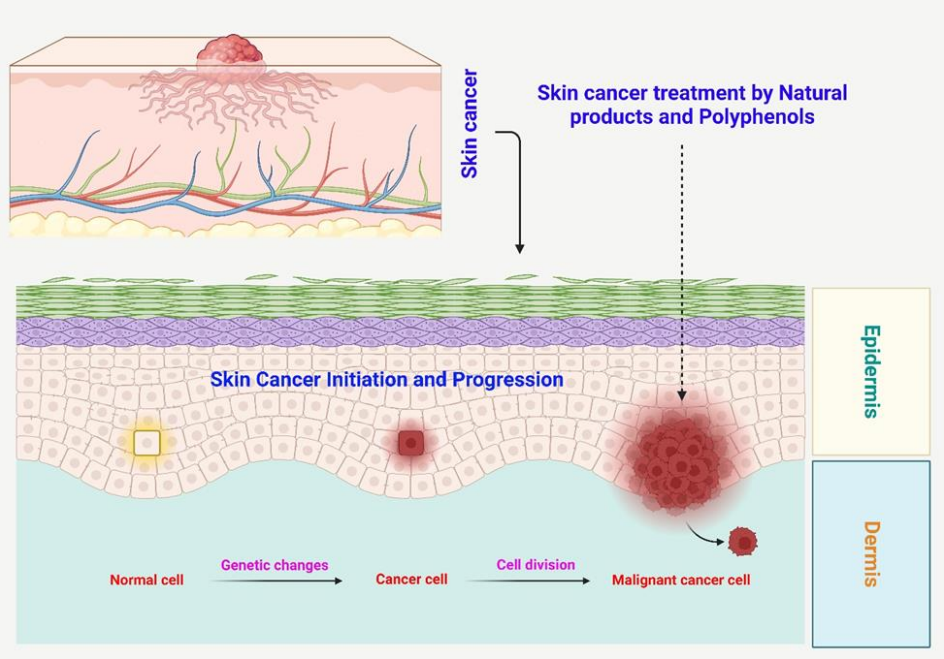


**Figure 1.** Influential factors driving the initiation and progression of skin cancer, UV radiation, DNA damage, oxidative stress, immune suppression, and genetic mutations (p53 and proto-oncogenes)

responses [16,20,21]. The DNA of epidermal keratinocytes absorbs a large portion of the UVR energy that penetrates the skin. The first molecular event resulting in immunological suppression is the formation of UVR-induced cyclobutane pyrimidine dimers, which are hypothesized to serve as the skin's photoreceptor [19]. The numerous and complex pathways of UVR-induced damage lead to skin cancer. UVR causes mutations in the p53 suppressor of tumors gene, which is involved in repairing DNA or in the cell death of DNA-damaged cells (apoptosis) [19]. Therefore, when the p53 gene is altered, it loses its ability to support DNA repair [17,19]. Skin cancer is caused by apoptotic dysregulation, unregulated keratinocyte mitosis, and the genetic capacity to metabolize free radicals. Glutathione S-transferase (GST) enzymes reduce the toxicity of UVR-induced free radicals, which are widely expressed in the skin. Deletion of the Glutathione S-transferase polymorphisms (GSTP) gene increases skin tumor susceptibility [22].

## 3. Skin Cancers

### *3.1. Melanoma*

The least frequent kind of skin cancer, melanoma, accounts for 2% of all skin lesions that have been diagnosed. The prevalence of melanoma is widely recognized since it is a malignancy that must be reported. In 2019, the US was expected to have 96,480 new diagnosis of invasive melanoma, and 7,230 people would pass away from the condition [23]. Melanoma affects more than a million Americans today [24]. In Queensland, Australia, there were 71 cases per 100,000 people between 2009 and 2013, which is much higher than anywhere else in the world. Melanoma is most common in Australia and New Zealand. Early-stage melanomas are known as "melanoma *in situ*" (MIS). Being contained in the epidermis limits the ability of the cells to spread at this stage. The treatment of MIS and primary cutaneous melanoma with broad margins of 0.5-2 cm is effective [25]. Primary melanoma is well treated surgically, with low metastatic spread,

and thin melanoma is less frequently treated with topical medications than *in situ*, in transit lesions, conditions or precancerous [26,27].

### *3.2. Basal cell carcinoma*

Basal cell carcinoma (BCC) is the most common type of cancer and is on the rise [28]. BCCs can have a significant morbidity despite having a low death rate, mostly because of local damage [29]. Keratinocyte carcinoma, the most common form of skin cancer, accounts for 80% of cases in clinics. According to estimates [30], approximately 4.3 million cases are found in the country each year. Age-standardized incidence rates for BCC were reported to be 770 per 100,000 person-years in a recent Australian research [31]. BCC most commonly affects middle-aged or older people's hands and faces. Follicle stem cells in the epidermis are the main source of BCC, and UV exposure is a major factor in its growth [32]. The most prevalent genetic changes influencing the development of BCC are those found in the genes encoding the tumor protein 53 (TP53) or patched homologue 1 (PTCH1), which have shown to be mutated in 70% and 60% of cases, respectively [32]. A study confirms that prolonged UV exposure, particularly on sun-exposed skin, leads to BCC growth [33].

### *3.3. Squamous cell cancer of the skin*

Squamous cell carcinoma (SCC) is the second most common type of cancer [34]. SCC is associated with severe morbidity, ulceration, deformity, and a mortality rate comparable to melanoma, especially in solid organ transplant recipients [35-37]. Chemotherapy, targeted therapy, and immunotherapy are used for metastatic and unresectable cancer, while surgery and radiation are the primary treatments for localized cancer in SCC [37-40]. Squamous cell carcinoma accounts for 20% of keratinocyte cancer cases, with 3-7% of patients developing metastases and over 70% dying from the disease [41]. The exact prevalence of cSCC and BCC in the population remains unclear [42]. In the U.S., there are about 1 million cases and over 15,000 fatalities per year [30]. Actinic keratosis or sun keratoses are precancerous lesions that can progress into cSCC [14]. Actinic keratosis affects sun-exposed body parts, and is classified as a premalignant lesion that may progress into cSCC or a continuum [43-45]. Some publications [46] have reported malignant conversion rates of up to 10%, despite the fact that other sources [47] have provided far lower percentages. TP53 and the kinetochore localized astrin/SPAG5 binding protein (KNSTRN) gene are not exclusive to either condition, even though they are often mutated in both actinic keratosis and cSCC [48]. UV radiation is the primary cause of actinic keratosis and cSCC, with the head and neck being the most susceptible areas [16,49]. The majority of cSCCs can be treated with radiation and surgery unless high-risk features are present [50]. Patients with cisplatin-resistant cancer have the best chance of recovery with platinum-based therapy; however, additional clinical trials are required to determine the most effective treatment strategies, particularly for older patients who are unable to receive cisplatin chemotherapy [51].

