Review

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A recent update on the connection between dietary phytochemicals and skin cancer: emerging understanding of the molecular mechanism

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Abstract

Constant exposure to harmful substances from both inside and outside the body can mess up the body's natural ways of keeping itself in balance. This can cause severe skin damage, including basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma. However, plant-derived compounds found in fruits and vegetables have been shown to protect against skin cancer-causing free radicals and other harmful substances. It has been determined that these dietary phytochemicals are effective in preventing skin cancer and are widely available, inexpensive, and well-tolerated. Studies have shown that these phytochemicals possess anti-inflammatory, antioxidant, and antiangiogenic properties that can aid in the prevention of skin cancers. In addition, they influence crucial cellular processes such as angiogenesis and cell cycle control, which can halt the progression of skin cancer. The present paper discusses the benefits of specific dietary phytochemicals found in fruits and vegetables, as well as the signaling pathways they regulate, the molecular mechanisms involved in the prevention of skin cancer, and their drawbacks.

Keywords: antioxidant, basal cell carcinoma, dietary phytochemicals, melanoma skin cancer, squamous cell carcinoma

Introduction

Skin structure

The skin is the largest organ in the human body and serves as a barrier between the internal and external environment. It plays a crucial role in protecting the body from physical, chemical, and biological damage, as well as in regulating body temperature, maintaining hydration, and providing sensory input[1]. The skin is composed of three main layers: the epidermis, dermis, and hypodermis (subcutaneous tissue) (Fig. 1)[2]. Each layer has its own unique structure and function, which work together to provide a protective and functional barrier. The epidermis is the outermost layer of the skin and is composed of several layers of keratinized epithelial cells. The thickness of the epidermis varies depending on the location on the body, with the thickest epidermis found on the soles of the feet and the thinnest on the eyelids. The epidermis is responsible for protecting the body from

HIGHLIGHTS

- Skin cancer is a type of cancer that arises from the uncontrolled growth of cells in the skin. There are three main types of skin cancer.
- This mutation also leads to the activation of the MAPK/ERK signaling pathway and abnormally promotes cell growth and division.
- The BRAF and NRAS genes are members of the RAS family of genes, which regulate cell growth and division.
- The CDKN2A gene encodes two proteins, p16INK4a and p14ARF, which act as tumor suppressors by regulating cell growth and division.
- Signaling pathways (MAPK pathway, PI3K/Akt pathway, Wnt pathway, Hedgehog pathway, Notch pathway, etc.) are involved in cell growth and proliferation.
- Phytochemicals found in fruits and vegetables, as well as the signaling pathways they regulate, the molecular mechanisms involved in the prevention of skin cancer.

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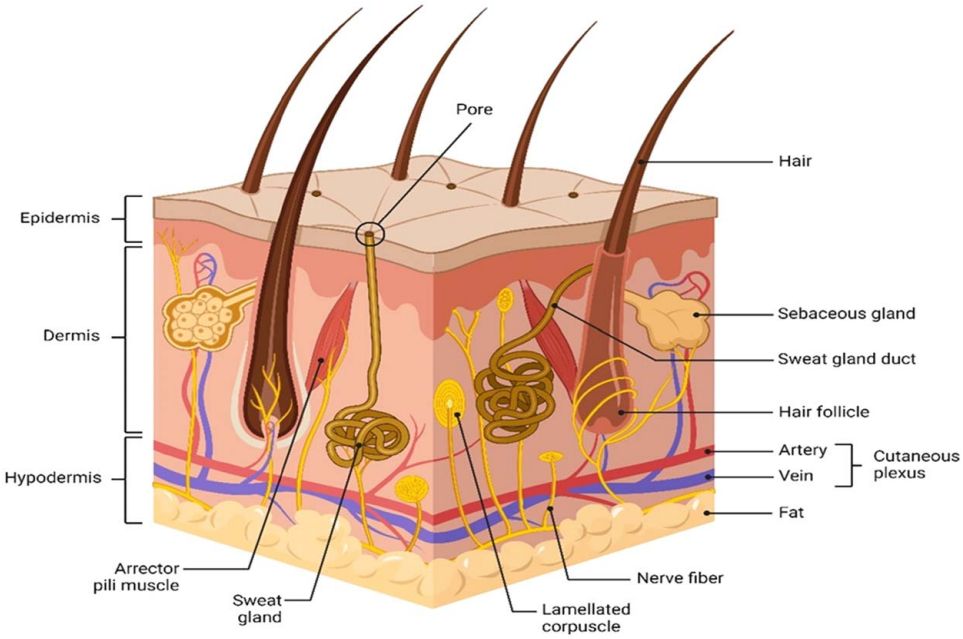


Figure 1. Skin anatomy (created with BioRender).

physical damage, UV radiation, and infection[3]. The dermis is the second layer of the skin and is located beneath the epidermis. The dermis is composed of connective tissue and is responsible for providing support and elasticity to the skin. The dermis also contains blood vessels, nerves, and sensory receptors. The hypodermis, also known as the subcutaneous tissue, is the deepest layer of the skin. The hypodermis is composed of adipose tissue and connective tissue and serves as a cushion for the underlying muscles and bones[4].

