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Review

Mechanistic insights into plant-derived natural compounds for the treatment of skin cancer: Targeting molecular signaling for therapeutic intervention

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ABSTRACT

Skin cancer, a prevalent global cancer, is primarily caused by chronic environmental exposures and cellular signaling pathway deregulation. Traditional therapies like radiation, chemotherapy, and surgery face toxicity, resistance, and recurrence issues. Natural compounds, with their diverse biological activity and minimal side effects, are increasingly recognized as potential therapeutic agents. This review explores the potential of natural compounds in treating skin cancer by modifying key molecular signaling pathways, including MAPK/ERK, PI3K/Akt, NF-κB, STAT3, and Wnt/β-catenin. Curcumin, resveratrol, quercetin, epigallocatechin gallate, and genistein are natural substances known to have potent anticancer effects by inhibiting cell proliferation, promoting apoptosis, and preventing metastasis. These substances regulate inflammation, prevent angiogenesis, enhance drug effectiveness, combat multidrug resistance, and have low toxicity to healthy skin cells, indicating potential therapeutic use. Additionally, their compatibility with current chemotherapeutic drugs underscores their significant role in combating drug resistance. The review underscores the importance of understanding the molecular mechanisms underlying phytochemicals' anticancer properties to facilitate their integration into modern treatment methods. Future initiatives should focus on clinical validation, increasing bioavailability, and targeting administration schemes to maximize the therapeutic potential of natural chemicals against skin cancer.

1. Introduction

Skin cancer can be classified into three types: squamous cell carcinoma (SCC), basal cell carcinoma (BCC), and cutaneous melanoma. Non-melanoma skin cancer encompasses cutaneous lymphoma, adnexal carcinoma, dermatofibrosarcoma protuberans, and Merkel cell carcinoma, among other primary skin neoplasms. Keratinocyte carcinoma, derived from epidermal keratinocytes, is the term used to describe basal cell carcinomas and cutaneous squamous cell carcinomas [1]. Melanoma (Fig. 1) is the most prevalent and fatal type of skin cancer globally. Melanoma cases are predicted to rise by 50 % by 2040, underscoring the necessity for preventative measures [2]. NMSC and

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melanoma are complex diseases primarily linked to prolonged, unprotected exposure to UV lamps or natural UV radiation. Oxidative stress, which disrupts signal transduction pathways like NF-κB/p65, MAPK, JAK, STAT, and Nrf2, is the primary cause of UV's harmful effects. Changes in skin structure can lead to skin injury as they weaken the integrity of skin cells and cause damage to certain biomolecules [3]. NMSCs, including AK, SCC, and BCC, are prevalent in the general population with a 2.5:1 ratio, with BCC being the most prevalent among Caucasians [4]. SCC has a 0.3–3.7 % metastatic potential, but BCC has less than 0.1 % potential [5]. BCC typically manifests in the sun-exposed regions of the forehead, face, and scalp after the age of fifty. BCC can be classified into several clinical variants, with the nodular variant being the most prevalent one [6]. The Hedgehog (Hh) pathway is responsible for driving basal keratinocyte-like tumors in the follicular and interfollicular epidermis [7]. BCC is frequently linked to mutations in the Hh pathway genes, specifically PTCH and SMO. Ninety percent of sporadic BCCs have somatic PTCH mutations, while SMO has gain-of-function mutations [8]. The PI3K pathway serves a vital function in oncogenesis by stimulating the activation of Hh signaling. The process is facilitated by downstream components like atypical protein kinase C (aPKC) and S6-kinase 1 (S6K1). Gli1 is phosphorylated by the Hh target gene aPKC, activating its DNA-binding capability and creating a positive feedback loop that boosts Gli-dependent transcription in BCC [9]. The priority is given to developing effective prevention and therapeutic strategies due to the high morbidity and mortality rates of NMSCs. Photoprotection is crucial for preventing non-melanoma skin malignancies, as UV light is involved in their etiology [10]. Skin cancer is caused by UV radiation exposure, with TLR4-dependent inflammatory dysregulation playing a significant role in its harmful effects. Major skin cancers, such as Merkel cell carcinoma, melanoma, and nonmelanoma skin cancer, are linked to TLR4 involvement. Targeted molecular therapies that modify TLR4 signaling could potentially help patients with skin cancer [11]. HPV, a double-stranded DNA viral agent, is engaged in the development and spread of skin cancers. Preneoplastic lesions, found in various parts of the body, have a higher chance of developing into cancer when infected with high-risk virus strains. Epidemiological studies suggest it may also cause melanocytic skin cancers like melanoma or non-melanocytic skin cancers like basal cell carcinoma [12]. Early detection of high-risk patients and the application of medications like retinoids are preventive measures to reduce the likelihood of pre-malignant cells developing into carcinomas [13]. The human epidermis is always subjected to environmental stressors, which can lead to skin damage and non-melanoma skin tumors. Dietary phytochemicals, located in whole fruits and vegetables, have anti-inflammatory, antioxidant, and anti-angiogenic properties against skin cancer. They also regulate physiological functions like angiogenesis, metastasis, and the cell cycle [14]. The review highlights that natural target key molecular signaling pathways to control angiogenesis, decrease metastasis, trigger apoptosis, and prevent tumor cell proliferation, offering promising anti-cancer effects and minimal toxicity as alternative treatments.

2. Evolving epidemiology and burden of skin cancer

The global incidence of skin cancer is increasing due to UVB radiation exposure, arsenic use, and climate change. Exposure to UVB (Fig. 2) radiation causes dose-dependent basal and squamous cell cancer, while arsenic use is linked to squamous and basal cell cancer. Rising temperatures may also increase skin cancer incidence due to alterations in human behavior and outdoor activities [15,16]. Epidermal cancers, including Merkel cell carcinoma, melanocyte cancer, and keratinocyte cancer, are prevalent in Australia, North America, and Europe. Keratinocyte tumors are the predominant variety, with melanoma and Merkel cell carcinoma being more significant causes of death. Risk factors include environmental factors like UV exposure and advanced age.

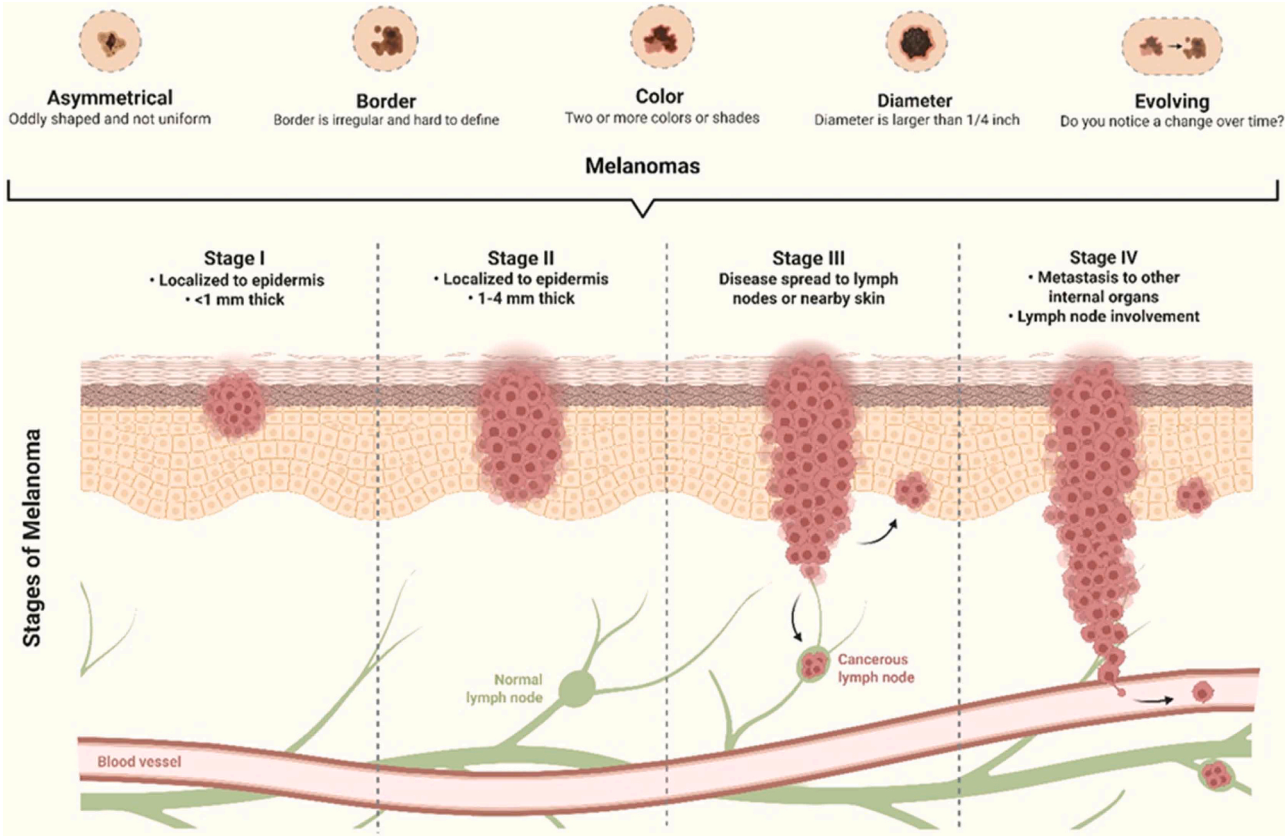

Fig. 1. Illustration of the clinical features and progression stages of melanoma skin cancer. It shows stages of progression, from localized skin involvement to systemic dissemination, emphasizing the importance of early detection based on visible skin changes.

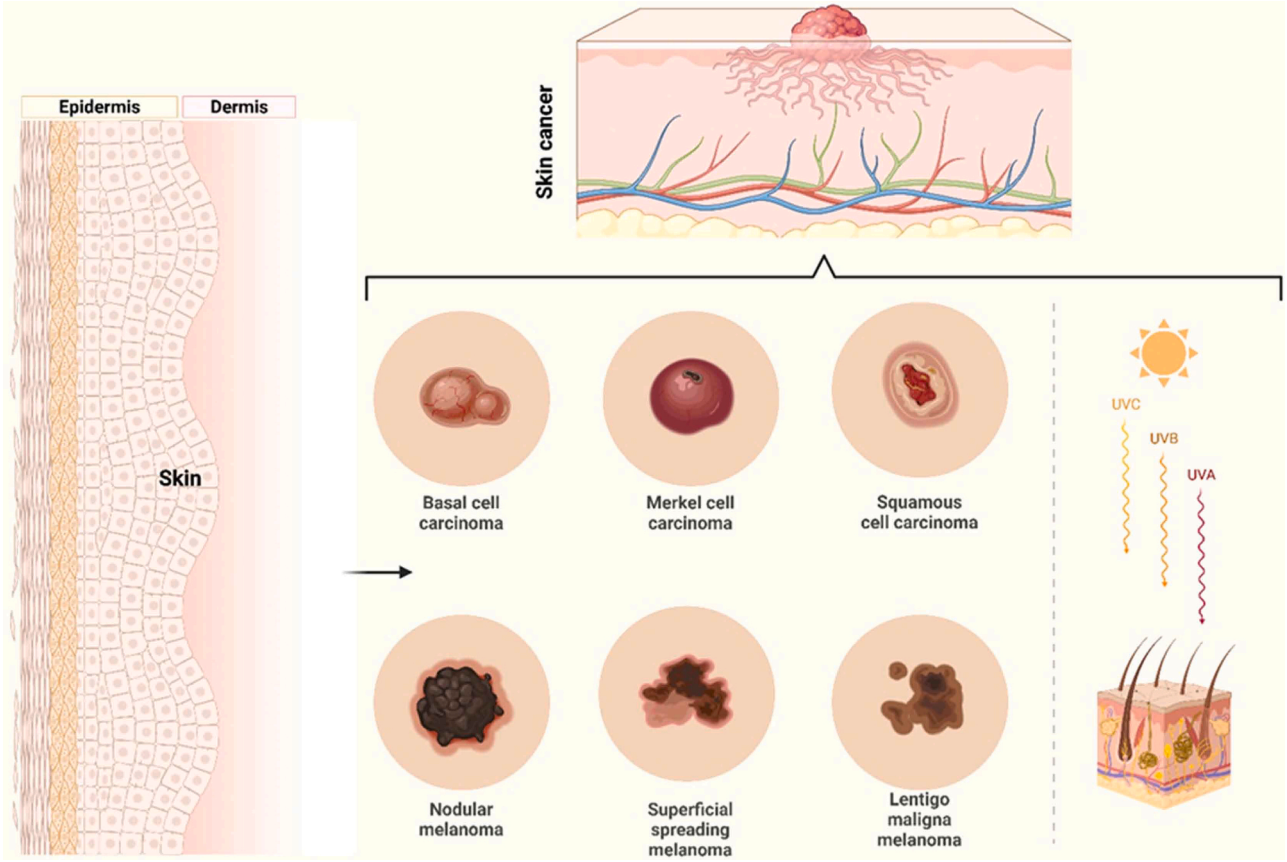

Fig. 2. Illustration of the structure of skin and various types of skin cancer, including Basal Cell Carcinoma, Merkel Cell Carcinoma, and Squamous Cell Carcinoma. It also shows melanoma subtypes and the effects of UV radiation on the skin, highlighting the correlation between UV exposure and the pathogenesis of different skin cancer types.