## 4. Antioxidant Defenses for the Skin

UV rays are exposed to the epidermal keratinocytes. The epidermis absorbs the majority of UVB light (280–320 nm), and epidermal damage can result in sunburns, early aging of the skin, and even skin cancer [52]. UVB exposure causes skin damage due to oxidative stress, primarily caused by the production of reactive oxygen species (ROS), such as hydrogen peroxide and superoxide anion [53]. Excessive UV radiation can disrupt the skin's antioxidant defense system, causing immunotoxicity, oxidative damage, premature skin aging, and skin cancer, as biological antioxidants inhibit substrate oxidation [54]. Antioxidant activities reduce malignant transformation, DNA damage, oxidative stress, and cancer prevalence. They reduce ROS effects, preventing or reversing processes that cause epidermal damage and disease. Increased free radical activity may accelerate skin cancer

and other cutaneous diseases. There are two types of antioxidant defenses: those that inhibit the production of ROS and those that scavenge any external radicals [55]. Cells have defensive mechanisms, either enzymatic or nonenzymatic, and natural antioxidants help repair systems flush out harmful biomolecules before they compromise cell viability or metabolism [55]. The skin is protected by an antioxidant network, including low-molecular-weight antioxidants such as glutathione peroxidase and vitamin E isoforms, as well as water-soluble antioxidants such as glucose and bilirubin [56]. Lipids such as ubiquinol-10, α-tocopherol, carotene, lycopene, and lutein are antioxidants found in the skin's epidermis, with higher content typically found in the dermis [57,58]. Tocopherol is the most prominent antioxidant in the lipophilic phase, while vitamin C and GSH are equally abundant. Uric acid, L-ascorbic acid, and GSH are the most common antioxidants in human skin [59]. The study investigates the impact of antioxidants on the epidermis and dermis of hairless mice, both enzymatically and non-enzymatically [56]. The epidermis contains more antioxidants than the dermis, such as lipophilic alpha-tocopherol and ubiquinol 9, and hydrophilic glutathione, ascorbic acid, and vitamins C and E [60]. The irregular dispersion of antioxidants on the skin's surface is likely caused by increased oxygen partial pressure in the upper layer, leading to OS and a decrease in antioxidant levels. The skin has an effective defensive mechanism, which includes manganese-superoxide dismutase, in addition to all the required antioxidant enzymes [61]. Frequent UVA exposure increases MnSOD induction, aiding skin adaptive UVA response during light hardening in phototherapy. Acute UV exposures alter glutathione reductase and catalase activities [62]. Photodamage, both chronic and acute, is primarily mediated by increased oxidative protein changes and reduced antioxidant enzyme expression [63]. Flavonoids possess antioxidant, anti-tumor, carcinogenic, mutagenic, antibacterial, antiviral, and anti-inflammatory properties, acting as reducing agents, hydrogen donors, and regulators of oxidative chain reactions [64].

## 5. Antioxidants' Role in Reducing ROS Production and Preventing Skin Cancer

Skin cancer is a condition characterized by abnormal cell growth, known as carcinogenesis, which can spread to other parts of the body [65]. The innate skin defenses against UVR, including melanin and enzymatic antioxidants, as well as dietary antioxidants such as vitamins A, C, and E, are crucial for maintaining oxidative equilibrium. UV radiation affects skin antioxidants, leading to depletion of ascorbate, GSH, SOD, catalase, and ubiquinol. UVR-induced damage includes ROS generation and depletion of natural antioxidant systems [66]. Antioxidants in the dermis and epidermis of hairless mice were studied [56] along with their responses to UV radiation. Superoxide dismutase, dermal, and epidermal catalase activity were significantly reduced following radiation exposure. The levels of tocopherol, ascorbic acid, dehydroascorbic acid, reduced glutathione, ubiquinol-9, and ubiquinone-9 dropped by 26–93% in both the epidermis and dermis. The amount of oxidized glutathione rose, although not significantly. Numerous studies have confirmed that pretreatment with antioxidants can prevent cellular macromolecule oxidation caused by *in vivo* exposure to UVR in human skin. Research has been conducted on various antioxidants or combinations of antioxidants and other phytochemicals to prove their effectiveness against ROS-induced damage. The exogenous antioxidants affecting the advantages of avoiding damage or photoaging have been reported by Pandel *et al.* [67] and Poljsak *et al.* [68].

## 6. Natural Sources of Anti-Cancer Compounds

Cancer is a major global concern, with 14 million new cases reported in 2012 and an estimated 22 million over the next 20 years [69]. A study emphasizes the ongoing need for

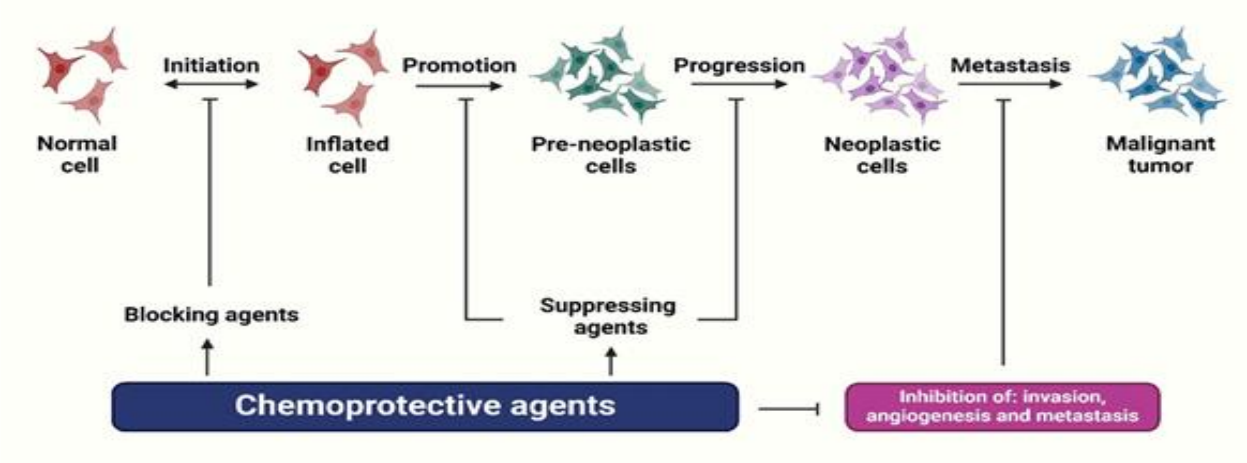


**Figure 2.** Exploring the anticancer potential of chemoprotective agents, natural compounds from plants, marine, and microbial sources, targeting proliferation, apoptosis, angiogenesis, and metastasis pathways

cancer therapy, highlighting the potential of natural chemicals (**Figure 2**) as a valuable resource for developing antiproliferative medicines [70]. Numerous natural resources globally are available for medical use, but many have not been fully utilized in the pharmaceutical sector. Over 50% of marketed medications, including 70% of anti-cancer medications, originate from natural sources such as microbes, plants, animals, and marine life [71]. VAs, first-class mitotic inhibitors, are used in cancer therapy as tubulin-targeting drugs. They may inhibit malignant angiogenesis and tumor growth [72].

### *6.1. Plant sources*

Skin cancer is primarily caused by proto-oncogene and cancer suppressor mutations in skin cells, resulting in cell imbalance and uncontrolled cutaneous cell development [73]. Skin cancer is the most prevalent type of cancer globally, causing more frequent fatalities than other diseases [1]. Most clinical medications worldwide are derived from plant-based chemicals [74]. The National Cancer Institute (NCI) initiated a plant collection program in 1960 to accelerate the search for plant-based anti-cancer therapies [75].