There are several types of cells present in the skin, each with its own unique function. Some of the main cell types in the skin include Keratinocytes, Melanocytes, Langerhans cells, Merkel cells, and Fibroblasts[5]. Skin cancer is the most common type of cancer in the United States and is caused by the uncontrolled growth of abnormal cells in the skin. The different cell types in the skin play a critical role in protecting against skin cancer. For example, melanocytes produce melanin, which helps to protect against UV radiation and reduces the risk of skin cancer. Langerhans cells are involved in the immune response and can help to identify and destroy abnormal cells before they can develop into skin cancer. Additionally, fibroblasts produce the extracellular matrix, which helps to prevent the uncontrolled growth and spread of abnormal cells. Overall, the different types of cells in the skin work together to maintain the integrity of the skin and protect against the development of skin cancer. Regular skin checks and sun protection can also help to reduce the risk of skin cancer[6,7].

Molecular mechanism of skin cancer

Skin cancer is a type of cancer that arises from the uncontrolled growth of cells in the skin. There are three main types of skin cancer: basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma[8–10]. The molecular mechanisms underlying skin cancer development involve mutations in several genes and pathways that regulate cell growth, division, and apoptosis[11,12]. BCC is the most common type of skin cancer, accounting for ~80% of all cases. It typically develops in the basal cells, which are located in the deepest layer of the epidermis. The molecular mechanisms underlying BCC development involve mutations in the sonic hedgehog (SHH) signaling pathway. The SHH signaling pathway plays an important role in embryonic development, and its activation is necessary for the development of the skin, hair, and nails. In adults, the SHH pathway is normally inactive in the skin. However, mutations in genes that regulate the SHH pathway can lead to its activation and the development of BCC[13,14]. The most common mutation in BCC is in the Patched-1 (PTCH1) gene, which normally acts as a tumor suppressor by inhibiting the SHH pathway. Mutations in PTCH1 lead to the activation of the SHH pathway, which results in the uncontrolled growth of basal cells and the development of tumors[15,16]. Other genetic and environmental factors can also contribute to the development of BCC. Mutations in the Tumor Protein 53 (TP53) gene, which is another tumor suppressor gene, can also lead to BCC development. Environmental factors, such as exposure to arsenic and ionizing radiation, can also increase the risk of developing BCC[17,18]. SCC is the second most common type of skin cancer, accounting for ~16% of all cases. It typically develops in the squamous cells, which are located in the upper layers of the epidermis[19]. The molecular mechanisms underlying SCC development involve mutations in several genes, including TP53, Cyclin-dependent kinase inhibitor 2A (CDKN2A), and Harvey rat sarcoma viral oncogene homolog (HRAS). Like BCC, mutations in TP53 and CDKN2A are commonly found in SCC. TP53 mutations can lead to the uncontrolled growth of squamous cells and the development of tumors[20,21]. CDKN2A mutations can also contribute to SCC development by preventing cells from undergoing apoptosis, which is a process that helps to eliminate damaged cells from the body[22,23]. Mutations in the HRAS gene, which is a member of

the Rat Sarcoma (RAS) family of genes, are also found in SCC. The RAS genes normally regulate cell growth and division, but mutations in these genes can lead to the development of tumors. In SCC, mutations in HRAS lead to the uncontrolled growth of squamous cells and the development of tumors[24,25]. Melanoma is a type of skin cancer that arises from the uncontrolled growth of melanocytes, which are the cells that produce the pigment melanin. Melanoma is the most dangerous type of skin cancer, as it can metastasize and spread to other parts of the body. The molecular mechanisms underlying melanoma development also involve mutations in several genes and pathways that regulate cell growth, division, and apoptosis[26–29].

B-Raf proto-oncogene, serine/threonine kinase (BRAF), and neuroblastoma RAS viral oncogene homolog (NRAS) mutations

The BRAF and NRAS genes are members of the RAS family of genes, which regulate cell growth and division. Mutations in BRAF and NRAS are commonly found in melanoma and can lead to the uncontrolled growth of melanocytes and the development of tumors[27]. The BRAF gene is mutated in ~50% of all melanomas. The most common mutation is a substitution of valine for glutamic acid at position 600 (BRAFV600E). This mutation leads to the activation of the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) signaling pathway, which promotes cell growth and division. The NRAS gene is mutated in ~15% of all melanomas. The most common mutation is a substitution of glutamine for arginine at position 61 (NRASQ61R). This mutation also leads to the activation of the MAPK/ERK signaling pathway and promotes cell growth and division[30,31].

CDKN2A mutations

The CDKN2A gene encodes two proteins, p16INK4a and p14ARF, which act as tumor suppressors by regulating cell growth and division. Mutations in CDKN2A are commonly found in melanoma and can lead to the uncontrolled growth of melanocytes and the development of tumors. Loss of p16INK4a function is found in ~50% of all melanomas. This loss can occur through mutations in the CDKN2A gene or through epigenetic silencing of the gene. Loss of p16INK4a function leads to the activation of the cyclin-dependent kinase (CDK) 4/6 pathway, which promotes cell growth and division. Loss of p14ARF function is found in ~20% of all melanomas. This loss can occur through mutations in the CDKN2A gene or through epigenetic silencing of the gene. Loss of p14ARF function leads to the stabilization of the oncoprotein mouse double minute 2 (MDM2) homolog, which promotes the degradation of the tumor suppressor protein p53[32,33].