Actinic keratosis, a low-risk condition, is prevalent in 79 % of men and 68 % of women aged 60–69. BCC and SCC are more prevalent in Australia, with a 9 % death rate despite melanoma rates increasing [17]. Skin cancer, comprising both NMSC and malignant melanoma (MM), is the most prevalent cancer among Caucasians [18,19]. The occurrence of both MM and NMSC is increasing with a yearly growth of 0.6 % among persons over 50. The quantity of newly reported cases of cutaneous melanoma reached an estimated 76,380, accounting for 4.5 % of all newly diagnosed cancer cases [20]. Nodular melanoma and T3/T4 tumors exhibit increased thickness. The melanoma epidemic is not solely due to increased detection pressure of T1/T2 lesions at an earlier stage [21]. Several investigations suggest that non-malignant diagnoses are being reclassified as MM from a dermatopathologic perspective [22]. Researchers found a 15-year increase in skin biopsies and MM prevalence, suggesting a possible link between the MM epidemic and increased biopsies and scrutiny [23]. NMSC, including Bowen's disease, SCC, and BCC, is 18–20 times more common in Caucasians than MM [24,25]. NMSC epidemiology faces constraints due to regional differences in incidence rates and low fatality rates, which prevent it from being included in large cancer registries [26]. The financial cost of NMSC is significant. In 2010, Australia spent AUS$511 million on the most expensive cancer [27]. The estimated annual cost of NMSC-related expenses in the USA is $650 million, with Medicare contributing 6–7 times more than melanoma treatment [28]. The ageing population, linked to an increased risk of NMSC, is a contributing factor to reported increases in skin cancer rates [29]. Studies indicate that increasing UV exposure at work and leisure significantly impacts health [30,31]. Indoor tanning is linked to a substantially elevated risk of BCC and SCC, particularly in early life (<25 years) [32]. Women under 40 years old also demonstrated a consistent linear increase in BCC incidence rates of 6.3 % from 1973 to 2009 [33].

3. Molecular mechanisms of carcinogenesis of skin cancer

UVB radiation significantly damages DNA by altering genes like p53, causing a change from C to T or CC to TT [34]. UVA exposure, specifically through 8-oxodG, can lead to mutations. The transition from AT to CG involves a shift in several genes that regulate the cell cycle, apoptosis, and genomic stability (p53) [34,35]. Initiated cells progress into the promotion stage (Fig. 3) as a result of genetic mutation and ongoing UV exposure. Initiation stage cells are less likely to undergo apoptosis and proliferate more aggressively [36]. Actinic keratosis (AK) is a common precancerous lesion in humans that exhibits significant alterations compared to normal human skin cells [37]. UV radiation, absorbed by all living things, can cause both life-sustaining and life-threatening consequences. UV-B sunlight is responsible for the progression of skin cancer, with mutations in genes linked to oncogenic, tumor-suppressive, and cell-cycle control signaling pathways. It focuses on UV rays, skin optics, and molecular processes involved in photocarcinogenesis [38]. UV radiation triggers the carcinogenesis process, leading to DNA damage, inflammation, and skin cancer. The p53 tumor suppressor protein, which promotes apoptosis or DNA repair, is phosphorylated and translocated to the nucleus. Overexposure to UV leads to p53 mutations, allowing keratinocytes with p53 mutations to gain a growth advantage. To prevent skin cancer, excessive UV-induced DNA damage is removed, resulting in squamous cell carcinomas and actinic keratoses [39]. The primary cause of non-melanoma cancer is sun exposure. UV-induced mutations alter genes that regulate cell growth and development, leading to the formation of neoplasms [40]. UVA radiation (320–400 nm) is 10,000 times less mutagenic than ultraviolet

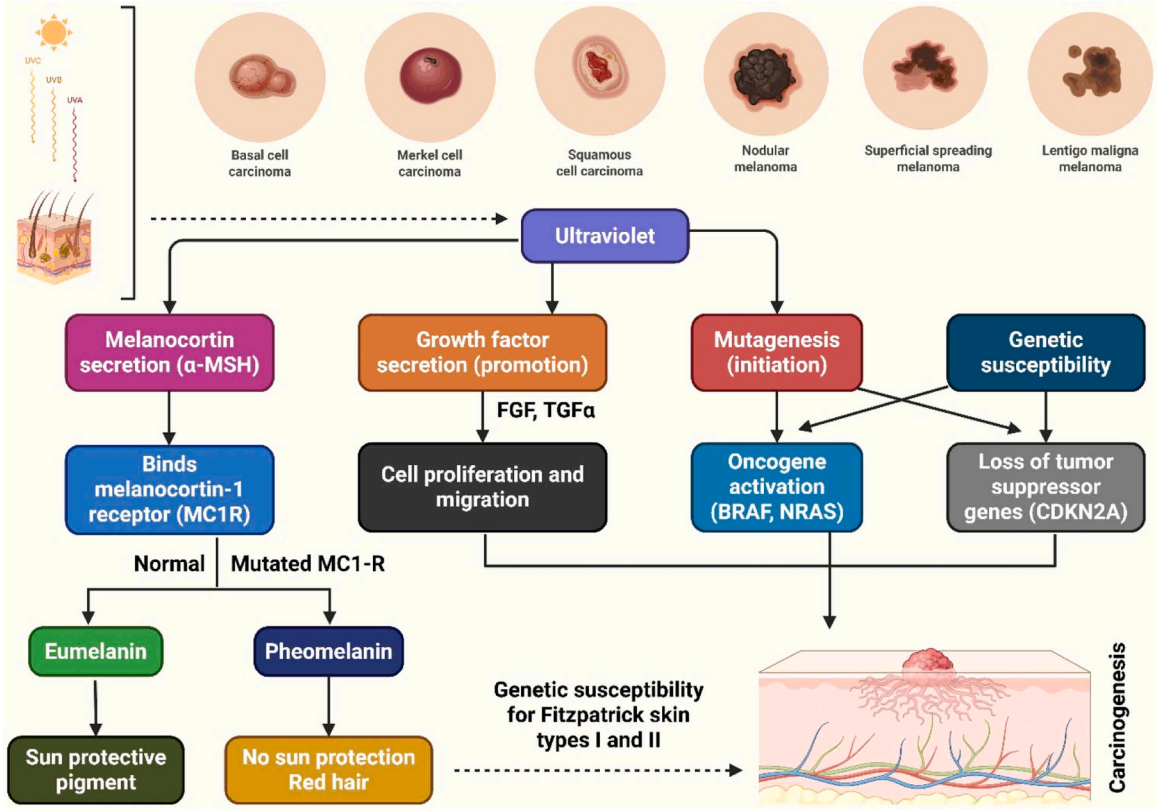

Fig. 3. Molecular mechanism and signaling pathways underlying skin carcinogenesis. The diagram illustrates key genetic alterations, cellular events, and dysregulated signaling cascades that drive the initiation, promotion, and progression of skin cancer.

B radiation due to its stronger absorption by DNA's nitrogenous bases and distinct mutation spectrum [41,42]. UVB radiation-induced mutations often involve nitrogenous base substitution in pyrimidines, particularly in the cytosine-thymine transition and the formation of thymine dimers [42,43]. Solar radiation-induced DNA alterations can cause skin cancer only if they are recurrent and sequential, entering a replication phase [44,45]. Mutation of tumor suppressor alleles, distinct proto-oncogenes, or a proto-oncogene and a tumor suppressor gene can occur. Proto-oncogenes are normal genes that can either encode proteins with novel activities or transform into active oncogenes due to mutations. Tumor suppressor genes no longer have a detrimental effect on tumor growth when altered or removed [44]. The progression from keratinocytes to papilloma and carcinoma is linked to various stages of SCC, characterized by cellular and molecular alterations [46,47]. A proto-oncogene mutation initiates clonal proliferation into pre-malignant cells during the early phase of cancer. The progression of neoplasia involves an increase in cell proliferation, leading to a benign squamous cell papilloma [48]. Malignant SCC, a spontaneous development linked to chromosomal abnormalities and aneuploidy, is the final stage of the disease [49,50]. Regression, a rare phenomenon where a malignant tumor disappears partially or entirely without treatment, is a common outcome of microscopic examination. Neuroblastoma, renal cell carcinoma, and melanoma are among the most frequent neoplasms to regress [51]. The p53 tumor suppressor gene is mutated in most malignancies, including non-melanoma carcinoma [52]. This kind of mutation is seen in BCC and a significant proportion of SCC. This protein is crucial for DNA damage response as it accumulates in damaged cells' nuclei, allowing them more time to repair or undergo apoptosis [53,54]. UV light damages epidermal cell DNA, triggering apoptosis through the p53 protein [55,56]. Additionally, UV radiation prevents non-melanoma carcinoma development by promoting cancer growth and inhibiting cell death through the p53 protein [53,57]. The majority of p53 protein mutations in SCC involve Type C → T and CC → TT transitions, indicating UVB radiation as the source of mutagenesis [55]. About half of the cases of BCC analyzed also contain a p53 protein mutation [58]. BCC often has mutations in two p53 protein alleles, while SCC loses one p53 allele and has isolated mutations in another [59]. Human neoplasms that develop early are also linked to mutations in the Ras protein [60].

In addition to encoding the G protein that hydrolyzes guanosine triphosphate (GTP), the Ras protein controls angiogenesis, death, proliferation, and cell shape. The Ras protein, encoded by the Ras oncogene, prevents the hydrolysis of GTP [61]. The injection of the Ras oncogene into normal keratinocytes results in the transformation of them into displaying other oncogenes, including the Fos oncogene [56]. The Ras oncogene is crucial for non-melanoma carcinoma development, with UVB ray-induced mutations in the Ras gene observed in squamous and basal cell carcinomas [62]. The membrane protein E-cadherin, which is produced in epithelial tissues and plays a crucial role in preserving epithelial integrity, is implicated in cell adhesion [63]. The inactivation of this protein is linked to the invasion of tumor cells and the spread of various malignancies, including SCC [64]. E-cadherin is inactivated through mutation and hypermethylation of the E-cadherin gene promoter, a process linked to gene silencing [65,66]. The tumor's invasive nature is strongly linked to an increase in E-cadherin hypermethylation [66]. The development of BCC traits is facilitated by the production of the Sonic hedgehog (SHH) glycoprotein in human skin [67,68]. BCC is linked to abnormal gene expression, triggered by alterations in the SHH signaling pathway and loss of function of the SHH protein receptor [67]. The treatment of NMSCs requires the complete removal of the lesion while maintaining the skin's structural and functional integrity. Excision, curettage, and electrodessication, cryosurgery, micrographic surgery, radiation, and photodynamic therapy are among the surgical interventions used in current treatment methods. Surgical techniques like the Mohs process are recommended over alternative approaches for low-risk lesions [69].