During this period, numerous cytotoxic medications were developed using plant extracts, but only a few were sold for medicinal purposes, taking over 20 years to convert [71,75,76]. Vinca alkaloids, such as vincristine, vinblastine, and vinorelbine, were anti-cancer medications approved, followed by podophyllotoxin derivatives such as paclitaxel, docetaxel, irinotecan, topotecan, etoposide, and teniposide [75,77]. Vinca alkaloids destroy dividing cells and prevent the formation of the mitotic spindle by interacting with tubulin [77]. Taxanes stabilize microtubules, preventing an imbalance between tubulin and microtubules, leading to cell death. Camptothecins and podophyllotoxins affect cell division, inhibiting topoisomerase I in different ways [71]. *Viscum album* L. is being investigated for its potential to treat advanced breast, non-small cell lung, advanced pancreatic, and metastatic colorectal cancer. Gemcitabine and the entire extract of *V. album* L. have been proven to be effective in a combination study [78]. A phase II clinical investigation has reported that green tea extract, polyphenol, has successfully treated chronic lymphocytic leukemia. Patients quickly absorbed this green tea extract, and it was commonly effective [79]. Berberine was found to decrease tumor development in human melanoma cells and mice when combined with

doxorubicin *in vitro* and *in vivo* studies [80]. *Tilia amurensis* and *Camellia sinensis* extracts are cytotoxic to skin cancer cell lines *in vitro* [81,82]. Research on phytochemicals such as apigenin and epigallocatechin-3-gallate is being conducted to understand their potential negative impact on melanoma and epidermoid carcinoma cells [83,84]. Millions worldwide are diagnosed with skin cancer annually, leading to the development of synthetic anticancer medications. Natural remedies, despite higher costs and severe side effects, remain popular [85].

### *6.2. Marine sources*

Marine flora and fauna have the potential to produce new therapeutic compounds with potent anti-tumor properties [71]. Extracts from sponges, algae, and marine cyanobacteria have anticancer properties [86-88]. Laminarans, carrageenans, alginic acids, fucoidans, and other marine compounds have all been shown to possess effective anticancer properties. The polysaccharides produced by bacteria, fungi, and marine organisms can prevent cancer growth [86]. Despite numerous marine-derived anti-cancer compounds being identified, evaluated, and tested, only four of these drugs have been released onto the market. Anticancer drugs such as cytarabine, trabectedin, eribulin mesylate, and brentuximab vedotin are derived from Cryptotethia crypta, Halichondria okadai, and Symploca hydnoides bacteria [89,90]. Cytarabine, a chemical that promotes apoptosis, also inhibits the proliferation of cancerous cells. Cytarabine, the first marine drug, was approved by the FDA in 1998 for clinical use in treating acute myelogenous leukemia. The European Commission approved trabectedin in 2007 for metastatic soft tissue cancer treatment, and in 2009, it was added to the list for platinum-sensitive ovarian cancer relapse treatment. In 2010, the FDA approved eribulin mesylate as a third-line therapy for metastatic breast cancer [90]. In 2011, the FDA approved brentuximab vedotin for Hodgkin's disease and anaplastic large cell lymphoma treatment, among four other anti-cancer drugs that have undergone clinical testing. Marine-derived compounds such as Bryostatin-1, aplidin, zalypsis, and salinosporamide are being investigated in clinical studies for potential use as anti-cancer drugs [91]. Preclinical studies are being conducted on other substances found in water that may be used to treat cancer [88,92]. The extracts exhibit anticancer properties, requiring further investigation into their transduction routes and molecular targets [93].

### *6.3. Microbial sources*

Ulcer-causing skin cancers require healing after local excision, and a lesion that ulcerates and spreads to multiple sites may indicate various malignant cancers [94-96]. The individual observed that unintentionally acquired *Streptococcus pyogenes* tumors in individuals had worsened [97]. The discovery of bacterial infection-induced regression led to the development of cancer immunotherapy, involving studies on microbes to determine their anti-neoplastic properties. Microbes are a significant source of chemically diverse, produced and fermented with therapeutic potential [71]. Microorganisms are used in the production of anticancer drugs such as anthracyclines, bleomycins, staurosporins, and actinomycins [71,91]. Bacteria can enhance immunological responses, but they may also cause negative effects that can be mitigated by utilizing bacteria-derived products. The use of bacterial spores, microbes, and toxins as gene therapy delivery vehicles is studied. Microbes producing poisons that kill tumor-proliferating cells may potentially benefit humans [98]. It describes the typical microorganisms in skin cancers with ulcerative lesions, suggesting that pathogenic germs may increase post-surgical complications [99].

## 7. Medicinal Plants for Preventing Melanoma

### *7.1. Phyllanthus emblica*

Amalaki is a crucial and frequently used herb in Ayurvedic medicine. Amalaki, also known as

*Emblica officinalis*, is a member of the Euphorbiaceae family and is beneficial for treating and curing human diseases due to its phytochemical components [100]. *Phyllanthus emblica* is a plant that is commonly grown in China, Southeast Asia, Sri Lanka, Nepal, and India [101]. The terms "Indian gooseberry" and "Amalaki" are also used to refer to it in Ayurveda. Another name for it is "the King of Rasayana." The fruit of this plant is traditionally used in Chinese and Indian Ayurvedic medicine to treat various diseases such as dyspepsia, bleeding, anemia, diarrhea, and eye and lung inflammation. Amla is a major component in the traditional remedy "Chyvanaprash," which is effective in treating eye conditions, asthma, anemia, and lung irritation. Amla is rich in minerals, vitamins, amino acids, flavonoids, phenolics, tannins, and vitamin C. Amla also has a number of health advantages, such as anti-ulcerogenic, antidiabetic, antibacterial, antioxidant, antimutagenic, and chemopreventive effects [101]. *P. emblica* functions as an anti-aging agent by reducing free radicals and UV-induced erythema [102]. Amla, a skin-lightening product, is used to treat scabies, itching, freckles, and age spots in Europe, the Middle East, and Asia [101,103,104]. Emblica, a major component of herbal medicine systems, holds numerous benefits and could potentially lead to a new era of healthcare in the coming decades [105].

### *7.2. Tinospora cordifolia*

*Tinospora cordifolia* is a popular plant in conventional medicine due to its spasmolytic, allergen-free, and anti-diabetic properties, which also enhance immunological function [106]. *T. cordifolia* is extensively found throughout South Asia, the Philippines, Bangladesh, China, and Sri Lanka. It is also known as "Amrita" or "Guduchi" in Ayurveda and is also referred to as the "heavenly elixir" [107]. *T. cordifolia* has been used in Ayurvedic and Chinese systems for treating various diseases such as skin disorders, fever, asthma, leprosy, and diabetes [106,108,109]. The substance contains various alkaloids, glycosides, sesquiterpenoids, hormones, phenolics, aliphatic compounds, and polysaccharides [110]. A study reveals its various properties, such as antibacterial, antioxidant, anti-inflammatory, immunomodulatory, antistress, antispasmodic, chemoprotective, radioprotective, neuroprotective, and hypoglycemic [111]. This treatment effectively addresses skin issues such as dark spots, zits, and acne, while also reducing the effects of aging [112]. *T. cordifolia* indicates its potential as a beneficial medication without any adverse or hazardous effects [106].