TP53 mutations

The TP53 gene encodes the tumor suppressor protein p53, which regulates cell growth, division, and apoptosis. Mutations in TP53 are found in ~25% of all melanomas and can lead to the uncontrolled growth of melanocytes and the development of tumors[34–36]. Loss of p53 function can occur through mutations in the TP53 gene or through the stabilization of the oncoprotein MDM2, which promotes the degradation of p53. Loss of p53 function leads to the inhibition of apoptosis and the promotion of cell growth and division[37,38].

Skin cancer therapy via diet-based phytochemicals

Dietary phytochemicals are naturally occurring compounds found in plant-based foods, including fruits, vegetables, whole grains, nuts, seeds, and herbs. Phytochemicals are not considered essential nutrients, but they have been shown to have a wide range of health benefits, including antioxidant, anti-inflammatory, anticancer, and neuroprotective properties[39–42]. There are thousands of different phytochemicals, each with its unique chemical structure and biological activity. Some of the most well-known and studied phytochemicals include flavonoids, carotenoids, phenolic acids, and lignans[43–46]. Flavonoids, such as quercetin and kaempferol, are potent antioxidants that have been shown to have anti-inflammatory and anticancer effects[47,48]. Carotenoids, such as β-carotene, are responsible for the red, orange, and yellow colors in fruits and vegetables and have been shown to have potent antioxidant and anticancer properties[49,50]. Phenolic acids, such as caffeic acid and ferulic acid, are found in a wide range of plant-based foods and have been shown to have antioxidant and anti-inflammatory effects[43]. Lignans are phytoestrogens found in flaxseeds, sesame seeds, and whole grains and have been shown to have anticancer effects[51,52]. The health benefits of dietary phytochemicals are believed to come from their ability to interact with cellular signaling pathways, enzymes, and other molecules in the body, thereby modulating various biological processes (Table 1A–N)[127–129].

Overall, skin cancer therapy via diet-based phytochemicals is a promising approach for the prevention and treatment of skin cancer. Further research is needed to identify the optimal dosage, duration, and combination of phytochemicals for maximum therapeutic efficacy. However, the evidence to date supports the inclusion of phytochemical-rich foods in the diet as an important strategy for skin cancer prevention and therapy. The goal of this review article is to give a basic understanding of phytochemicals in the context of diet by describing their most important sources, chemical classes, and ability to prevent skin cancer.

Rosmarinic acid

Rosmarinic acid is a naturally occurring polyphenol found in various plant species, particularly in the *Lamiaceae* family[130,131]. Some of the most common botanical sources of rosmarinic acid include Rosemary (*Rosmarinus officinalis*), Sage (*Salvia officinalis*), Lemon balm (*Melissa officinalis*), Oregano (*Origanum vulgare*), Thyme (*Thymus vulgaris*), Mint (*Mentha* spp.), Basil (*Ocimum basilicum*), Perilla (*Perilla frutescens*), *Lavender* (*Lavandula angustifolia*), *and* Peppermint (*Mentha piperita*)[132–134].

Rosmarinic acid has been shown to have potential chemopreventive effects against skin cancer through multiple molecular mechanisms[135]. Rosmarinic acid has potent antioxidant properties, which can protect skin cells from oxidative stress caused by environmental factors such as UV radiation. This can prevent DNA damage and mutations that can lead to the development of skin cancer[136–141]. One mechanism through which rosmarinic acid may prevent skin cancer is by inhibiting the activity of enzymes called matrix metalloproteinases (MMPs). MMPs play a crucial role in the breakdown of collagen and other extracellular matrix components. Overactive MMPs can lead to the destruction

Table 1

Some important dietary phytochemicals effective in preventing skin cancer.