4. Natural agents in skin cancer

4.1. Resveratrol

Resveratrol (Fig. 4) is a naturally occurring polyphenol that can be found in peanuts, berries, and grapes, among other plants. It is especially well-known for being found in red wine. It may have a beneficial impact on decelerating the aging process and preventing and treating cancer and inflammatory diseases [70,71]. Resveratrol is a medication that has pleiotropic effects, allowing it to act on multiple organs simultaneously. It inhibits proliferation, epithelial-mesenchymal transition, invasion, migration, and angiogenesis by downregulating NF-κB, decreasing β-catenin-dependent pathways, and blocking HIF-1 and accelerating its ubiquitination [72–74]. A study on oral squamous cell carcinoma cell lines demonstrated that resveratrol leads to cell cycle arrest and apoptosis during the G2/M phase [75]. Another study found the optimal dosage of resveratrol to maximize its health advantages and reduce toxicity risk [76]. Resveratrol targets various tumor formation elements, making it an effective complement to other treatments, enhancing their synergy [71]. Apart from its antioxidant properties, resveratrol also reduces inflammation by preventing COX-1 activity in vitro [77] and COX-2 activity in mouse skin [78]. Resveratrol's ability to prevent UV-mediated cutaneous damage is attributed to its modulation of cell cycle regulatory proteins through the suppression of the MAPK pathway [79]. Hypothesized methods involve downregulating aquaporin 3 (AQP3), a water channel protein overexpressed in hyperplastic epidermal diseases, by inhibiting ERK phosphorylation and survivin, an anti-apoptotic protein [80,81]. Resveratrol, a synergistic phytochemical, possesses the capability to serve as an adjuvant therapy for melanoma. Resveratrol, when combined with other phytochemicals, effectively controls carcinogenesis and reduces murine epidermal hyperplasia by decreasing Bcl2 expression, p21 expression, and COX-2 expression. It decreases COX-2, Bcl-2, and p21 expression levels, suppresses carcinogenesis, and reduces murine epidermal hyperplasia [82]. Moreover, resveratrol considerably reduced melanoma cell viability and increased temozolomide's cytotoxicity, suggesting potential use as a supplementary treatment to chemotherapy for distant metastatic melanomas. It increased the cytotoxic effects of temozolomide and decreased the viability of skin cancer cells during melanoma treatment [83]. Resveratrol inhibits redox factor-1, increasing melanoma cells' susceptibility to the alkylating chemotherapeutic agent dacarbazine. It enhances skin cancer cell sensitivity to dacarbazine by inhibiting the activity of redox factor-1 [84].

Furthermore, resveratrol has chemopreventive effects on melanoma by reducing the expression of the proto-oncogenic and anti-apoptotic protein Akt/PKB in highly invasive melanoma cells [85]. Resveratrol exhibits potent anticancer properties, effectively reducing ROS levels in human skin fibroblasts by scavenging them. Oral resveratrol's suboptimal bioavailability in vivo results from quick elimination by intestinal and hepatic metabolism [86]. Oral administration of a drug to mice with melanoma tumors may limit its ability to reach the skin and tumor, potentially causing tumor growth [87]. The topical administration of resveratrol might be a greater practical chemopreventive strategy. Resveratrol-containing cream has been shown to significantly enhance skin hydration, suppleness, and brightness in healthy individuals without any adverse effects. Researchers are now utilizing parenteral or topical delivery methods for resveratrol. Resveratrol cream is known for its exceptional properties, like skin hydration, brightness, and elasticity. Resveratrol, when conjoined with vitamin E and baicalin, significantly enhanced the healing of photodamaged skin after 12 weeks [88]. In a study involving 55 individuals, topical resveratrol, baicalin, and vitamin E were found to significantly improve photodamaged skin over 12 weeks [89]. Resveratrol has anti-melanoma properties in both in vitro and in vivo settings. In this study, 7 μg/mL resveratrol caused a 50 % reduction of cell development, preventing melanoma cells from proliferating [90]. Furthermore, resveratrol also prevented A431 cells (SCC cells) from growing [91]. In FaDu, Cal27, and Det562 cells, resveratrol decreased cellular growth and caused cell death. A 50 mg/kg dose of oral resveratrol significantly reduced tumor volume and mouse weight by over 50 % in an in vivo study [92]. A 72-hour treatment with 25 μM resveratrol reduced DNA synthesis [93].

4.2. Curcumin

Curcumin, a yellow plant polyphenol, has been a valuable medical ingredient and a popular spice throughout history [94]. Curcumin significantly reduces UVB-induced damage in animals and in vitro by lowering lactate dehydrogenase release, intracellular ROS, and DNA damage [95]. Curcumin used topically and orally prior to long-term UV exposure postponed the start of tumors in animal research [96]. UVB radiation activates the mTOR and FGFR signaling pathways, crucial for the development of skin tumors like SCC, BCC, and AK. The C3 curcuminoid complex, when pretreated, has been discovered to inhibit the expression of UVB-induced fibroblast growth factor-2 and its associated cell proliferation, progression, and colony formation. It also suppresses the FGFR2 phosphorylation and the mechanistic target of rapamycin (mTOR) pathway (mTORC1/mTORC2 network) in promotion-sensitive JB6 epithelial cells. Oral C3 complex treatment substantially impedes UVB-induced epidermal hyperplasia and hyperproliferation in mice [97]. A clinical trial was used to examine curcumin's potential role in HNSCC. Microgranular curcumin treatment may reduce FGF-2, interleukin-17, and macrophage colony-stimulating factor, which regulate angiogenesis and cellular invasion of HNSCC. Curcumin may act as a possible angiogenic inhibitor in HNSCC, preventing pre-neoplastic lesions from developing into invasive malignancy [98]. The topical administration of a curcumin-loaded liposome-siRNA combination significantly suppressed SCC cell model growth and apoptotic incidents in relation to the control group [99]. The nanopatterned films coated with curcumin showed strong cytotoxicity toward the same SCC cell type [100]. The clinical trial addressed the problems related to oral curcumin administration. Oral transmucosal administration of microgranular curcumin increases its bioavailability, potentially preventing pre-neoplastic lesions from developing into invasive SCC [98]. Curcumin exhibits anticancer properties against melanoma in a mouse model, enhancing the control of cellular proliferation by increasing miRNA-205–5p. Curcumin's oncostatic effects were demonstrated in a melanoma-bearing mouse model (C57BL/6 mice) by increasing miRNA-205–5p expression, a crucial regulator of cell proliferation and apoptosis [101]. Moreover, curcumin oral gavage significantly reduced cutaneous SCC formation in immunodeficient mice and downregulated pS6, a biomarker of MEK/ERK and mTOR pathways. Curcumin treatment at 20 μM or higher significantly reduced SRB12-p9 cell proliferation, suggesting a strong anticarcinogenic effect in skin cancer. In the mouse skin model, topical and oral food delivery seem to have comparable effects. Curcumin has shown promising potential in preventing skin cancer due to its successful clinical trials. In a mouse model, curcumin's impact on the SRB12-p9 skin cancer cell line. Oral curcumin successfully suppressed SCC proliferation and reduced pS6, a key biomarker of MEK/ERK and mTOR signaling pathways, at doses of 20 μM or more. Curcumin effectively suppressed the growth of SRB12-p9 cells at concentrations of 20 μM or higher [102].

Curcumin inhibited invasion and proliferation and caused cell death by downregulating PCNA, Bcl-2, and JAK/STAT signaling and upregulating mmu-miR-205–5p [103]. Additionally, curcumin prevents chemically induced skin cancer in mice caused by DMBA and decreases the phosphorylation of 4EBP, IRS-1, ILGF-1 receptor, S6K, and Akt in mouse keratinocytes [104]. Curcumin induces autophagy in melanoma cell lines. Additionally, it diminished the expression of AKT and mTOR and inhibited P70S6K activation [105]. Moreover, curcumin significantly decreased cell invasion in A431 cells by inhibiting the STAT3 signaling pathway [106]. Curcumin promoted mPTP opening in WM-115 melanoma cells, which led to apoptosis [107]. Furthermore,

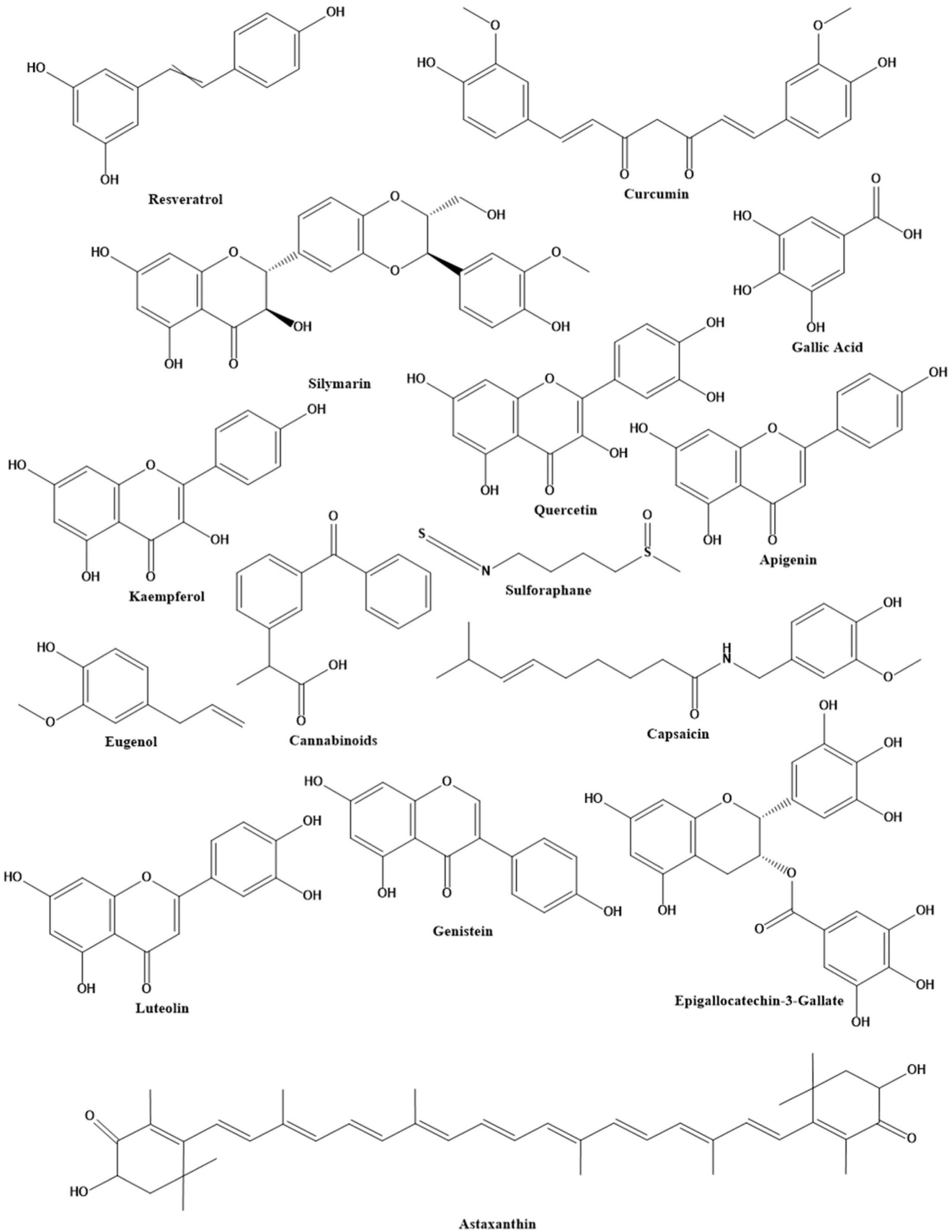

Fig. 4. Chemical structures that are used to prevent and treat skin cancer.

curcumin caused cell death and prevented skin cancer by inhibiting the NF-κB pro-survival pathway, downregulating Bcl-2 expression, and activating the p53 tumor suppressor protein [108].