### *7.3. Azadirachta indica*

The neem tree has been utilized in Ayurvedic medicine for over 4,000 years due to its antiseptic, antiviral, antipyretic, inflammatory, and antiulcer properties [113]. The neem plant is used in Ayurveda, Unani, and homeopathic medical systems to treat various diseases such as blood, eye, persistent fever, malarial fever, leprosy, skin diseases, ulcers, and wounds. Neem possesses antifungal, anthelmintic, antibacterial, antiviral, antidiabetic, contraceptive, and sedative properties due to its alkaloids, flavonoids, glycosides, and amino acids [114]. The bioactive neem compounds nimbolide and azadirachtin have been proven to aid in cancer management through their anticancer and antioxidant properties [115]. *Azadirachta indica* protects the skin from harmful UV radiation, chemical pollutants, skin conditions, and wounds [116-118].

### *7.4. Withania somnifera*

*Withania somnifera* (Ashwagandha) has been used as a herbal remedy since its development around 6000 B.C [119]. *W. somnifera* is used to treat ulcers, rheumatic swelling, inflammation, discomfort, constipation, and backaches through its root infusion [119,120]. Additionally, its roots have sedative, aphrodisiac, and nerve tonic properties. It exhibits immunomodulatory, anti-arthritis, antioxidant, anticancer, and neuroprotective activities due to the presence of steroidal

alkaloids and steroidal lactones [121]. *W. somnifera* has an anticancer impact against human and mouse cancers of the colon, prostate, blood, lung, breast, pancreas, kidney, and head and neck [122,123]. The pharmacological effects of Ashwagandha are primarily attributed to withanolides withaferin A and withanolide D, but there is limited research supporting its clinical use for various cancer treatments [124]. Ashwagandha is beneficial for the skin as it regenerates natural oils and produces hyaluronan, elastin, and collagen, providing moisture, suppleness, and strength [125,126]. *W. somnifera* has a wide range of cytotoxic and anticancer properties, and is a promising option for advanced cancer treatment [119].

### *7.5. Ocimum tenuiflorum*

*Ocimum tenuiflorum* is a globally grown plant, particularly in Eastern Asia, Africa, China, and America [127]. Basil, a major ingredient in Ayurveda, is utilized to treat various diseases such as anxiety, coughing, asthma, diarrhea, malaria, fever, arthritis, eye problems, UTIs, indigestion, vomiting, back pain, gastrointestinal disorders, and bug bites [128]. Tulsi, rich in nutrients including fatty acids, sitosterol, eugenol, and apigenin, has active ingredients such as eugenol, ursolic acid, linalool, and isoeugenol. These compounds can reduce UV radiation and the dermatoxic effects of xenobiotics, aiding in skin infections [129]. Tulsi also protects against blackheads and treats wounds and fungal diseases on the skin [130]. A study investigated the potential of four solvent extracts from *Ocimum tenuiflorum* for treating malignant melanoma. Four crude extracts were prepared and tested on the A375 cell line. Results showed high cytotoxic potential against the cells, with $IC_{50}$ values below 50 µg/mL. The extracts caused late apoptosis in 44.2 ± 2.54%, 73.6 ± 1.13%, and 67.4 ± 0.70% of A375 cells, respectively. The study suggests the potential for developing anticancer treatments targeting the A375 cell line [131].

## 8. Potential Polyphenols Used as Anti-Skin Cancer Agents

Research has demonstrated the efficacy of natural compounds such as polyphenols in treating and preventing diseases through various preclinical, clinical, and epidemiological studies [132]. Plant-derived substances such as anthocyanins, EGCG, and resveratrol have shown promising anticancer potential [133-137]. Polyphenols are a type of antioxidant found in fruits, vegetables, cereals, chocolate, olive oil, and beverages [138]. Preclinical studies have investigated the anticancer properties of resveratrol on various cancers, including skin, prostate, gastrointestinal, and lung [139]. The major inhibitory mechanisms of resveratrol in mouse skin cancer models include activating antioxidant systems, inducing apoptosis, suppressing inflammation, and controlling the cell cycle [140-144]. Resveratrol inhibited growth in DMBA-induced mammary tumors and xenograft breast cancer models by downregulating proliferation, angiogenesis, apoptosis, and modulating hormones such as estrogen and progesterone [145-149]. The primary anticancer mechanism of resveratrol involves the modification of genetic and epigenetic factors. This study suggests that resveratrol demethylates tumor suppressor genes to inhibit DNA methyltransferase activity in esophageal, gastric, and colorectal cancer cells [150]. Additionally, multiple clinical investigations have demonstrated the anticancer properties of resveratrol. Phase I trials reveal resveratrol reduces lymphoid and colon cancer development, requiring further clinical studies for full chemopreventive and therapeutic potential [139]. The use of polyphenols such as EGCG, their synthetic analogs, and prodrugs, has been confirmed as effective in cancer prevention and treatment [151-156]. Curcumin is known for its anti-inflammatory, antioxidant, and anticancer properties [157,158]. This compound has chemopreventive effects on various malignancies by stimulating apoptosis [158,159]. Curcumin-containing nanoparticles decrease cell viability and induce apoptosis,

exhibiting anti-metastatic properties in both *in vivo* and *in vitro* studies [160]. The molecular mechanism of biocompounds can significantly prevent skin cell carcinogenesis and metastasis [161]. Recent clinical and translational studies underscore the potential of polyphenols in skin cancer therapy while addressing their bioavailability limitations. Topical EGCG protects against UV-induced DNA damage and erythema, and curcumin-loaded nanoparticles enhance cutaneous penetration and reduce tumor burden. Resveratrol- and quercetin-based gels are being tested to slow the progression of actinic keratosis and photoaging, thereby lowering non-melanoma skin cancer risk. Clinical translation has been limited by poor oral bioavailability, rapid metabolism, and low dermal absorption; however, advances in nanocarriers, liposomes, micelles, and polymeric nanoparticles have improved solubility, skin permeation, and controlled release. Nanoformulated curcumin achieves higher tumor accumulation with reduced toxicity, while quercetin liposomes prolong dermal retention and photoprotection, bridging preclinical findings with clinical applications.

## 9. Polyphenols and Their Chemoprotective Activities

Polyphenols are used for the treatment of skin cancer through various mechanisms (**Table 1**). The chemical structures of polyphenols are shown in **Figure 3**. Polyphenols exhibit chemopreventive and therapeutic effects in both melanoma and non-melanoma skin cancers. Specifically, compounds such as resveratrol, quercetin, and EGCG have been extensively studied in melanoma models, while others like curcumin, silymarin, and proanthocyanidins demonstrate significant activity against non-melanoma types, including basal cell carcinoma and squamous cell carcinoma.