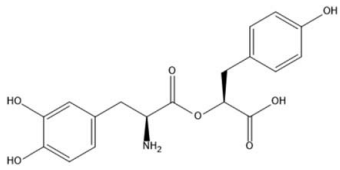
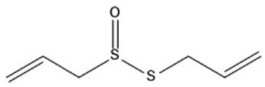
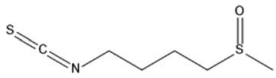
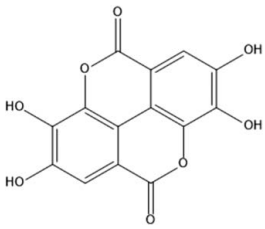
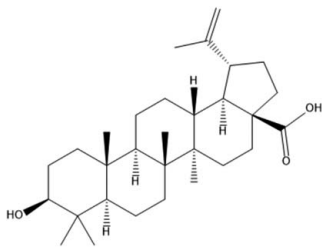
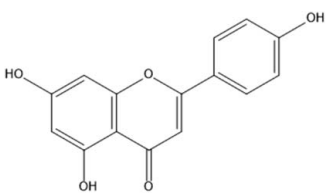
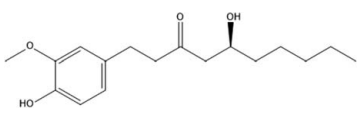
S. no.	Dietary phytochemical	Structure	IUPAC name	Signaling pathway	References
A					
1.	Rosmarinic acid		(2S)-2-[(3-(3,4-dihydroxyphenyl)-l-alanyl)oxy]-3-(4-hydroxyphenl)propanoic acid	(1) Inhibition of PI3K/AKT/mTOR pathway. (2) Inhibition of MAPK/ERK pathway. (3) Inhibit the activation of NF-κB. (4) Inhibit the Wnt/β-catenin pathway by decreasing the expression of β-catenin and its downstream target genes, leading to decreased cell proliferation and invasion.	[53] [54] [55] [56,57]
B					
2.	Allicin		2-propene-1-sulfinothioic acid S-2-propen-1-yl ester	(1) Inhibit the activation of NF-κB, potentially reducing the risk of various types of cancer development, including skin cancer. (2) Inhibit the activation of the Wnt/β-catenin pathway, potentially reducing the risk of various types of cancer development, including skin cancer.	[58] [59]
C					
3.	Sulforaphane		(RS)-1-isothiocyanato-4-(methylsulfinyl)butane	(1) Activate the Nrf2–Keap1 pathway, leading to increased production of antioxidant and detoxification enzymes that help protect against the damaging effects of environmental toxins and UV radication. (2) Inhibit the activation of these PI3K/Akt and MAPK pathways potentially reducing the risk of cancer development, including skin cancer.	[60] [61,62]
D					
4.	Ellagic acid		2,3,7,8-tetrahydroxychromeno [5,4,3-cde]chromene-5,10-dione	(1) Inhibit the activation of NF-κB signaling pathway to prevent the proliferation of skin cancer cells and induce apoptosis. (2) Activate the p53 signaling pathway, which can induce cell cycle arrest and apoptosis in skin cancer cells. (3) Modulation of MAPK signaling pathway. (4) Inhibition of PI3K/Akt signaling pathway.	[63–65] [66] [63] [67]
E					
5.	Betulinic acid		(1R,3aS,5aR,5bR,7aR,9S, 11aR,11bR,13aR,13bR)-9-hydroxy-5a,5b,8,8,11a-pentamethyl-1-prop-1-en-2-yl-1,2,3,4,5,6,7,7a,9,10,11,11b,12,13,13a,13b-hexadecahydrocyclopenta[a] chrysene-3a-carboxylic acid	(1) Inhibit the activation of NF-κB signaling pathway. (2) Activation of p53 signaling pathway. (3) Modulation of MAPK signaling pathway. (4) Inhibition of PI3K/Akt signaling pathway. (5) Inhibition of Notch signaling pathway.	[68] [69,70] [71] [72] [73]
F					
6.	Apigenin		4′,5,7-trihydroxyflavone	(1) Inhibition of PI3K/Akt signaling pathway. (2) Inhibition of MAPK signaling pathway. (3) By inhibiting the activation of signal transducer and activator of transcription 3 (STAT3). (4) Apigenin can activate the p53 signaling pathway, which can induce cell cycle arrest and apoptosis in skin cancer cells. (5) By inhibiting NF-κB signaling pathway.	[74] [75] [76] [77] [78,79]
G					
7.	Gingerol		(S)-5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-3-decanone	(1) Inhibition of PI3K/Akt/mTOR signaling pathway. (2) Inhibition of NF-κB signaling pathway. (3) Activation of nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway. (4) Inhibition of MAPK signaling pathway. (5) Induction of apoptosis.	[80] [81] [82] [83] [80]

Table 1

(*Continued*)