4.3. Silymarin

The seeds of the perennial Mediterranean native herb milk thistle (*Silybum marianum*) are the source of silymarin [109]. Silymarin, known for its potential to prevent UVB-induced NMSC in pre-clinical skin cancer research, has been increasingly used in dermatology and cosmetology [110]. Over the past 20 years, numerous studies have demonstrated its anti-cancer properties, including one by Agarwal and colleagues on a mouse skin carcinogenesis model. Silymarin effectively inhibited the proliferation of skin cancer by reducing the activity of epidermal ornithine decarboxylase. Furthermore, silibinin has been shown to suppress carcinogenesis by raising p53 levels and acting against UVB-induced thymine dimer production in animal models in vitro. It also inhibits abnormal signaling pathways, promotes DNA repair, and triggers anti-inflammatory reactions. Silibin has been shown to effectively treat skin cancers like SCC and BCC due to its ability to target inflammatory and OS signals [110]. Skin cancer is mostly attributed to exposure to chemical carcinogens and UV radiation emitted by the sun. Silymarin has shown chemopreventive benefits against both chemical and photocarcinogenesis. In animal tumor models, silymarin prevented skin carcinogenesis and inhibited UV-induced skin cancer. Its immunomodulatory, anti-inflammatory, and antioxidant properties may assist in averting skin cancer in in vivo animal models. Silymarin is a pharmacologically safe and potentially chemopreventive drug for human skin cancer treatment [111].

A study showed significant decreases in tumor volume, lower IL-1α and TNF-α levels, and higher levels of glutathione, catalase, and superoxide dismutase in the silymarin-NLC gel-treated group [112]. Silymarin inclusion complex was prepared using freeze-drying and cyclodextrins. The complexes were characterized for stability and complexation efficiency. The selected complex was converted into a topical gel and tested for antioxidant, protein denaturation, and cell viability. The complex showed a stable release pattern and improved antioxidant activity compared to free silymarin. The gel system, which included F2G2, could be an ideal delivery system for skin cancer treatment [113]. Silymarin has a therapeutic effect against skin cancers. When fed to SENCAR mice, silymarin led to tumor regression and decreased growth. It increased the apoptotic index and decreased the proliferation index. Phospho-ERK1/2 levels in tumors from silymarin-fed mice were lower than in controls. Silymarin's plasma concentration can be applied to human skin cancer, leading to growth suppression and apoptosis in human epidermoid carcinoma A431 cells. Silymarin and/or its main active ingredient may prove beneficial in the prevention and treatment of skin cancer in humans [114].

4.4. Gallic acid

Many plants, such as oak bark, tea leaves, witch hazel, sumac, gallnuts, and others, naturally contain gallic acid (GA) [115]. GA effectively combats BCC by targeting and inhibiting HSP90AB1, a protein linked to cancer belligerence. It inhibits the migration and multiplication of BCC cells without elevating ROS levels or killing healthy skin cells, keratinocytes. It is also a promising therapeutic agent for treating BCC due to its ability to effectively target and damage BCC cells while protecting healthy ones. It affects SCC by blocking HSP90AB1, a protein linked to the aggressiveness and invasiveness of malignancy. It lowers HSP90AB1 levels in SCC cells and promotes cell death by successfully reducing cell migration and proliferation in SCC cells [116]. GA impedes the proliferation of human cancer cells, particularly in skin cancer. This study investigated GA's effects on melanoma cell motility, invasiveness, and MMP-2 and MMP-9 expression. Results showed that GA lowers MMP levels in A375.S2 melanoma cells, potentially reducing their invasiveness. Additionally, GA inhibits MMP-2 by interfering with Ras and p-ERK signaling pathways, indicating its potential as a cancer chemotherapeutic drug [117].

A study analysis of poloxamer gels containing GA used to treat melanoma. The gels were tested on Franz cells attached to various membranes, and the diffusion of GA was assessed using various membranes. The type of membrane significantly impacted GA diffusion in both the gel and the solution. Experiments showed that GA-loaded gel could prevent cellular migration, suggesting its potential as an adjuvant treatment [118]. UVA-mediated melanogenesis is influenced by OS, and enhancing the GSH redox system may help attenuate aberrant melanin synthesis. GA has positive effects on hyperpigmentation. This study evaluated GA's antimelanogenic effect on UVA-treated melanoma cell lines, showing reduced basal GSH levels and GST activity in G361 cells. GA's protective benefits may be due to enhancing antioxidant defenses [119].

4.5. Quercetin

Among the numerous qualities, cardioprotective, anti-arthritic, antimicrobial, antioxidant, anti-inflammatory, anti-diabetic, anti-cancer, and wound-healing effects are possible uses for quercetin [120]. The Sun Protection Factor (SPF) of a few chosen natural substances was determined mathematically in an in vitro investigation. Quercetin, unlike apigenin and kaempferol, has low UVB protection but high absorption levels (360–375 nm) in comparison to other flavonoids. Quercetin demonstrated the superior UVA protection amongst flavonoids according to the UVA/UVB ratio criterion [121]. Quercetin, encapsulated in chitosan nanoparticles, was easily absorbed by HaCaT cells and penetrated the epidermal layer, providing improved stability and reduced cytotoxicity. The NF-κβ/COX-2 signaling pathway was discovered to be inhibited by quercetin [122]. A study demonstrated quercetin nanoemulgel's efficacy in vitro on skin cancer A431 cell lines and in vivo on male Wistar rats using ultrasonication emulsification. The nanoemulgel effectively reduced skin edema caused by UVB exposure in male Wistar rats without causing organ damage or skin irritation [123, 124]. Another study developed a dual drug-loaded nanostructured lipid carrier (NLC) gel to improve the disposition of quercetin and resveratrol in the dermal and epidermal layers. The NLC formulation, containing a lipid binary mixture and Cremophor RH40 as a surfactant, showed higher flow and permeability coefficients for quercetin and resveratrol. The gel's dermatokinetic tests showed higher disposition than the conventional gel. FTIR and DSC spectra were used to analyze the gel's penetration dynamics. The MTT assay evaluated the cytotoxic actions of the gel on the human epidermoid carcinoma cell line. The results suggest NLC gel may be a suitable formulation for skin cancer treatment [125, 126]. Additionally, a study developed quercetin-loaded transliposomes for skin cancer prevention. Box-Behnken Design improved quercetin-loaded transliposomes with an 82.1 % entrapment efficiency, a zeta potential of −31.89 mV, and a polydispersity index of 0.181. Quercetin-loaded transliposomes showed greater in vitro release and increased ex vivo dermal permeation. Its antioxidant activity is 1.3 times higher than pure quercetin. Quercetin-loaded transliposomes showed the lowest IC50 value against B16F10 melanoma cells, suggesting a quercetin indication for skin malignancies [127].

Another study demonstrates the formation of liposomes for delivering resveratrol and quercetin. The formulation increased cellular absorption and ROS scavenging capacity in fibroblasts. A mouse model showed liposomes significantly reduced oedema and leukocyte infiltration, ameliorating tissue damage and suggesting a method for treating OS and inflammation in precancerous or cancerous skin lesions [128, 129]. Moreover, a study found a topical nanogel for the prevention of skin cancer utilizing inorganic titanium dioxide and quercetin. The nanocrystal formulations were adjusted employing the Box-Behnken design and quadratic response surface model. The nanogels demonstrated a drug release above 70 % and improved skin deposition of

quercetin after 24 h. The quercetin (0.12 %) + TiO2 (15 %) nanogel-pretreated group had lower tumor numbers and decreased expressions of −2 PCNA, EP3, EP4, COX, and cyclin D1. This combination inhibits UVB-induced skin photocarcinogenesis [130]. Combining nanoparticles with natural and chemotherapeutic drugs in combinational cancer therapy can reduce side effects and increase synergistic therapeutic effects. TNT, a larger surface area carrier molecule, has been studied for its anti-tumor activity and tumor growth reduction. TNT-quercetin treatment significantly improved skin health, decreased squamous cell carcinoma, and suppressed blood vessel development. TNT conjugated with quercetin may be a potential combinational molecule for effective skin cancer treatment [131,132]. Quercetin inhibits IGF-1 signaling, preventing carcinogenesis and reducing tumor incidence and progression. In a study on BK5.IGF-1 transgenic mice, a 20-week quercetin diet significantly decreased tumor multiplicity and delayed skin tumor occurrence. Quercetin also reduced skin hyperplasia and inhibited IGF-1-induced phosphorylation, indicating its potential as a strong anticancer agent [133].

4.6. Apigenin

The anti-cancer properties of apigenin, a chemical found in oregano, vine spinach, celery, chamomile, and parsley, have been studied in SCC cell lines [134]. Apigenin can induce apoptosis by activating the MAPK signaling pathway and inhibiting the production of sulfiredoxin [135]. Additionally, apigenin treatment reduced GFP-LC3 and LC3 turnover in an in vitro SCC model, indicating autophagy suppression [136]. Apigenin has the highest potential of any flavonoid for UVB protection (SPF = 28.8) [121]. Moreover, apigenin inhibited IKKα expression in mouse cell lines, reducing EMT, suggesting potential anti-metastatic action [137]. In animal models, apigenin decreases the synthesis of EP2, EP1, PGE2, and COX-2 [138]. Skin cancer is primarily caused by UVB radiation. Apigenin has been found to prevent UV-induced skin cancer by inhibiting basal mTOR activity in keratinocytes. This inhibition reduced UVB-induced mTOR activation, cell proliferation, and cell cycle progression. This suggests apigenin's role in UVB protection and a new approach for effective skin cancer prevention [139]. Researchers investigated the effectiveness of nano-encapsulation in improving the anti-carcinogenic effect against UVB and BaP-induced skin tumors and mitochondrial dysfunction in mice. They loaded apigenin with poly (lactic-co-glycolide) NPs and investigated tumor incidence, chromosomal abnormalities, and mitochondrial function. NPs showed better effects than apigenin, decreasing tissue damage and increasing ROS buildup, rendering it a viable contender for skin cancer treatment [140].

A study found the role of thrombospondin-1 (TSP1) in apigenin's anticancer effects. A mouse model with a THBS-1 gene knockout was formed to study UVB-induced skin damage and carcinogenesis. TSP1 is crucial for apigenin's chemopreventive role in UVB-induced skin cancer. Topical apigenin administration reduced inflammatory cytokine levels in WT mice's skin while preserving TSP1 expression [141]. A study found Lyotropic Liquid Crystal (LLC) NPs loaded with Apigenin for cutaneous distribution in skin cancer treatment. The optimized apigenin-LLC NPs showed improved permeability profiles, sustained release, and cytotoxic activity on B16F10 cell lines. The QbD technique was used to improve penetration and entrapment efficiency. These NPs show promise for deeper skin layers, rendering them a viable topical drug delivery nanocarrier for skin cancer management [142]. Apigenin has anti-melanoma properties. It decreased cell migration and invasion in melanoma cells and suppressed lung metastasis in mice. It also inhibited STAT3 transcriptional activity, reduced nuclear localization, and depressed phosphorylation. It partially restored cell invasion and migration when overexpressing Twist1 or STAT3 [143].