**Table 1.** The molecular targets and mechanisms of action. Lists of selected polyphenols in their mechanisms and molecular targets in skin protection

| Polyphenols | Source | Mechanism of action | Clinical Relevance | Ref. |
|---|---|---|---|---|
| Resveratrol | Grape skin | Inhibition of inflammation, $H_2O_2$, LPO, COX-2, and PGs. | Demonstrated chemopreventive effects in non-melanoma skin cancers; explored as an adjuvant for melanoma therapy | [141,143,162] |
| Catechin | Tea leaves | Inhibition of DNA damage | Provides photoprotection against UV-induced genotoxicity, reducing the risk of skin cancer initiation | [163,164] |
| Epigallocatechin gallate (EGCG) | Green tea | EGCG prevents β-catenin in skin cancer cells by inhibiting the levels of cAMP and PGE2. | Reduced UVB-induced skin damage; under evaluation for melanoma immunotherapy enhancement | [82] |
| Silymarin | Milk thistle | Inhibition of $H_2O_2$, LPO, NO, iNOS, and MPO | Effective in reducing OS and inflammation; topical formulations evaluated for chemoprevention of actinic keratosis and NMSC | [165,166] |
| Proanthocyanidin | Nuts and Grape seeds | Inhibition of $H_2O_2$, iNOS, LPO, and MPO | Protected against UV-induced OS and tumor promotion. | [167-169] |
| Apigenin | Tea and onions | Apigenin inhibits UVB-induced mTOR activation, cell proliferation, and cell cycle progression. | Demonstrated protective effects against UVB-induced skin carcinogenesis in preclinical models; potential topical preventive agent | [170] |

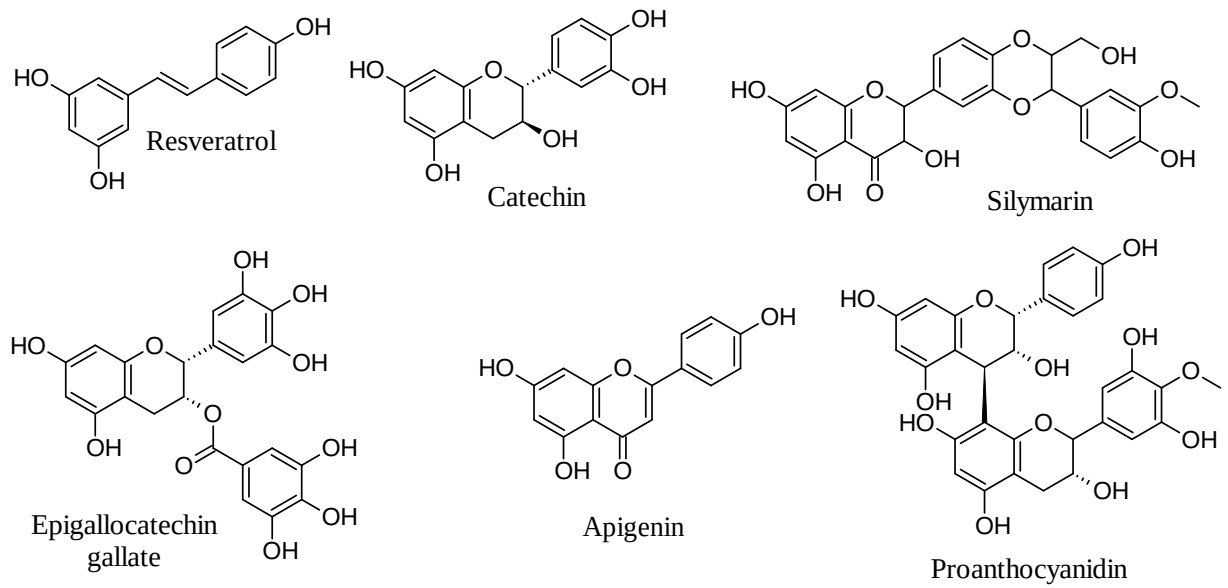


**Figure 3.** Chemical structures of polyphenols, including resveratrol, EGCG, Catechin, Silymarin, Proanthocyanidin, and Apigenin, with chemoprotective activity

### *9.1. Antiproliferative activities*

Melanoma has various stages. Surgery is a common treatment for early stages of the disease, alongside other therapies such as immuno-, biologic-, radio-, and chemotherapy [171-173]. The majority of these chemotherapeutic drugs have risky side effects that restrict their use [174,175]. The most lethal phases of melanoma are those with high metastasis rates and spread to areas where other cancers do not frequently affect people [174]. Cell proliferation is a biological process where cells continuously multiply over time, thereby increasing the overall number of cells [176]. Berries showed a dose-dependent inhibitory effect on the growth of human melanoma cell line (A375) tumor cells, with different heat treatment that induces cell multiplication [177]. The flavones tangeretin and baicalein, myricetin and gallic acid, and myricetin and gallic acid showed the most significant dose-dependent effects on cell proliferation [178]. Researchers found that black pomegranate peel extract inhibits B16-F10 melanoma cell growth in a dose-dependent manner, possibly due to its antioxidant activity and polyphenol content [179,180]. Curcumin significantly reduced the development of B16-F10 cells and the percentage of cells in the G1 phase [181]. A study investigated the non-cytotoxic effects of ethanolic extracts on melanocyte growth inhibition. The extract is found to be cytotoxic to healthy HaCaT skin cells and selectively inhibits the development of A375 melanoma cells. It has potential as an anti-melanoma drug, potentially reducing cell survival and proliferation [182].

### *9.2. Cytotoxic activities*

Skin cancer is caused by OS, which damages DNA through base damage, protein-DNA cross-linking, and single- and double-strand breaks [183]. Skin cancer chemotherapy aims to kill skin cancer cells, with a secondary goal of causing apoptosis to aid neighboring phagocytic cells in removing them quickly [184]. The efficacy of chemotherapy for skin cancer has been inconsistent due to inefficient systemic transport and absorption of these drugs [185]. The cytotoxic effect refers to the toxicity caused by chemotherapy medications on living cells [176]. Green tea polyphenols inhibit skin cancer cell proliferation by increasing the number of cancer-fighting $CD8^+$ cells [152]. A study

investigates the effects of blueberry fruit extracts on B16-F10 melanoma cells, finding anthocyanidins to be more cytotoxic. No significant difference in cell viability was observed. The extracts showed minimal to no cytotoxicity for normal cells and were highly effective *in vivo* inhibitors of B16-F10 metastatic murine melanoma cells [186]. Chrysin therapy effectively inhibited melanoma tumor development by 71% after 21 days, boosting macrophage, T lymphocyte, and natural killer (NK) cell cytotoxic activity. The effective anticancer effects of Chrysin in the mouse melanoma model suggest potential use in further anti-melanoma treatment, highlighting the importance of NK cells in tumor monitoring [187]. Resveratrol has anticancer activity [188]. A study investigated the cytotoxic effects of resveratrol on melanoma-derived DM738 and DM443 cell lines, revealing variations in effects based on dosage and duration. It selectively kills tumor cells at a concentration of 50 μM without cytotoxic effects on non-cancerous cell types [189]. Anthocyanin-enriched extract from elderberries showed anti-proliferative and anti-cancer properties, increasing total lactate dehydrogenase synthesis in B16-F10 murine melanoma cells, causing cytotoxic effects after 24 hours [190]. Honokiol significantly reduces melanoma cancer cells by lowering AKT/mammalian target of rapamycin and Notch signaling, and is currently being tested in clinical trials alongside standard chemotherapy regimens [191].