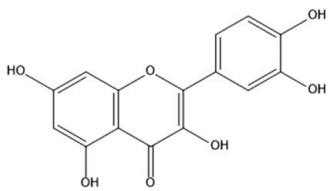
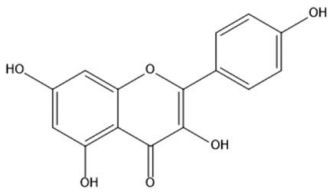
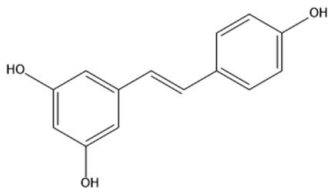
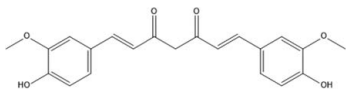
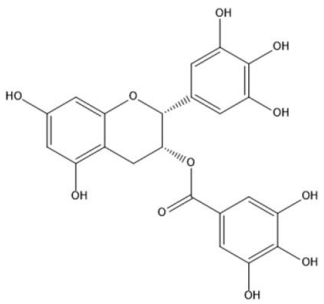
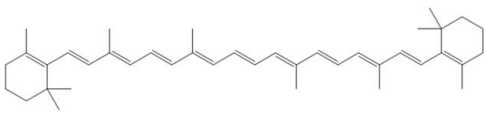
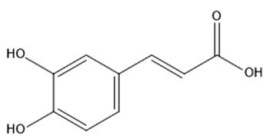
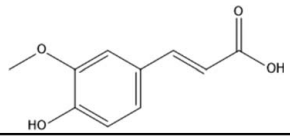
S. no.	Dietary phytochemical	Structure	IUPAC name	Signaling pathway	References
H					
8.	Quercetin		3,3′,4′,5,7-pentahydroxyflavone	(1) Inhibition of oxidative stress. (2) Inhibit the production of pro-inflammatory cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α). (3) Inhibition of cell proliferation. (4) Inhibition of angiogenesis.	[84] [85,86] [58] [87]
I					
9.	Kaempferol		3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one	(1) Inhibition of oxidative stress. (2) Inhibition of inflammation. (3) Inhibition of cell proliferation. (4) Inhibition of angiogenesis.	[88,89] [90] [88] [91,92]
10.	Resveratrol		3,5,4′-trihydroxy-trans-stilbene	(1) Inhibition of oxidative stress. (2) Inhibition of inflammation. (3) Inhibition of cell proliferation. (4) Inhibition of angiogenesis.	[93] [94,95] [96] [97,98]
J					
11.	Curcumin		(1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione	(1) Inhibition of oxidative stress. (2) Inhibition of inflammation. (3) Inhibition of cell proliferation. (4) Inhibition of angiogenesis.	[99,100] [101] [102,103] [104,105]
K					
12.	Epigallocatechin gallate		[(2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-1-benzopyran-3-yl] 3,4,5-trihydroxybenzoate	(1) Inhibition of oxidative stress. (2) Inhibition of inflammation. (3) Inhibition of cell proliferation. (4) Inhibition of angiogenesis.	[106,107] [108,109] [110,111] [112,113]
L					
13.	β-Carotene		1,3,3-trimethyl-2-[3,7,12,16-tetramethyl-18-(2,6,6-trimethyl-1-cyclohexenyl) octadeca-1,3,5,7,9,11,13,15,17-nonaenyl]cyclohexene	(1) Inhibition of oxidative stress. (2) Modulation of immune function. (3) Inhibition of inflammation. (4) Regulation of cell cycle and apoptosis. (5) Inhibition of angiogenesis.	[114,115] [116,117] [118,119] [115] [120]
M					
14.	Caffeic acid		3-(3,4-dihydroxyphenyl)prop-2-enoic acid	(1) Inhibit the activation of NF-κB by preventing the degradation of its inhibitor protein, IκBα. (2) Regulates the expression of mitogen-activated protein kinases (MAPKs), which regulate cell proliferation and survival, and cyclooxygenase-2 (COX-2), which promotes inflammation and cell proliferation.	[121,122] [123,124]

Table 1

(*Continued*)

S. no.	Dietary phytochemical	Structure	IUPAC name	Signaling pathway	References
N					
15.	Ferulic acid		(E)-3-(4-hydroxy-3-methoxyphenyl)prop-2-enoic acid	(1) Inhibit the activation of NF-κB by preventing the degradation of its inhibitor protein, IκBα. (2) Regulates the expression of MAPKs, which regulate cell proliferation and survival, and COX-2, which promotes inflammation and cell proliferation.	[125] [126]

of the extracellular matrix, which can promote the development of skin cancer. Rosmarinic acid has been shown to inhibit the activity of MMPs, which may help prevent skin cancer[142,143]. Chronic inflammation is a key contributor to skin cancer development. Rosmarinic acid has been shown to have anti-inflammatory effects by inhibiting the production of pro-inflammatory cytokines and enzymes such as cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS). By reducing inflammation, rosmarinic acid can prevent the progression of precancerous lesions to skin cancer[144,145]. Rosmarinic acid has been shown to induce apoptosis (programmed cell death) in skin cancer cells, which can inhibit their growth and proliferation[146–150]. Rosmarinic acid has been shown to arrest the cell cycle of skin cancer cells, preventing them from dividing and proliferating[151,152]. Angiogenesis, the formation of new blood vessels, is necessary for tumor growth and progression. Rosmarinic acid has been shown to inhibit angiogenesis in skin cancer cells, preventing their growth and spread[153].

In recent years, researchers have investigated the molecular mechanisms underlying the effects of rosmarinic acid on skin cancer cells, including its ability to induce apoptosis, inhibit inflammation, and regulate cell cycle progression. For example, Gupta *et al*. investigated the toxic effects of UVB radiation on the skin and the potential therapeutic effects of plant-based natural agents. The study found that UVB exposure induced endoplasmic reticulum (ER) stress and inhibited mitophagy, leading to intracellular damage and apoptosis. Treatment with the natural agent rosmarinic acid prevented intracellular damage by alleviating ER stress and promoting mitophagy. The study highlights the potential of rosmarinic acid as a therapeutic agent for photodamage and provides mechanistic insights into the toxic effects of UVB radiation on skin[154]. Another study, conducted by Huang *et al*., investigated the anticancer effects of rosmarinic acid in melanoma cells by downregulating (a disintegrin and metalloproteinase 17) ADAM17. Results showed that rosmarinic acid treatment reduced cell viability, proliferation, migration, and invasion abilities while increasing apoptosis and reducing melanin content. Rosmarinic acid also inhibited the expression of ADAM17/epidermal growth factor receptor (EGFR)/protein kinase B (AKT)/glycogen synthase kinase 3 beta (GSK3β), which was further suppressed by TPD, an ADAM17 inhibitor. The study concludes that rosmarinic acid exerts an inhibitory effect on melanoma cell growth and promotes apoptosis, potentially through the inhibition of the ADAM17/EGFR/AKT/GSK3β axis[155]. A study by Sharmila *et al*. investigated the mechanisms by which rosmarinic acid affects the expression of MAPK signaling proteins and their downstream targets in mice with dermal cancer, as well as to analyze the docking interaction of rosmarinic acid with the extracellular signal-regulated kinase 2 (ERK2) protein. Dermal cancer was induced in mice by applying 7,12-dimethylbenz[a]anthracene (DMBA), and various analyses were performed to observe the expression of proteins related to MAPK signaling, as well as histopathological changes. The study found that rosmarinic acid significantly reduced the expression of various proteins related to MAPK signaling in dermal tissues and inhibited the activation of ERK2 protein, which may contribute to the inhibitory effect of rosmarinic acid on dermal cancer in mice[156]. The study conducted by Lukmanul Hakkim *et al*. aimed to investigate whether natural antioxidants including caffeic acid, rosmarinic acid, trans-cinnamic acid, *p*-coumaric acid, and hydroxyphenyllactic acid could offer radiation protection for skin cells. Non-toxic concentrations of these compounds were tested for radiation protection in human keratinocytes. Results showed that pretreatment with caffeic acid, rosmarinic acid, and trans-cinnamic acid could protect skin cells by scavenging γ-radiation-induced reactive oxygen species and decreasing the number of post-irradiation DNA double-strand break foci. The inclusion of these compounds in chemo-radiotherapy could potentially facilitate achieving multiple target protection, including anticancer and skin radio protection[157].