4.7. Kaempferol

Kaempferol exhibits high absorption levels (360–375 nm) when compared to other flavonoids. It maintains a moderate level of UVB protection (SPF = 24.9) [121]. A study found that kaempferol significantly slows tumor development in mice exposed to UV-induced carcinogenesis, targeting RSK2 and MSK1. It can inhibit the phosphorylation of RSK2 and MSK1 in mice's skin. It also interacts with these proteins at the ATP-binding pocket, inhibiting their kinase activity. This results in a strong inhibitor of SUV-induced skin cancer development in mice, reducing SUV-induced phosphorylation of histone H3 and cAMP-responsive element binding protein [144]. Kaempferol reduces melanoma B16 cell proliferation and inhibits growth in mice xenografts. It increased CD8 T and NKT cells in the spleen, thereby boosting anti-tumor immunity [145]. Additionally, kaempferol was studied for its impact on melanogenesis and response to OS in PIG1 normal human skin melanocytes. Results showed increased tyrosinase activity, melanin content, and phosphorylation of ERK1/2, mRNA and protein expression of enzymes, and a boost in HO-1 protein expression. Kaempferol also protected PIG1 cells from OS damage [146]. UVB radiation constitutes a significant ecological risk variable for nonmelanoma skin cancer. Kaempferol diminished UVB-induced transcriptional activity of AP-1 and COX-2, inhibited COX-2 production in mouse skin epidermal JB6 P + cells, and decreased Src kinase activity. Kaempferol's inhibitory interaction with Src makes it a powerful chemopreventive agent against skin cancer [147].

4.8. Isoflavonoids

Assessing the inhibitory effects of fifteen isoflavonoids from Millettia plants on Epstein-Barr virus early antigen activation in Raji cells. All drugs showed efficacy against EBV without cytotoxicity. Auriculasin and millepurone demonstrated more potent activity, with millepurone showing significant inhibitory effects on mouse skin tumor promotion [148]. Phytoestrogens, acting through estrogen receptors, stimulate collagen, hyaluronic acid, and extracellular protein matrix synthesis, enhance skin vascularization, cell division, and defense against infections [149]. Daidzein is a phytoestrogen isoflavone derived from soybeans and other leguminous plants. Research indicates that 7,3′, 4′-trihydroxyisoflavone (734-THIF), a secondary metabolite of daidzein, exhibits anti-oxidant, anti-atopic dermatitis, anti-melanin, and anti-skin cancer chemopreventive properties [150,151]. A study proposed 734-THIF nanoparticles loaded with E100–polyvinyl alcohol, which showed enhanced aqueous solubility and increased skin penetration on HaCaT cell lines [150]. The 734-THIF nanoparticles, powdered from polyvinylpyrrolidone K30, showed enhanced physicochemical properties. Furthermore, in HaCaT keratinocytes exposed to particulate matter, 734-THIF downregulated MAPK pathway activation, which decreased the excessive expression of COX-2 and MMP-9 [152]. Genistein has potential defense against UVB-induced inflammation and aging. It inhibits inflammatory cytokines, specifically PLANH1, MIF, IL-1, and CXCL1. It also reduces the amount of UVB-induced skin folds and wrinkles in animal models, specifically rat dorsal skin. Additionally, it decreased the degree of UVB-induced wrinkles in human subjects [153].

A study found a mechanism that might connect genistein to photoprotection. Nitric oxide (NO) is an element that helps inhibit cell division following UVB exposure. Genistein prevents the reaction between H_2O_2 and NO, thereby reducing the production of ONOO-. It increases tissue preservation and cell division [154]. Biochanin A suppresses UV-induced COX2 expression through MLK3 suppression. It is a promising prospective anti-cancer drug since COX2 may reduce the proliferation of SCC cells in vivo [155]. A study investigates the anticarcinogenic properties of isoflavone equol in protecting hairless mice from skin cancer. Using equol lotions daily, mice were found to delay tumor emergence and decrease tumor multiplicity. The oil also significantly decreased the average diameter of SCC and the percentage of tumors that progressed from benign to malignant [156].

4.9. Cryptolepine

Cryptolepine, an alkaloid, is derived from the roots of the shrub *Cryptolepis sanguinolenta*, a common plant in Central and West Africa. TNFα and iNOS cryptolepine have been found to have anti-inflammatory properties across several animal model systems by inhibiting COX-2/PGE signaling. The study investigates the anti-tumor potential of cryptolepine, as inflammation is linked to the development and spread of malignancies. The SCC-13 and A431 cell lines were used as an in vitro model in the study to identify the ramifications of criptolepine on cancer cells. Cryptolepine treatment markedly decreased topoisomerase activity, likely attributable to DNA damage, resulting in NMSCC cell viability loss, colony formation impairment, and increased apoptosis. Topoisomerases, crucial for DNA replication and cell proliferation, can be disrupted by cancer cells, leading to DNA damage and death. It is investigated the impact on the proliferation of human NMSCC. SCC-13 and A431 cells have higher levels and activity of topoisomerase compared to normal human epidermal keratinocytes. Cryptolepine treatment reduced topoisomerase activity, leading to DNA damage. This damage caused increased phosphorylation, activation of the p53 signaling cascade, downregulation of cyclin-dependent kinases, and disruption of mitochondrial membrane potential [157].

Criptoleptine's mode of action involves enhancing phosphorylation of ATM/ATR, BRCA1, Chk1/Chk2, and γH2AX, leading to DNA impairment. Additionally, this substance downregulated cell division-related proteins, cyclin-dependent kinases, cyclin D1, cyclin A, and cyclin E, and activated the p53 signaling pathway. Furthermore, Cytokines c are released, causing a weakening of the integrity of the mitochondrial membrane potential [109,157]. A study used NMSCC, SCC-13, and A431 as in vitro models to investigate their therapeutic impact. The results showed that after treatment with cryptolepine, topoisomerase expression and activity significantly decreased, leading to significant DNA damage and increased DNA-PK expression. Cryptolepine also activated the p53 signaling cascade, leading to increased protein expression and cell death [158]. Another study evaluated the therapeutic impact of cryptolepine on melanoma cell proliferation. It significantly suppressed the development of melanoma cells but not normal melanocytes, leading to decreased mitochondrial membrane potential, decreased protein expression, and decreased mTOR signaling. It also significantly inhibited tumor growth in A375 xenograft-bearing nude mice, suggesting that phytochemicals with minimal toxicity could be investigated for melanoma treatment [159].

4.10. Glycyrrhizic acid

Glycyrrhizic acid (GIA) is a promising anti-cancer agent, and its permeability, bioavailability, and solubility were optimized using transethosomes. The GA-TE gel was found to be effective in treating skin cancer, with improved permeability and penetration, retention, deposition, and distribution compared to traditional gels [160]. GIA is the terpenoid under investigation in the field of skin malignancies. *Glycyrrhiza glabra* is the source of GlA, which targets the TME and alters immune responses to exhibit strong anti-tumor efficacy against melanoma. GlA is a treatment method that induces melanoma cells to undergo apoptosis and reduces their proliferation. The process involves reducing the anti-apoptotic protein Bcl2 and increasing pro-apoptotic factors like caspase 3 and Bax. GlA alters TME cytokine profiles, promoting a Th1 immune response favorable to tumor rejection by shifting anti-inflammatory to pro-inflammatory cytokines. GlA inhibits STAT3 phosphorylation, crucial for the immunosuppressive activity of Myeloid-Derived Suppressor Cells (MDSCs) and T Regulatory Cells (Tregs). As a result, MDSC-associated factors are downregulated while Treg markers are decreased. GlA's efficacy increases when amalgamated with *Mycobacterium indicus* pranii, particularly for treating advanced-stage melanoma [161]. The GlA approach to melanoma treatment and immunotherapy makes it a viable option for cancer treatment. Most non-melanoma skin malignancies are generated by UVB radiation, which damages skin cells. GlA protects skin cells from these stressors. GlA exhibits photoprotective properties against UVB radiation-induced damage in primary human dermal fibroblasts (HDFs) via a variety of routes. GlA substantially diminishes cell mortality in UVB-irradiated HDFs and prevents the formation of Cyclobutane Pyrimidine Dimers, a key DNA damage mechanism. Additionally, it reduces DNA fragmentation, which may indicate that it protects HDFs from UVB-induced DNA damage. GlA demonstrates robust antioxidant capabilities through inhibiting the production of ROS due to UVB exposure. HDFs are produced through the release of ER stress resulting from oxidative stress from GlA. Additionally, it affects autophagy, a mechanism that breaks down and recycles cells. Furthermore, GlA therapy, particularly in the early hours after UVB irradiation, has been found to alter the expression levels of autophagy-related proteins like p62, BECN1, mTOR, and ATG7. GlA downregulates DNA damage marker proteins in UVB-exposed HDFs, stabilizes the AKT/PTEN axis, and protects cells from UVB-induced damage. Its defense against UVB damage is enhanced by rapamycin and chloroquine [162,163]. A study investigated the impact of GIA on DNA damage repair and melanoma cell apoptosis induced by cisplatin. SK-MEL-28 cell viability decreased with GIA concentration increase, while apoptosis increased significantly. Cisplatin plus GIA reduced melanoma cell viability and accelerated cytological cell death compared to GIA or cisplatin therapy alone. The combination therapy increased protein expression levels and increased molecular-level DNA damage [164].

4.11. Sulforaphane

Broccoli and its sprouts are rich in sulforaphane (SFN), a key component of the isothiocyanate family [165,166]. SFN affects both cancerous and healthy cells differently, triggering apoptosis and inhibiting proliferation by inducing cell cycle regulatory proteins, like p21 and p16 [167]. The increase in cancer cell activity can be ascribed to the suppression of histone deacetylase (HDAC) expression and activity. Green tea polyphenols (GTP) and SFN, when combined with dietary DNMT inhibitors, have been found to reactivate the p21 and Klotho genes through histone acetylation [168]. Normal keratinocytes, unlike cancer cells, exhibit resistance to SFN-induced suppression of HDAC and cell proliferation [169]. SFN, by inhibiting HDACs and DNA methylation, exhibits potent anti-cancer properties, particularly in combating skin cancer [170]. SFN inhibits DNA methyltransferases and HDACs in JB6 mouse skin epidermal cells exposed to TPA, thereby reactivating Nrf2, a transcription factor that regulates antioxidant enzymes, and preventing malignant transformation [171]. SFN, when applied topically to mouse skin, enhances the synthesis of GSH and GST4, thereby preventing skin mutagenesis via the Nrf2-dependent pathway (Table 1) [172]. Polycomb group proteins, involved in chromatin remodeling and gene expression suppression, are another epigenetic regulator-related anti-tumor mechanism of SFN. Several skin malignancies have been found to increase the expression of polycomb group proteins, such as Bmi-1, Ezh2, and SUZ12 [170]. The most common non-melanoma skin cancer that has been studied in SFN treatment is SCC. SFN exposure in SCC prevents cancer growth and in vivo metastasis by reducing arginine methylation at histone 3 (H3). SFN-induced proteasomal degradation of methylosome protein 50 (MEP50) and arginine N-methyltransferase 5 (PRMT5) is responsible for this reduction. The reduction of dimethylated arginine 3 at H4 (H4R3me2) is a result of arginine methylation at H3 and H4, a process facilitated by both enzymes [173]. Furthermore, kinetic analysis and a biotin-tagged SFN analog (Biotin-ITC) showed that SFN covalently binds to recombinant type 2 transglutaminase (TG2), permanently blocking its transamidase activity. The aggressive SCC phenotype is maintained by partially inhibiting GTP binding and inducing an open/extended conformation [174].

Additionally, SFN and cisplatin combination therapy for SCC reduced the quantity of cancer stem cells within the tumor and inhibited

Table 1
An overview of natural compounds is used to prevent and treat skin cancer.