### *9.3. Cell cycle and apoptosis*

Apoptosis is a process involving metabolic changes that lead to cellular alterations, primarily affecting the cell membrane [192]. The cell cycle regulates cell division, growth, and proliferation after DNA damage, with apoptosis, or controlled cell death, being crucial for cancer prevention [193,194]. Polyphenols can induce melanoma cells to undergo apoptosis. The study investigated the impact of the natural flavonoid sanggenol on cell proliferation in murine melanoma cells, specifically SK-MEL-2, SK-MEL-28, and B16. Treatment with sanggenol significantly altered the morphology of the research cells and prevented cell division. This flavonoid was found to cause cell death in B16 and SK-MEL-2 cells in melanoma skin cancer [193]. Pomegranate polyphenols have been found to decrease tumor incidence in a mouse skin carcinogenesis model by inhibiting cell proliferation and promoting apoptosis [195]. The survival of A373, Hs294t, SK-Mel28, and SK-Mel 119 cells following exposure to green tea polyphenols is reported to be dose- and time-dependent [196]. Resveratrol significantly decreased B16F10 and B6 cell growth, while increasing B16F10 and A375 cell death [197]. The PI3K/AKT/mTOR axis is a crucial regulator of anthocyanins, autophagy, and cell death, as studied based on cyanidins [198]. The phosphorylation levels of AKT and mTOR in melanoma decreased due to their ability to induce apoptosis and decrease cell growth [190]. The concentrations of ellagic acid in three malignancy cell lines, 1205Lu, WM852c, and A375, have been determined. The treatment of A375 with gallic acid resulted in morphological changes and a decrease in the proportion of viable cells [199]. Gallic acid may have anti-carcinogenic properties due to its ability to cause apoptosis in a dose-dependent and time-dependent manner [200]. A study investigated the potential anticancer effects of caffeine on the human melanoma cell line SK-Mel-28. Caffeic acid treatment increased apoptosis-related cell death and reduced caspase gene expression, suggesting it may inhibit tumor growth in human melanoma cells [201]. Another study investigates the impact of quercetin on the cancer cells A375SM and A375P. It showed no effect on A375P cells, but it inhibited the growth and survival of A375SM cells and, in a dose-dependent manner, led to apoptosis. It also inhibits A375SM melanoma cell proliferation through apoptosis, reducing tumor size *in vivo* [202]. Consequently, this polyphenol is an effective melanoma therapy. Luteolin has potential anticancer treatment for human melanoma [203]. Polyphenols have the same effect on melanoma cell lines as the

majority of chemotherapeutic drugs, which qualifies them for use as chemoprophylactic agents [204]. Luteolin suppresses HaCaT and A375 cell development, induces cell cycle arrest, and has significant apoptotic potential against human skin cancers [205].

### *9.4. UV radiation defense*

The impact of UVR exposure on skin cancer development is still unclear, influenced by factors such as dose and time [206]. The importance of UVR exposure is highlighted by the fast-rising incidence of BCC, the most prevalent type of skin cancer [207]. Numerous polyphenols in food may protect skin from UV rays [208]. Green tea polyphenols have been proven to protect against UV-induced skin cancer and photodamage [209]. The flavanols in green tea protect against the negative effects of UV radiation, such as skin aging, lipid peroxidation, and erythema, whether consumed or administered topically [210]. Green tea polyphenols can protect the skin from UVB-induced inflammatory leukocytes by inhibiting systemic immunological suppression before sun exposure [211]. Additionally, green tea polyphenols protect human skin from OS, reduce cyclobutane pyrimidine production, and lessen the UVB-induced erythema response [163,212]. A study demonstrates UV absorption properties of polyphenols, their high molar extinction coefficients, and photoprotective properties, while estimating the sun protection factor of stilbenes, flavonoids, and certain hydroxycinnamic acid homologues. Resveratrol, kaempferol, and aigenin are the top flavonoids in terms of UVB defense, with resveratrol having a close to 20 SPF rating and kaempferol second with 24.9. Caffeine and caffeic acid are the hydroxycinnamic acid compounds with the highest SPF values. The study investigated whether polyphenols can be utilized as active ingredients in UV compositions due to their significant UVB protective properties [213]. UV light is one of the major causes of DNA deterioration. UV photons can cause DNA damage, particularly through the production of ROS, which can lead to reactive DNA changes. The two main techniques for DNA repair are base excision repair and nucleotide excision repair. Oxidized 8-oxoG and other small lesions that appear in seven steps are eliminated by base excision repair [214]. A study using a mouse photocarcinogenesis model showed that green tea polyphenols can protect against UV-induced DNA damage, reducing skin cancer incidence. Interleukin-2, a substance that stimulates DNA repair, has been found to act as a mediator in this effect [215].

### *9.5. Metastasis of cancer*

Melanoma is the most fatal type of skin cancer due to its spread [216]. Cell adhesion, invasion, and angiogenesis are phases in the tumor metastasis process [217]. The extracellular matrix (ECM) and basement membrane need to be damaged for a tumor to enter and spread throughout the body. Melanoma growth and dissemination are greatly influenced by tumor angiogenesis [218]. A study investigated the impact of anthocyanins from *Hibiscus sabdariffa* (HAs) on metastasis, aiming to demonstrate the limiting effect of polyphenols on melanoma malignancy. The HAs effectively inhibited tumor-driven angiogenesis, reducing migration *in vitro* and *in vivo*, by inhibiting factors such as tumor Ras, NF-κB, CD31, and VEGF/VEGF-R. HAs not only inhibited angiogenesis and cancer cell migration but also other processes that contribute to cancer cell growth [219]. Another study investigated the potential of various polyphenolic substances to prevent mice from developing lung metastases caused by B16F10 cancer cells. The use of oral catechin and curcumin treatment at specific doses resulted in an 80% reduction in lung metastases. Rutin, epicatechin, naringin, and naringenin have the same impact as polyphenols [220]. Furthermore, a study investigated the impact of resveratrol on three melanoma cell lines. Resveratrol, at 40 mg/kg, effectively reduced the growth of a lung tumor in vitro, a potential addition to clinical therapy plans without any additional side effects or toxicity [197]. While these preclinical and mechanistic studies highlight the strong chemopreventive and

therapeutic potential of polyphenols, their clinical translation remains limited due to poor bioavailability. Most polyphenols suffer from low water solubility, instability in physiological conditions, and extensive first-pass metabolism, which markedly reduces systemic absorption. Rapid conjugation in the gut and liver further decreases their effective concentration at tumor sites. Advanced delivery approaches, such as nanoformulations, liposomal carriers, and prodrugs are crucial for improving stability, targeted delivery, and overall therapeutic efficacy in overcoming pharmacokinetic barriers. The incidence of metastatic skin cancer is significantly lower than in Western countries due to racial and genetic differences [221].