Rosmarinic acid has been shown to regulate several major signaling pathways in the human body including:

The phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) pathway

The PI3K/AKT/mTOR pathway is frequently activated in various types of cancer, including skin cancer. Rosmarinic acid has been shown to inhibit this pathway by decreasing the phosphorylation of AKT and mTOR, leading to decreased cell proliferation and survival[53].

The MAPK/ERK pathway

The MAPK/ERK pathway is another important signaling pathway involved in skin cancer development. Rosmarinic acid has been shown to inhibit this pathway by decreasing the phosphorylation of ERK, leading to decreased cell proliferation and invasion[54].

The nuclear factor-κB (NF-κB) pathway

The NF-κB pathway is a transcription factor that plays a critical role in inflammation and cancer development. Rosmarinic acid has been shown to inhibit the activation of NF-κB by preventing the degradation of the inhibitor of kappa B alpha (IκBα), leading to decreased inflammation and cell proliferation[55].

The Wnt/β-catenin pathway

The Wnt/β-catenin pathway is involved in the regulation of cell proliferation, differentiation, and apoptosis. Dysregulation of this pathway has been linked to various types of cancer, including skin cancer. Rosmarinic acid has been shown to inhibit this pathway by decreasing the expression of β-catenin and its downstream target genes, leading to decreased cell proliferation and invasion[56,57].

The ability of rosmarinic acid to regulate major signaling pathways in the human body suggests that it may have therapeutic potential for the prevention and treatment of various diseases, including cancer[158]. While rosmarinic acid has shown promising anticancer properties *in vitro* and in animal studies, there are several potential drawbacks and limitations to its use in treating skin cancer[131,159]. While rosmarinic acid is generally considered safe, there are some potential side effects, including nausea, vomiting, and allergic reactions[160]. Rosmarinic acid has poor bioavailability, which means that it may not be absorbed well by the body when taken orally or applied topically[161]. The amount of rosmarinic acid in herbal supplements or preparations can vary widely, which makes it difficult to establish a standardized dose or formulation for treating skin cancer. This may limit its effectiveness in treating skin cancer[162,163]. More research is needed to determine its safety and efficacy and to optimize the dosage and delivery of rosmarinic acid for maximum efficacy.

Allicin

Allicin is a natural compound found in garlic (*Allium sativum*)[164]. Allicin belongs to the class of secondary metabolites called organosulfur compounds. These compounds are characterized by the presence of sulfur atoms in their chemical structure and are often produced by plants as a defense mechanism against pests and pathogens[165–167]. When garlic is crushed or chopped, an enzyme called alliinase is activated, which converts alliin, a sulfur-containing amino acid derivative, into allicin[168]. Allicin is responsible for the characteristic odor and flavor of fresh garlic, and it is also believed to be responsible for many of the health benefits associated with garlic consumption[169,170]. The molecular mechanism of allicin's action against skin cancer is not completely understood, but several studies have suggested that it targets multiple pathways involved in cancer development and progression[171]. A study investigated the effect of allicin on the migration and invasion of human melanoma cells (A375 and SK-MEL-28). Allicin was found to inhibit the migration and invasion of melanoma cells by downregulating the expression of genes involved in epithelial–mesenchymal transition (EMT), a process that allows cancer cells to acquire invasive and metastatic properties. Allicin was also found to downregulate the expression of the COX-2 gene, which is involved in inflammation and cell proliferation. Furthermore, allicin was found to inhibit the activation of the NF-κB pathway and the expression of its downstream target genes, which are involved in cell survival, inflammation, and tumor progression[58]. In a study conducted by Wang *et al*., it was observed that several compounds, including allicin, allyl sulfides, ajoene, diallyl trisulfide (DATS), and S-allyl cysteine (SAC), have shown anticancer activity against various types of cancer, including skin cancer. DATS is more potent than mono- and disulfides against skin cancer. DATS inhibits cell growth of human melanoma A375 cells and basal cell carcinoma (BCC) cells by increasing the levels of intracellular reactive oxygen species (ROS) and DNA damage, inducing G2/M arrest, endoplasmic reticulum (ER) stress, and mitochondria-mediated apoptosis, including the caspase-dependent and caspase-independent pathways[171]. In one of the studies, Jobani *et al.* aimed to investigate the potential of allicin to sensitize malignant melanoma cells to all-trans retinoic acid (ATRA) therapy. The CD44+ and CD117+ melanoma cell subpopulations were sorted, and the effects of ATRA, allicin, and allicin/ATRA on cell proliferation and cell cycle arrest were examined. The results showed that CD44+ melanoma cells were more resistant to ATRA and allicin than CD117+ cells. However, allicin was found to sensitize melanoma cells to ATRA-induced cell death, and the combination treatment significantly reduced the IC_{50} value obtained for ATRA alone in CD44+ melanoma cells. Furthermore, allicin and ATRA combination treatment showed inhibitory effects on CD44+ and CD117+ melanoma cells, and allicin alone reduced matrix metalloproteinase-9 (MMP-9) mRNA expression in both cell subpopulations. The findings suggest that allicin may reinforce the ATRA-mediated inhibitory effects on melanoma cells, providing a new approach for the treatment of malignant melanoma[172].