Natural compounds	Study type	Finding	Ref.
Resveratrol	*In vitro* and *Ex vivo*	Developed a dual drug-loaded nanostructured lipid carrier gel to improve the disposition of quercetin and resveratrol in the dermal and epidermal layers.	[125, 181]
Curcumin	*In vivo*	Prevented skin cancer in SKH−1 mice caused by UV Radiation.	[96, 182]
Silymarin	*In vivo*	Decreased tumor incidence, multiplicity, and volume per mouse in the UVB-induced tumor initiation protocol, 100–60 % in the UVB-induced tumor promotion protocol, and 97 % in the UVB-induced full carcinogenesis protocol.	[183, 184]
Gallic Acid	*In vitro*	Inhibited cell migration and proliferation in BCC, lowers HSP90AB1 levels in cancer cells, accelerates cell death, and decreases cell migration and proliferation in SCC.	[116, 185]
Quercetin	*In vitro*	Decreased UVB-induced skin edema by inhibiting the NF-Kβ/COX−2 signaling pathway.	[122, 186]
Apigenin	*In vitro*	Triggered apoptosis by reducing sulfiredoxin expression and activating the MAPK signaling pathway.	[135, 187]
Kaempferol	*In vivo*	Inhibited the growth of tumors by focusing on RSK2 and MSK1.	[144, 147]
Isoflavonoids	*In vivo*	Prevented hairless mouse skin from carcinogenesis caused by UV radiation alone or in combination with a chemical cocarcinogen.	[156]
Cryptolepine	*In vitro*	Activated p53, promotes apoptosis, increases ATM/ATR, BRCA1, Chk1/Chk2, and γH2AX phosphorylation, inhibits cyclin-dependent kinases, and has anti-proliferative effects.	[157, 158]
Glycyrrhizic acid	*In vitro*	Prevented skin cells from UVB rays, reduced DNA damage, and promoted autophagy, restoring the AKT/PTEN axis, which is influenced by autophagy regulators.	[162, 164]
Sulforaphane	*In vivo*	The application of SFN on mouse skin enhances the production of GSH and GST4, thereby preventing skin mutagenesis via the Nrf2-dependent pathway.	[172, 176]
Lycopene	*In vitro*	Inhibited the growth of normal skin cells during the promotion phase and lowered the frequency and number of cutaneous tumors.	[188, 189]
Cannabinoids	*In vivo*	Cannabinoid receptors 1 and 2 (CB1/2) are directly activated by UV radiation, and animals lacking CB1/2 exhibit reduced UVB-induced skin carcinogenesis and resistance to inflammation.	[190, 191]
Astaxanthin and Fucoxanthin	*In vitro*	Suppressed the transformation of mouse skin JB6 P + cells induced by TPA.	[192, 193]
Capsaicin	*In vivo*	Regulated inflammation, Erk, and p38, influencing DMBA/TPA-induced skin carcinogenesis in mice.	[194, 195]
Eugenol	*In vivo*	Inhibited DMBA-induced croton oil-induced skin carcinogenesis in mice.	[196, 197]
Epigallocatechin−3-Gallate	*In vitro*	Exhibited anti-proliferation potential by deactivating β-catenin signaling and decreasing its targets, including MMPs, c-Myc, and VEGF, while also lowering PGE2 and COX−2 levels.	[198, 199]
Genistein	*In vitro* and *In vivo*	Inhibited UVB-induced inflammatory cytokines CXCL1, IL−1, MIF, and PLANH1 in vivo, and reduced skin creases and wrinkles in animal models and human subjects.	[153, 200]
Luteolin	*In vitro* and *In vivo*	Inhibited UVB-induced cell production and reduces mitogen-activated protein kinases and Akt signaling by attenuating PKCε and Src kinase activities.	[201, 202]

tumor formation [175]. A study on SFN is effective in preventing skin cancer in animal models. SFN acts as a protective agent, preventing cell growth, reducing tumor onset, and reducing carcinogenesis. It also blocks the activator protein 1 signaling pathway, protecting against UVB-induced skin carcinogenesis. While more research is needed to determine the best dosage, application time, and administration technique for humans, SFN could potentially supplement or provide an alternative to current skin cancer prevention strategies [2]. A study investigated whether SFN could lower skin cancer in mice by inhibiting the sulfatase-2 enzyme. The results showed that sulforaphane inhibited sulfatase-2 activity, increasing heparan sulphate proteoglycans (HSPGs) and decreasing glypican–3. It also decreased the expression of NFκB, TNF-α, IL-1β, and caspase-3 and stimulated Nrf2. Additionally, SFN-treated skin cancer mice showed a decrease in epithelial dysplasia, acanthosis, and hyperkeratosis [176]. Another study was conducted to assess ethosomes® and transfersomes® as ultradeformable vesicular carriers for percutaneous delivery of SFN for skin cancer treatment. *In vitro* research showed increased percutaneous penetration of sulforaphane through human stratum corneum and epidermal membranes, and enhanced anticancer activity when combined with SFN [177]. Moreover, a study using next-generation sequencing (NGS) technology found that SFN decreased tumor incidence and quantity, with early protective effects more pronounced. The main pathways linked to SFN treatment include Th1 and Th2 activation pathways, PTEN signaling pathways, p53 signaling, and cell cycle G2–M DNA damage checkpoint regulation [178]. SFN improves carcinogen detoxification and prevents chemically induced carcinogenesis in animal models. SFN also prevents tumor growth, stops the cell cycle, and promotes apoptosis. Topical SFN significantly inhibited TPA-induced mouse skin tumorigenesis, reducing ornithine decarboxylase activity, a molecular mechanism linked to cancer prevention that is SFN-dependent [179]. A study investigates the effects of SFN treatment on melanoma in zebrafish and B16F10 melanoma cell lines. SFN treatment boosts tyrosinase synthesis and decreases cell growth, while controlling protein expression of tyrosinase, PKCβ1, and MTF. Treatment with Cytochalasin D and Jasplakinolide reveals a link between melanin biosynthesis and SFN-induced alterations in the actin cytoskeleton. SFN causes the B16F10 melanoma cell line to produce more melanin [180].

4.12. Lycopene

Plants including tomatoes, watermelons, red carrots, and papayas contain the antioxidant lycopene, which has significant health advantages and possible bioactivity. Eight isoprene units are joined to form a tetraterpene structure in this molecule. Research on eleven linear double bonds has explored their anti-cancer properties, including influencing signal transduction pathways and preventing apoptosis and cell proliferation. Numerous studies have emphasized its biological action against

skin malignancies and photoprotection [203,204]. Regular lycopene intake protects human skin from harmful UVR effects like erythema, extracellular matrix changes, and mitochondrial DNA damage [205]. Lycopene inhibited normal cutaneous cell carcinogenesis and reduced the prevalence and frequency of cutaneous neoplasms in mice and chemically produced cell models. The impact of this impact was linked to the transcription factor Nrf2 and the activation of antioxidant enzymes. Furthermore, lycopene's upregulation of autophagy protein p62 led to the degradation of Keap1, the primary protein responsible for maintaining Nrf2 in the cytoplasm [188].

4.13. Cannabinoids

Research indicates that both synthetic and natural cannabinoids can impact various biological processes in various forms of cancer [206]. Research on endocannabinoid system-targeting medications for cancer palliative care and systemic chemotherapeutic therapies has shown potential in preclinical models. Cannabinoids have been demonstrated to have anticarcinogenic impacts at various stages of skin cancer development, including causing apoptosis and inhibiting tumor growth. Furthermore, cannabinoids could be used as a treatment or preventative measure for skin cancer, and emphasized the critical role that the endocannabinoid system plays in controlling skin processes [191]. CB1 and CB2 are the two cannabinoid receptors that make up the endocannabinoid system. The G-protein coupled receptors CB1 and CB2 interact with endogenous ligands, such as N-arachidonylethanolamine (AEA) for CB1 and 2-arachidonylglycerol (2AG) for CB2 [207]. Another study found that cannabinoid receptors 1 and 2 (CB1/2) are directly activated by UV radiation, and animals lacking CB1/2 exhibit reduced UVB-induced skin carcinogenesis and resistance to inflammation. CB1/2 receptors are crucial for skin cancer and UV light-induced inflammation. Research indicates that while cannabis chemicals cause cell death, chemical carcinogens and UVB radiation can activate cannabinoid receptors, potentially increasing tumor growth. The effects of cannabinoids on skin cancer cells may be influenced by their concentrations. Exogenous cannabinoids at micromolar levels inhibit tumor growth, whereas endogenous endocannabinoids at nanomolar levels associated with carcinogen exposure enhance it [190]. Furthermore, endocannabinoid Arachidonoyl-ethanolamine (AEA) induces apoptosis in a variety of tumor types, particularly in cancers that overexpress COX-2. COX-2 is responsible for converting AEA into J-series prostaglandins, which in turn trigger endoplasmic reticulum stress. The high levels of COX-2 in NMSCs and other epithelial malignancies set them apart from healthy cells. AEA may be a viable topical treatment for the eradication of various types of skin cancer [208,209]. A study on the ramifications of cannabinoids, specifically THC, on skin cancer in mice found that THC significantly suppressed tumor growth *in vivo*, based on its receptor binding. This finding supports the effectiveness of exogenous cannabinoids in treating melanoma, but contradicts the idea that the endogenous cannabinoid system contributes to skin cancer [210].

4.14. Carotenoids

Plants contain a large number of bioactive antioxidant molecules called carotenoids. The polarity of carotenoids allows for their classification. Carotenes and xanthophylls, like β-carotene and lycopene, are more polar owing to their presence of hydroxy- or keto-functional groups in their molecular structures [211,212]. UVR exposure is a significant risk factor for the development of skin cancer. OS, which disrupts signal transduction pathways, is the primary cause of numerous adverse effects [3]. Carotenoids are considered protective factors against skin cancer development due to their antioxidant and photoprotective properties. Controlling the connexin gene expression enhances gap junctional cell-cell communication and activates the transcription machinery of the antioxidant response element [211]. A study assessing the relationship between α-tocopherol and carotenoids and the danger of nonmelanoma skin cancer found no correlation between serum levels of these nutrients and the danger of acquiring a later BCC. The study also found no independent correlation between serum levels of α-carotene, β-carotene, lycopene, and α-tocopherol and the risk of a later SCC. Serum lutein, zeaxanthin, and β-cryptoxanthin were positively associated with SCC risk [213]. Another study investigated the relationship between skin cancer incidence and dietary components like vitamins A, C, E, folate, total carotene, and carotenoids. The study followed two cohorts of men and women for up to 10 years, using FFQs to monitor diet and medical records. Results showed no negative correlation between these dietary components and skin cancer incidence after adjusting for behavioral, sun exposure, and sun sensitivity risk factors [214].

4.15. Astaxanthin and fucoxanthin

Two distinct marine carotenoids that are well-known for their exceptional antioxidant properties are astaxanthin (ASX) and fucoxanthin (FX). Two terminal β-ionone-type rings are joined by a polyene chain to form ASX. Additionally, the molecule has a hydroxyl group at each end and two asymmetric carbons at the 3,3′-position of the β-ionone ring. Furthermore, hydroxyl and keto groups are added to the ring structure to incorporate oxygen [215]. The unique structure of FX includes a 5,6-monoepoxide, nine conjugated double bonds, an unusual allenic link, and several oxygenic functional groups, including hydroxyl, epoxy, carbonyl, and carboxyl moieties [216]. FX and ASX activate the Nrf2 signaling pathway, leading to CpG site demethylation and TPA-induced transformation in mouse skin JB6 P + cells [192]. Furthermore, FX therapy increases cellular antioxidant defense in human keratinocytes by triggering Nrf2-driven expression of GSH synthesis-related enzymes through PI3K/Akt signaling [217]. Research shows that applying 0.02 % ASX gel after chronic UVB irradiation in Wistar mice or 24 h before exposure to 5 μM of ASX in human keratinocytes can prevent oxidative DNA damage [218]. UV rays are a strong physical carcinogen, causing melanoma and non-melanoma skin cancers. Antioxidants, such as ASX and ellagic acid, protect cells from DNA damage and radiation-induced cell death. A study aimed to develop a gel to treat radiation dermatitis and assess the ROS scavenging capabilities of these antioxidants in Skin Melanoma (SK-Mel-28) cells. Results showed that both antioxidants reduced intracellular ROS and increased lipid peroxidation levels, enhancing their anticancer impact. The ASX-ellagic acid gel formulation was suggested to reduce UV-induced skin malignancies more effectively due to its beneficial synergism [219]. A study evaluated FX's molecular effects on melanoma cell lines (B16F10 cells). It induces cell cycle arrest and apoptosis, and decreases cell proliferation in a dose-dependent manner. Additionally, FX's anti-tumor efficacy was evaluated in vivo in Balb/c mice, showing significant tumor growth reduction [220].