## 10. Tea Polyphenols Control UVB-Mediated Ovulation

The skin acts as a barrier against UV radiation, categorizing it into UVA and UVB based on wavelength. About 95% of UV radiation is long-wave UVA radiation, which ranges in wavelength from 320 to 400 nm. ROS, which penetrate deeply into the dermis, can damage DNA, proteins, lipids, and cell signaling pathways, potentially leading to photocarcinogenesis [222-224]. Only 5% of UV sunlight is UVB radiation, which is short-wave (290–320 nm). The absorption of this substance in the epidermis leads to direct DNA damage, inflammation, dysregulation of cellular signaling pathways, and photocarcinogenesis [225, 226]. The tumor suppressor gene p53 regulates the cell cycle, suppressing proliferation and initiating apoptosis to protect the genome. p53 triggers the upregulation of the pro-apoptotic protein Bax and the downregulation of the protein that blocks apoptosis, Bcl2 [227]. Apoptosis-resistant cells can enter the cell cycle without DNA repair when this tumor suppressor gene is mutated [228]. After UVB exposure, the epidermis of SKH-1 hairless rats may develop patches of mutant p53. Green tea diluted in water prevented hairless SKH-1 mice from generating UVB-induced mutant p53-positive patches when compared to water-diluted mice. It induces chemopreventive apoptosis in early precancerous lesions, which is a chemoprotective mechanism against UVB radiation [229]. A study on hairless SKH-1 mice found that EGCG treatment combined with UVB exposure reduced skin cancers and promoted apoptosis by increasing caspase 3 expression in epidermal dysplastic areas. EGCG can be utilized as a photoprotective medicine against UVB-induced skin carcinogenesis by causing tumor apoptosis and preventing tumor development [230]. The pretreatment with EGCG reduces the impact of UVB radiation on p53 expression in live skin analogs [231]. Body lotion with green tea extract was applied to the skin that had been exposed to UVB rays in humans. It decreases the expression of p53, thus preventing apoptosis. It also reduces OS and promotes apoptosis as its mode of action [231]. The Fas ligand system serves as an additional apoptosis marker and regulator, further enhancing its anti-inflammatory properties. UV radiation can induce apoptosis by activating the death receptor Fas [232]. Fas expression was enhanced by UVB irradiation using live skin analogues, but this was stopped by pretreatment with EGCG [233]. Tea polyphenols' potential in UVB-induced skin cancer chemotherapy has been demonstrated in various studies, including *in vitro*, *in vivo*, and human trials. Tea polyphenols aid in DNA repair, reduce OS, inhibit UVB-induced signaling pathways, and reverse epigenetic changes induced by UVB exposure [234].

## 11. Tea polyphenols Reduce Oxidative Stress and UVB-Mediated Inflammation

Patients are advised to use sunscreen frequently, wear broad-brimmed hats and long-sleeved clothing, and avoid direct sunlight during peak UV radiation exposure. Sunscreen effectiveness is primarily based on preventing UV-induced sunburns, with their chemopreventive action against non-melanoma skin cancers [235]. UVB light exposure increases vascular permeability and vasodilation, leading to skin inflammation

characterized by erythema and edema. Prolonged UVB exposure results in chronic inflammation, which in turn promotes the growth, progression, and spread of skin cancer [225-237]. The phospholipids in the cell membrane contain arachidonic acid, which is released by the enzyme phospholipase A2, which is activated by absorbed UVB radiation. Cyclooxygenase (COX) and lipoxygenase (LOX) are enzymes that convert arachidonic acid into eicosanoids, producing prostaglandins (PGE) and 12-hydroxyeicosatetraenoic acid (12-HETE). UVB exposure leads to an increase in COX-2 expression, thereby elevating the levels of PGE in the body. The enzyme COX-2 is responsible for regulating the rate of arachidonic acid metabolism. UVB light exposure enhances the COX-2 production by human keratinocytes [238]. PGE2's capacity to accelerate proliferation and its vasodilatory properties have been widely recognized [239]. The overexpression of this gene is observed in tissue samples from advanced BCC and SCC tumors [240], suggesting a link between it and the onset of metastasis. The study investigates the anti-inflammatory properties of EGCG in preventing photocarcinogenesis [241]. Human skin biopsied after exposure to UVB radiation or EGCG therapy showed that applying EGCG topically significantly reduced erythema compared to untreated skin. EGCG consumption decreased COX production in PG metabolites with lower PGE2 levels. A study was conducted on healthy human volunteers to assess the effectiveness of GTPs and their constituents, EGCG, EC, and EGC, in protecting against UV-induced photodamage [242]. The study involved applying identical pretreatments containing 5% GTP and its ingredients to skin areas before UV exposure. EGCG and ECG, polyphenolic fractions with a galloyl group at position 3, effectively reduced UV-induced erythema, unlike EGC and EC. GTP-treated skin showed reduced UV radiation damage, fewer burned cells, and protection from its effects [242]. Another study investigated the effectiveness of oral administration of GTPs in reducing inflammation. Human participants exposed to UVB radiation before and after 12 weeks of GTP therapy showed a significant reduction in erythema compared to pre-treatment exposure. The concentration of 12-HETE decreased after treatment compared to pre-treatment exposure [243], indicating that 12-HETE is a powerful leukocyte chemoattractant. Long-term exposure to UVB in mice reduced the levels of inflammation-associated cytokines (TNF-, IL-1, and IL-6) and pro-inflammatory markers (COX-2 and PGE2) with oral administration of GTPs [164]. UVB light enhances vasodilation and vascular permeability, allowing leukocytes, primarily neutrophils, to infiltrate the exposed area. Nitric oxide synthase (iNOS), an enzyme stimulated by UVB light, is the major cause of the enhanced vasodilation [244]. Leukocytes entering the tissue produce ROS through the actions of NADPH oxidase and myeloperoxidase (MPO) [245]. EGCG inhibited UVB from inducing MPO activity and leukocyte infiltration in C3H/HeN mice [246]. Additionally, EGCG significantly reduced MPO activity in human skin exposed to UVB [241]. The amount of NO and $H_2O_2$ produced when EGCG was applied topically to human skin was significantly reduced [212]. ROS cause cell damage by oxidizing cell molecules, leading to OS [237, 247]. Cells possess inherent defenses against ROS by activating endogenous ROS detoxifying enzymes and antioxidant substances. UVB radiation frequently depletes molecules and enzymes, leading to oxidative damage to cells [225,237,247]. Tea polyphenols, as potent ROS scavengers, prevent oxidative cell damage [247]. Vitamins C and E are stronger antioxidants compared to them [248]. Therefore, their antioxidant activity was studied in SKH-1 hairless rats after UVB exposure. The study found that applying GTPs or EGCG in a hydrophilic ointment USP to mice before UVB exposure reduced UVB-mediated depletion of glutathione, GPx, and catalase [249]. The delivery of GTP in drinking water prevents the depletion of antioxidants due to single or repeated UVB exposure [212]. Tea polyphenols' potential in UVB-induced skin cancer chemotherapy has been demonstrated in various studies, including *in vitro*, *in vivo*, and

human trials. Tea polyphenols aid in DNA repair, reduce OS, inflammation, slow down UVB-induced signaling pathways, and reverse epigenetic changes induced by UVB exposure [234].