In another study conducted by Omar and Al-Wabel, it was observed that garlic contains chemical compounds that have been shown to protect against several diseases, including cancer, particularly in the stomach, colorectal, breast, and skin. The protective effects are related to the presence of organosulfur compounds (like allicin, etc.), which inhibit carcinogenesis in various experimental animals. The compounds modulate the activity of several metabolizing enzymes and inhibit the formation of DNA adducts. Antiproliferative activity has been observed in tumor cell lines, possibly mediated by induction of apoptosis and alterations of the cell cycle. Garlic's organosulfur compounds are potential cancer-preventive agents, but clinical trials are necessary to define the effective dose with no toxicity in humans[173].

Allicin has been shown to scavenge free radicals and protect against oxidative damage induced by UV radiation, which can contribute to the development of skin cancer[174]. Allicin has been shown to suppress the production of inflammatory cytokines, such as interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α), which can promote the development and progression of skin cancer[175]. Allicin has been shown to induce apoptosis (programmed cell death) in cancer cells, including skin cancer cells, by activating caspases and other apoptosis-related proteins[176]. Allicin has been shown to arrest the cell cycle of cancer cells, preventing them from dividing and multiplying, which can help to prevent the growth and spread of skin cancer[177]. Allicin has been shown to inhibit the formation of new blood vessels, which is a critical step in the growth and spread of cancer[178].

The major signaling pathways that have been reported to be regulated by allicin are as follows:

NF-κB pathway

Allicin has been shown to inhibit the activation of NF-κB, a transcription factor that plays a key role in inflammation and cancer development[58].

PI3K)/Akt/mTOR pathway

Allicin has been shown to inhibit the activation of this pathway, which is frequently dysregulated in cancer cells and promotes cell survival, growth, and proliferation[179].

Wnt/β-catenin pathway

Allicin has been shown to inhibit the activation of this pathway, which is frequently dysregulated in cancer cells and promotes cell proliferation and survival[59].

MAPK pathway

Allicin has been shown to inhibit the activation of the MAPK pathway, which plays a critical role in cell proliferation, differentiation, and survival[180].

STAT3 pathway

Allicin has been shown to inhibit the activation of STAT3, a transcription factor that plays a critical role in inflammation and cancer development[181].

Overall, these pathways play important roles in regulating cell growth, survival, and inflammation and dysregulation of these pathways can contribute to the development and progression of skin cancer. By regulating these pathways, allicin has the potential to prevent or slow down the progression of skin cancer[178–180]. While allicin may have some benefits, there are also potential drawbacks when it comes to using it against skin cancer. Allicin can be a skin irritant and may cause redness, itching, or burning when applied topically. This can be especially problematic for people with sensitive skin or those who are already experiencing skin irritation due to cancer treatments[182]. Allicin is not widely available in a standardized form for medical use, which can make it difficult to obtain and ensure quality[183]. It can be concluded that while allicin may have potential benefits for skin cancer, there are also potential drawbacks and limitations to its use.

Sulforaphane

Sulforaphane is a naturally occurring compound found in cruciferous vegetables, such as broccoli, cauliflower, Brussels sprouts, and kale[184]. Sulforaphane belongs to the family of isothiocyanates. It is formed when the enzyme myrosinase comes into contact with glucoraphanin, a glucosinolate compound present in these vegetables[185]. Broccoli is the richest dietary source of sulforaphane, with broccoli sprouts containing even higher concentrations of the compound[186]. Sulforaphane is also available as a dietary supplement, which is typically derived from broccoli sprouts or broccoli seed extract[187]. It is important to note that the content of sulforaphane in cruciferous vegetables can vary widely depending on factors such as plant variety, growing conditions, and preparation methods. For example, chopping, chewing, or blending cruciferous vegetables can activate myrosinase and increase the formation of sulforaphane, whereas cooking or boiling can reduce the amount of the compound[188,189].