4.16. Capsaicin

Among the primary popular spices in the world is capsaicin. The primary pungent ingredient that gives red peppers like jalapenos and red chilli peppers their spiciness is phenolic acid [221]. A study on mice showed that capsaicin increased skin carcinogenesis through COX-2 and EGFR activation, indicating a pro-carcinogenic effect in mice given TPA. It found that the administration of 12-O-tetradecanoylphorbol-13-acetate (TPA) to mice increased skin carcinogenesis by activating EGFR and COX-2 [222]. Capsaicin did not significantly accelerate the proliferation of murine cutaneous neoplasms relative to controls, preventing the formation of papillomas [223]. Capsaicin's chemopreventive properties involve activating cell cycle arrest, apoptosis, or cancer cell reduction by inhibiting the expression of COX-2, AP-1, NF-κB, and STAT3. The study linked capsaicin's chemopreventive action to cell death, cell cycle arrest, and reduced proliferation by suppressing COX-2, NF-κB, AP-1, and STAT3 expression [224]. Furthermore, by inhibiting

mitochondrial function, capsaicin has been shown to cause apoptosis in human cutaneous squamous cell carcinoma cell lines [225]. A study found that capsaicin significantly reduced melanoma cell migration without causing damage. This was due to the down-regulation of PI3-K and Akt, which inhibited cellular processes, suggesting capsaicin as an effective strategy for reducing invasion and metastasis in malignant melanoma treatment. Capsaicin impedes the propagation of extremely metastatic melanoma cells by inhibiting PI3-K and its downstream target, Akt [226]. Capsaicin, when amalgamated with HA14–1, an apoptosis inducer, can induce apoptosis in melanoma cell lines, potentially offering a potential therapy option for metastatic melanoma [227]. A study found that topical capsaicin marginally inhibited the development of papillomas in mice and did not encourage the growth of tumors on the skin of mice [228]. Capsaicin has a cocarcinogenic effect on skin tumorigenesis caused by DMBA and TPA. Topically treating mice's dorsal skin with capsaicin accelerates tumor formation and progression, causing more and larger tumors. The study also found that inflammation, Erk, and P38 work together to promote cancer in mice with carcinogen-induced skin cancer [194].

A study found that Capsaicin exerts an inhibiting impact on human melanoma A375 and C8161 cell lines. It triggers apoptosis, autophagy, and cell death in melanoma cells, suggesting it could be a unique candidate medication for melanoma treatment [195]. Capsaicin has selective anticancer properties and can function as a nutraceutical agent. It directly inhibited the tumor-associated NADH oxidase, tNOX, in melanoma cells, increasing its capacity for protein degradation. It also inhibited SIRT1 and tNOX, increased ULK1 acetylation, and triggered ROS-dependent autophagy in melanoma cells [229].

4.17. Eugenol

A phenolic component of cloves, eugenol, is additionally located in aromatic spices like basil, nutmeg, bay leaves, and cinnamon that are consumed by humans. Mice with skin cancer showed a delayed and decreased incidence of papilloma formation when eugenol was applied topically and when cloves were infused into their mouths [230]. Topical eugenol treatment can reduce inflammation by inhibiting COX-2 and iNOS expression, lowering proinflammatory cytokine levels, and modifying NK-κB expression [231]. Eugenol can modify p53 expression, suppress oncogenes like c-Myc and H-ras, and induce apoptosis by reducing E2F1 transcription activity [196,232]. A study found that a 2 % eugenol formulation demonstrated superior anti-inflammatory action in murine skin in comparison to topical piroxicam after 1.5 h [233]. Another study revealed that eugenol has a preventive effect on NMSC in Swiss albino mice. The application of DMBA, a carcinogen, to the dermis of mice yielded the development of tumors. Tumor initiation may be accomplished through a single administration of DMBA through DNA mutation. Then, during 28 weeks, 12-O-tetradecanoylphorbol-13-acetate (TPA) was administered biweekly to stimulate the skin tumors. TPA activates protein kinase C (PKC), which promotes cell proliferation. Eugenol pretreatment significantly slowed tumor growth and decreased the quantity of tumors relative to the control group treated with DMBA and TPA. Eugenol's anti-proliferation and pro-apoptotic properties were demonstrated by TUNEL staining and immunohistochemistry of the proliferation marker, proliferating cell nuclear antigen. Eugenol pretreatment led to elevated protein expression associated with DNA damage biomarkers P53 and P21WAF1, triggering apoptosis. Eugenol significantly reduced inflammatory biomarkers, iNOS and COX-2, due to decreased phospho-IkBα levels and inhibited NF-κB accumulation in the nucleus. TPA produces proinflammatory cytokines like IL-6, TNF-α, and PGE2, which increase inflammatory cell infiltration, vascular permeability, and epidermal hyperplasia [234], and were likewise decreased by eugenol therapy [231]. In the NMSC model of DMBA/croton oil-induced skin carcinogenesis in Swiss albino mice, the anticarcinogenic efficacy of eugenol was also investigated. Croton tiglium seeds are used to produce toxic, viscous Croton oil, which was used topically to cause a tumor. Oral eugenol was given 15 days before DMBA and croton therapy. Eugenol treatment significantly enhanced the survival rate of mice while decreasing the incidence and size of skin cancers. Eugenol reduced cell growth by inhibiting the expression of c-Myc and H-ras oncogenes through mRNA and protein suppression. Eugenol therapy caused apoptosis in mice's skin lesions by upregulating proapoptotic genes Bax, p53, and active caspase-3 and downregulating antiapoptotic gene Bcl2 [196].

Additionally, eugenol (Fig. 5) was discovered to be a strong suppressor of melanoma cell growth. Eugenol therapy significantly reduced tumor size in B16F10 xenograft mice by 62 % and delayed their growth by 19 %. Furthermore, the eugenol-treated mice did not show indications of invasion or metastasis, while 50 % of the control group did. The TUNEL analysis of tumor sections indicates that Eugenol triggers apoptosis in melanoma neoplasms. The anti-proliferation mechanism was assessed utilizing the human malignant melanoma cell line, WM1205Lu. Eugenol induces apoptosis by causing a cell cycle arrest in the S phase [232]. A class of transcription factors known as the E2F proteins is essential for regulating the cell cycle [235]. Melanoma cells proliferate continuously due to dysregulated transcriptional activity of the E2F family, with E3F2 and E2F4 being particularly prevalent in actively proliferating melanoma cells [236]. Eugenol's antiproliferative effects were demonstrated by inhibiting E2F1 transcriptional activity in WM1205Lu [232].

4.18. Epigallocatechin-3-gallate

Green tea contains a polyphenol component called epigallocatechin-3-gallate (EGCG). Green tea phenols (GTP), which have antiproliferative, anti-inflammatory, and anti-oxidant qualities, are the most researched chemopreventive component [237]. A study found GTP and discovered that its anti-inflammatory qualities may be associated with the suppression of COX and lipoxygenase activity, which would reduce the burden of skin tumors by reducing epidermal edema and hyperplasia [238]. EGCG has an antioxidant effect on human skin through topical application, which decreases the generation of nitric oxide and hydrogen peroxide in the epidermis and dermis caused by UV light [239,240]. The suppression of MAPK signaling pathways may be connected to this decrease [241,242]. Modification of NF-κB pathways [243], suppression of tumor promoter-induced activator protein (AP-1) activation [244], prevention of angiogenesis, and recruitment of cytotoxic T lymphocytes [66] are further hypothesized to have anti-proliferative activities [245]. EGCG increases the susceptibility of melanoma cells to growth suppression brought on by interferon, which reduces cell proliferation and triggers apoptosis [246]. EGCG and interferon demonstrated superior performance when combined, suggesting their combined effect on tumor reduction. The downregulation of the inflammasome may reduce NF-κB activity and IL-1β release, thus reducing tumor growth [247]. Additionally, EGCG, by reducing TNF receptor-associated factor 6 (TRAF6) activity, prevents melanoma cell invasion and migration [248]. EGCG is a well-studied option for chemoprevention of skin cancer. Mice administered green tea components orally or by injection showed reduction or even regression of ultraviolet-induced skin papillomas [249]. Nevertheless, a study found that topically applying pure EGCG to mice reduced tumors, while oral administration was not effective [250]. The oral and topical EGCG therapy is the inadequate skin dispersion of EGCG following oral intake. The study involving human volunteers validated the preventive impacts of green tea polyphenols on UV-induced erythema [251].

A randomized clinical trial found that healthy individuals who received vitamin C supplementation with green tea did not show considerably lower skin erythema or leukocyte infiltration levels [252]. EGCG has anti-carcinogenic properties in skin tumor models. Its cytotoxic actions may be partially mediated by its implications on β-catenin signaling, which is increased in skin malignancies. EGCG treatment of human skin cancer cell lines A431 and SCC13 led to decreased cellular

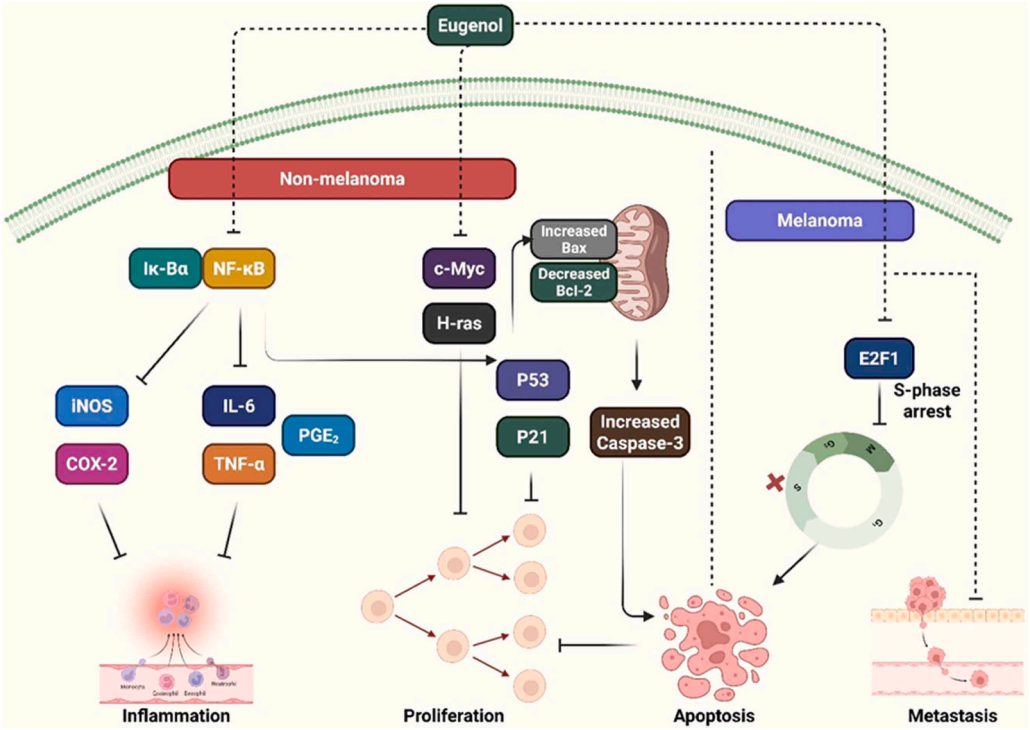

Fig. 5. Eugenol prevents skin cancer by suppressing inflammatory markers, inhibiting NF-κB, and inhibiting E2F1 expression in melanoma. It also prevents metastasis, apoptosis, and cell cycle arrest.

viability and increased cell death, with β-catenin signaling inactivation being linked to these effects [198]. EGCG affects the activity of two PcG proteins, Bmi-1 and Ezh2, leading to a decrease in cell survival rates in SCC-13 cells. This is due to reduced expression of proteins promoting cell cycle progression and greater production of proteins impeding cell cycle progression. EGCG therapy also decreases Bcl-xL expression and promotes Bax, indicating its impact on PcG-mediated epigenetic pathways [253]. A study using EGCG reduced cell proliferation and viability in a dose-dependent manner. It increased cyclin kinase inhibitor levels and diminished cyclin D1 and cdk2 protein levels. It may also be beneficial in treating melanoma, either alone or in combination with existing treatments [254].