## 12. Tea Polyphenols Enhance DNA Repair Mechanisms and Decrease UVB-Mediated DNA Damage

The conserved NER system aids in DNA repair, potentially repairing CPDs and preventing apoptosis in skin keratinocytes, depending on DNA damage caused by UVB exposure [250-252]. Keratinocytes stop the cell cycle if irreparable DNA damage occurs, turning into sunburn cells, the first sign of epidermal cell death, and can initiate DNA repair [252]. UVB rays damage skin DNA by promoting cyclobutane pyrimidine dimers (CPDs), which can cause mutations if not treated, and are prevalent, damaging, and slow-repair premutagenic photoproducts in mammalian cells [253]. The NER process is used by cells to repair nicks and eliminate dimers from damaged DNA. The protective function of NER is demonstrated in xeroderma pigmentosum patients with NER deficiency, indicating an increased risk for photocarcinogenesis and higher mutagenicity [254]. Incorrect treatment during replication or non-correction by NER can cause recurrent CPDs to transition between C and T or CC and TT. UV signature mutations are common abnormalities in tumor suppressor genes [255]. Blocking UVB radiation with sunscreens can reduce CPD development, while NER-boosted CPD repair may prevent skin cancer. Green or white tea extracts effectively prevent skin from UV radiation, despite indirect UVB absorption and sunscreen effects [256]. The topical application of GTPs effectively protected both the human dermis and epidermis from UVB-induced CPDs [163]. A study on EGCG found that this polyphenol aids in the body's recovery from UVB-induced chronic inflammatory diseases. Mice treated with UVB exposure showed a significant, time-dependent reduction in the number of CPDs compared to control animals. Animals that were administered GTPs orally also had a similar reaction [164]. GTPs enhance DNA repair, leading to further investigation into the impact of NER on the process. UVB exposure reduces CPDs in mice, activating NER-related genes through oral GTPs. A study examines NER role in GTP-induced DNA repair in xeroderma pigmentosum patients. The experiment using XPA// mice showed similar results, indicating that a functional NER system is crucial for GTP-induced DNA repair [257]. EGCG, an immunoregulatory cytokine, has anticancer effects, but it fails to inhibit photocarcinogenesis when administered topically to IL-12 knockout mice [252]. IL-12 KO mice treated with EGCG and untreated mice experienced UVB-induced DNA damage, while oral administration of GTPs resulted in similar outcomes [164]. Subcutaneous administration of IL-12 to IL-12 KO mice undergoing EGCG treatment significantly reduced the number of UVB-induced CPDs [258]. A study investigated the photoprotective properties of GTPs on normal human epidermal keratinocytes (NHEK), finding that IL-12 facilitates the fast healing of UVB-induced CPDs [215]. GTPs and EGCG can prevent UVB-induced skin damage by reducing DNA damage, stopping apoptosis, and boosting IL-12 production in NHEK cells and human keratinocytes [215]. Another study is exploring the potential benefits of topical EGCG and dietary green tea as sun radiation supplements [259].

## 13. Toxicity

Resveratrol and piceatannol were tested for cytotoxicity in cultured cells. They inhibited the viability of mouse macrophages, tumor-derived human T cells, and human epidermoid carcinoma cells in a concentration-dependent manner. Piceatannol reduced macrophage viability in a concentration-dependent way. Both piceatannol and resveratrol were less cytotoxic when stimulated with zymosan. The cytotoxicity is caused by a mechanism other than oxidative stress. Cytotoxicity is more pronounced in zymosan-activated cells, suggesting that the toxicity of both piceatannol

and resveratrol toward macrophages depends on their activation status [260]. Mammals exhibit good tolerance to resveratrol even at high concentrations, such as 1000–1500 mg/day [261]. Clinical studies and *in vivo* animal models indicate the safety of resveratrol as a dietary polyphenol at doses of 100-1,000 mg/day [262, 263]. Resveratrol is considered safe and nontoxic even at large dosages of up to 5 g [264]. Clinical studies suggest that daily intake of 2.5-5 g of resveratrol can cause mild to moderate gastrointestinal problems [265]. Diarrhea has been reported while taking 2 g of resveratrol twice a day [266]. A study indicates a correlation between resveratrol micronization and improved tolerability [267]. Resveratrol can reduce nonhematological toxicities associated with chemotherapy, making cancer therapies more tolerable [268]. Additionally, resveratrol affects cell proliferation in different ways depending on the type of cell. Research on cancer biology reveals that it cytotoxically destroys cancerous cells while preserving healthy ones [269]. Resveratrol exposure in chronic doses has complex effects on human mesenchymal stem cells, varying depending on the duration and concentration [270]. Furthermore, resveratrol causes irreversible cell cycle arrest and cellular senescence in proliferating MSCs at higher concentrations, potentially limiting their therapeutic potential. Resveratrol, when consumed long-term, can negatively impact stem cell function and overall health by disrupting goitrogens and thyroid function [271]. The claim that chronic high-dose resveratrol ingestion, such as 5 g/day, is nontoxic [272]. High-dose resveratrol consumption raises concerns as it may cause oxidative stress by activating Phase II detoxifying enzymes, potentially leading to liver damage. Enzymes, typically involved in detoxification processes, can occasionally produce reactive intermediates that can cause cellular damage and oxidative stress. Recent research explores the potential of resveratrol to modify the Nrf2-Keap1 signaling pathway, a crucial component of cellular antioxidant defense mechanisms, to protect against oxidative stress and liver damage [273, 274]. A study tested the cytotoxicity of curcumin-loaded chitin nanogels on human dermal fibroblast cells and A375 human melanoma cell lines. These exhibited specific toxicity on melanoma within a concentration range of 0.1-1.0 mg mL−1, with less toxicity towards human dermal fibroblast cells. These also increased transdermal curcumin flow, allowing penetration of the skin and preventing inflammation [275]. Another study demonstrates that skin cancer cells can be selectively sensitized to quercetin through brief exposure to low-frequency ultrasound. Ultrasound pretreatment at 20 kHz, 2 W cm−2, 60 s caused cytotoxicity in skin cancer cells, with minimal impact on normal cell lines. After 48 hours of ultrasound-quercetin (50 μM) treatment, approximately 90% of the viable skin cancer cell population was eliminated. Ultrasound significantly decreased the $LC_{50}$ of quercetin by nearly 80-fold for skin cancer cells, despite not impacting nonmalignant skin cells [276].

## 14. Conclusion and Future Perspectives

Research on natural remedies and polyphenols for skin cancer combats molecular mechanisms, providing hope for developing new strategies for prevention and treatment. Polyphenols such as resveratrol, EGCG, curcumin, quercetin, and apigenin have antioxidant, cancer cell growth inhibiting, anti-inflammatory, and apoptotic properties, potentially targeting skin cancer. Future research should focus on molecular pathways, dosage optimization, and clinical trials for safety evaluation. Natural remedies and polyphenols offer promising cancer prevention and treatment strategies, but further understanding is needed to enhance outcomes for skin cancer patients. Future research in this field could involve clinical trials, formulation optimization, and potential synergistic therapies. Biomarker identification could help stratify patients for treatment efficacy. Mechanistic studies could help understand the molecular targets of polyphenols' anticancer effects. Public health

interventions could promote polyphenol-rich foods and beverages or develop dietary supplements for skin cancer prevention in high-risk populations. These areas could lead to more targeted and personalized therapeutic approaches. Research on natural remedies and polyphenols' potential in combating skin cancer is progressing, but additional research is needed to develop effective clinical strategies.

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## Conflict of Interest

All authors are declared that there is no conflict interest exists.

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