4.19. Genistein

One isoflavone component that comes from soybeans is genistein [255]. Genistein has cancer chemopreventive qualities in several cancers, such as neuroblastoma and breast cancer, in addition to melanoma and non-melanoma skin cancers [256–259]. Additionally, genistein has anti-angiogenesis effects, inhibits tumor growth and spread, and causes cell cycle arrest [260], and increases cell death [261]. By protecting against photoaging and UV-induced skin cancer, genistein treatment decreased UV-induced sunburn in people. Genistein pretreatment effectively prevented UVB-induced oxidative damage in hairless mice's epidermis by inhibiting hydrogen peroxide and malondialdehyde lipid peroxidation. In humans with UV-induced sunburn, genistein inhibited photoaging and Ultraviolet-induced cutaneous carcinoma. In the epidermis of hairless mice, Genistein pretreatment before UVB exposure was shown to inhibit UVB-induced oxidative dysfunction [262]. Genistein's photoprotective properties have been shown in human-reconstituted skin, as it effectively suppresses UVB-induced pyrimidine dimer production in a dose-dependent manner. The research indicated that genistein, when applied to reconstructed human skin, efficiently prevents the production of UVB-induced pyrimidine dimers [263]. Furthermore, in a xenograft model, genistein has positive effects on melanoma cells by interfering with cell cycles and preventing tumor growth and spreading [264]. Genistein inhibits the advancement of the melanoma cell cycle by targeting p53, p21, and a checkpoint kinase called Chk2 [265].

Furthermore, genistein (50 μM for 4 days) interacted with the cell cycle, prevented metastasis, and inhibited neoplastic proliferation in xenograft models, demonstrating strong inhibitory actions in opposition to melanoma cells [265,266]. Genistein regulates the cell cycle and stabilizes protein-linked DNA strand breaking, promoting the differentiation of melanoma cells [267]. Moreover, genistein has anticancer properties in animal models and cultured cells. It is a selective inhibitor of protein tyrosine kinase (PTK), which suppresses skin cancer induced by DMBA and accelerated by TPA. In a bifurcated carcinogenesis model, genistein significantly reduced tumor frequency and quantity by 20 and 50 % in DMBA-induced skin cancers. In promotion trials, genistein reduced tumor multiplicity by 60 and 75 %, inhibiting TPA-promoted skin carcinogenesis. It also reduced TPA-stimulated H_2O_2 and inflammatory reactions in mouse skin [268].

4.20. Luteolin

A flavonoid molecule called luteolin is located in a wide range of foods, including olives, celery, peppers, and carrots. Besides its antioxidant, antitumor, and anti-inflammatory properties, luteolin has been shown to block angiogenesis, induce apoptosis, and make cells more sensitive to anti-cancer treatments in a range of cancers [269,270]. Luteolin, by controlling the β3 integrin/focal adhesion kinase (FAK) signal pathway, promotes melanogenesis and reduces the invasive capacity of melanoma cells [271,272]. Furthermore, luteolin suppresses cellular proliferation and promotes apoptosis in melanoma cells by attenuating ERK1/2 signaling, downregulating Bcl-3, and upregulating Bax [273,274]. Luteolin has strong chemopreventive attributes against UVB-induced cutaneous carcinoma. It inhibited the production of cyclooxygenase-2, activator protein-1, and NF-κB in JB6 P + cells, reduced UVB-induced activation of mitogen-activated protein kinases and the Akt signaling pathway, and binds directly and ATP-competitively to Src and PKCε. It also targets these pathways to

prevent skin cancer [201]. A study used phospholipid and edge activator to form luteolin-loaded nanosized vesicles using a solvent evaporation-hydration process. Luteolin-loaded nanosized vesicles showed an encapsulation efficiency of 92.43 ± 4.12 % and a particle size of 189.92 ± 3.25 nm. The formulation was further transformed into Carbopol 934 gel for improved skin retention. The study found ideal medication content, pH, viscosity, and spreadability, increased luteolin release and permeation, and superior antioxidant and antibacterial activity. The IC50 value was lower than pure luteolin, making it an alternative to traditional delivery methods [275]. Luteolin has potential therapeutic benefits for melanoma due to its low bioactivity and poor water solubility. Researchers formed nanoparticles encasing luteolin with ROS-responsive material, PPS-PEG, to improve luteolin's water solubility, speed up its release, and intensify its anti-melanoma effect. Luteolin-PPS-NPs were formed, and their size and shape were assessed using TEM and DLS. *In vitro* tests showed minimal cytotoxicity against HSF and were well absorbed by SK-MEL-28 cells. Luteolin-PPS-NPs also reduced tumor cell invasion, migration, and proliferation [276].

Luteolin has been studied for its potential anti-cancer effects in melanoma cells. The study investigated its impact on A375 human melanoma cells, demonstrating its effects on growth, apoptosis, and expression of MMP-2, MMP-9, and PI3K/AKT1. Luteolin reduced the expression of MMP-2 and MMP-9 via the PI3K/AKT pathway, inhibiting proliferation and causing apoptosis. In a xenograft mouse model, luteolin suppressed the proliferation of A375 cells in tumors. Overall, luteolin shows promise as an anti-cancer treatment for human melanoma [277]. A study evaluates the in vitro and in vivo anti-melanoma characteristics of luteolin. It decreased melanoma cell viability, inhibited migration and invasion, and caused apoptosis. It also decreased the expression of STAT3-targeted genes involved in invasion and cell survival. It has anti-melanoma properties by reducing STAT3 activation and increasing STAT3 protein degradation, which in turn reduces STAT3 signaling [278].

5. Clinical trials

Curcumin's low solubility and hydrophobicity inhibit its oral bioavailability, making therapeutic application challenging. Topical therapy regimens may provide clinical benefits and lessen these difficulties. Recent studies have explored nanoformulations like liposomes and PEGylated solid lipid nanoparticles to enhance solubility and address issues [279]. The clinical trial addressed the challenges associated with oral curcumin administration. Oral transmucosal administration of microgranular curcumin has been found to increase its bioavailability, potentially preventing pre-neoplastic lesions from developing into invasive SCC [98]. A study involving genetically modified mice found that calcipotriol, a topical TSLP inducer, inhibited skin carcinogenesis in mice. The study found that calcipotriol plus 5-FU treatment significantly reduced the number of actinic keratoses by 87.8 % compared to Vaseline plus 5-FU. This was due to the expression of TSLP, HLA class II, and natural killer cell group 2D ligands in lesional keratinocytes, leading to a significant infiltration of CD4 + T cells. The ClinicalTrials.gov website provides information on trial registration, specifically NCT02019355 [280]. A study found that beta-carotene treatment does not lower the incidence of new skin cancers in those who have already had a nonmelanoma skin cancer. The study involved randomly allocating 50 mg of β-carotene or a placebo daily to 1805 patients with recently developed nonmelanoma skin cancer. The active treatment group had significantly higher plasma β-carotene levels than the control group, indicating good adherence to the recommended treatment [281]. The Phase II study, randomized, double-blind, placebo-controlled, and focused on topical EGCG dosage, found no significant impact on NMSC prevention [282]. A study found that applying 5 % fluorouracil to the face and ears twice daily reduced the number of surgeries for SCC and NMSC/KC treated with Mohs surgery [283]. The therapeutic chemopreventive properties of EGCG have not been evaluated in many clinical trials. A human study found that topical green tea polyphenols can protect against UV-induced erythema [249]. A recent clinical experiment involving 50 healthy people found no significant decrease in skin erythema or leukocyte infiltration after taking oral green tea extract with vitamin C [250]. EGCG has been studied as a chemopreventive drug in clinical trials. A double-blind phase II clinical research study involved 51 volunteers with AK who received topical EGCG for 12 weeks. The formulation's ineffectiveness and low absorption may have contributed to the lack of significant differences between the treatment and placebo groups in NMSC prevention [284]. A study involving 932 participants with a history of two keratinocyte carcinomas treated with topical fluorouracil as a chemoprevention measure for NMSC [285].

6. Conclusion and future perspectives

Natural compounds provide a promising treatment for skin cancer by targeting biochemical pathways involved in carcinogenesis, including cell proliferation, apoptosis, inflammation, angiogenesis, and metastasis. These drugs are potential medicines for chemoprevention and therapeutic intervention due to their multi-targeted mechanisms, minimal toxicity, and synergistic benefits with traditional therapy. This review highlights the therapeutic significance of phytochemicals like curcumin, quercetin, EGCG, and resveratrol in altering key signaling pathways like PI3K/Akt, MAPK, NF-κB, and Wnt/β-catenin. To effectively implement these promising preclinical findings in clinical settings, several challenges must be overcome. These consist of inadequate pharmacokinetic information, low bioavailability, and a lack of extensive human clinical trials. Subsequent investigations must concentrate on developing innovative delivery systems like liposomes and nanoparticles, conducting structure-activity connection analyses, and combining conventional therapies for improved efficacy. Furthermore, the combination of molecular profiling and omics technology may help to customize treatments based on natural compounds. Further research is needed to fully utilize natural chemicals' therapeutic potential for effective and long-term skin cancer treatment. Future research should focus on strategic translation of phytochemicals into clinical practice, rather than descriptive studies, as several important directions emerge. Integrating natural substances into conventional therapies like immunotherapy, chemotherapy, or targeted therapy can enhance their effectiveness while reducing their toxicity. Synergistic treatments can improve therapeutic outcomes, especially in cases of recurrent or resistant skin cancers. Advanced delivery systems like transdermal platforms, liposomes, micelles, and nanoparticles are promising in overcoming challenges like low bioavailability, instability, and poor solubility in phytochemical clinical success. Personalized medicine involves tailoring phytochemical-based treatments to individual patient profiles, considering factors like metabolism, genetics, and tumor biology, to enhance therapeutic efficacy. Clinical validation is lacking despite robust in vitro and in vivo evidence linking preclinical and clinical research. Thorough randomized controlled studies are desperately needed to verify human safety, effectiveness, and dosage. Future research should explore understudied substances like eugenol, glycyrrhizic acid, and cryptolepine to understand their long-term safety profiles, synergistic interactions, and dual functions. Natural compounds provide a promising yet underutilized method for treating skin cancer. The drugs could transition from lab results to evidence-based, integrated therapy through addressing current constraints, implementing advanced delivery systems, and conducting meticulous clinical trials. Phytochemical-based therapies have the potential to revolutionize skin cancer prevention and treatment by enhancing traditional medicine through multi-targeted, individualized, and patient-centered approaches.

CRediT authorship contribution statement

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Declaration of Competing Interest

There is no conflict of interest exists.

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Data Availability Statement

No new data were created or analysed in this study.

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