Sulforaphane has been shown to exhibit chemopreventive and therapeutic effects against various types of cancer, including skin cancer[190,191]. Its mechanism of action against skin cancer involves several pathways and cellular processes:

Induction of phase II detoxification enzymes

Sulforaphane activates the nuclear factor erythroid 2-related factor 2–antioxidant response element (Nrf2–ARE) signaling pathway, leading to the induction of phase II detoxification enzymes, such as glutathione S-transferases (GSTs), which are involved in the elimination of carcinogens and other toxic compounds from the body[192].

Inhibition of inflammation

Sulforaphane can modulate the expression of genes involved in inflammation and immune responses, such as NF-κB and COX-2, leading to a reduction in pro-inflammatory cytokines and chemokines[193]. Chronic inflammation is known to contribute to the development and progression of skin cancer.

Induction of apoptosis

Sulforaphane can induce apoptosis (programmed cell death) in cancer cells by activating caspases and other apoptotic pathways[194].

Inhibition of angiogenesis

Sulforaphane can suppress the formation of new blood vessels (angiogenesis) that supply nutrients to cancer cells, thereby inhibiting their growth and proliferation[195].

Modulation of epigenetic mechanisms

Sulforaphane can modulate epigenetic mechanisms, such as DNA methylation and histone acetylation, leading to changes in gene expression that can affect various cellular processes, including those involved in the development and progression of cancer[196–198].

Several studies have been conducted by researchers to investigate the molecular mechanism of action of sulforaphane against skin cancer. For instance, Eom *et al*. investigated the effects of sulforaphane treatment on B16F10 melanoma cells and zebrafish models. The results showed that sulforaphane treatment reduced cell proliferation, increased tyrosinase production, and induced cytoskeletal reorganization, leading to an elongated appearance of melanoma cells. Sulforaphane treatment also regulated the protein expression of microphthalmia-associated transcription factor (MITF), protein kinase C beta 1 (PKCβ1), and tyrosinase. The study further demonstrated that sulforaphane-induced biosynthesis of melanin in melanoma cells occurs through changes in actin, as shown by co-treatment of sulforaphane with cytochalasin D (CD) and jasplakinolide (JAS). The same results were obtained in zebrafish models, where sulforaphane upregulated melanin levels despite the presence of the melanin inhibitor phenylthiourea (PTU)[199]. A study performed by Balasubramanian *et al*. investigated the impact of sulforaphane (SFN), a potential cancer-preventative agent found in cruciferous vegetables, on the expression and function of PcG proteins, which are known to promote cell survival and suppress gene expression in cancer cells. The study found that SFN treatment resulted in a concentration-dependent reduction of PcG protein expression in skin cancer cells, leading to a decrease in histone H3 trimethylation and an accumulation of cells in the G2/M phase. The treatment also increased apoptosis, as evidenced by enhanced cleavage of caspase and PARP proteins. The results suggest that SFN may

inhibit PcG-dependent pro-survival epigenetic events via proteasome-dependent degradation, thus suppressing cancer progression[196]. In another study, Dickinson *et al*. investigated the chemopreventive properties of sulforaphane, an isothiocyanate found in cruciferous vegetables, against UVB-induced squamous cell carcinoma in mice. The study found that sulforaphane treatment reduced the multiplicity and tumor burden of squamous cell carcinoma in mice co-treated with the carcinogen and sulforaphane. The study also showed that sulforaphane was able to reduce the activity of the transcription factor activator protein-1 (AP-1) in the skin of transgenic mice after UVB. Chromatin immunoprecipitation analysis revealed that sulforaphane inhibited c-Fos, a constituent of the AP-1 dimer, from binding to the AP-1 DNA-binding site. The study also found that sulforaphane and diamide, both known to react with cysteine amino acids, effectively inhibited AP-1 from binding to its response element. Mutation of critical cysteines in the DNA-binding domain of c-Fos and c-Jun resulted in loss of sensitivity to sulforaphane and diamide. These findings suggest that inhibition of AP-1 activity by sulforaphane may be an important mechanism for the chemoprevention of squamous cell carcinoma[200].

While sulforaphane may have some benefits, there are also potential drawbacks when it comes to using it against skin cancer. The potency of sulforaphane can vary depending on how it is prepared and stored. This can make it difficult to determine the appropriate dosage and ensure consistent results[201]. Sulforaphane may interact with certain medications, including blood thinners and medications used to treat HIV. Overall, the multiple mechanisms of action of sulforaphane suggest its potential as a promising chemopreventive and therapeutic agent against skin cancer. However, more research is needed to fully understand its effects, safer dose, drug interaction studies and to develop effective treatment strategies.

Ellagic acid

Ellagic acid is a naturally occurring polyphenolic compound found in several fruits and vegetables, including strawberries, raspberries, blackberries, pomegranates, and walnuts[202]. It is formed from the hydrolysis of ellagitannins, which are water-soluble compounds present in these foods[203]. Ellagic acid has been shown to exhibit chemopreventive and therapeutic effects against various types of cancer[204], including skin cancer. Its mechanism of action against skin cancer involves several pathways and cellular processes:

Antioxidant activity

Ellagic acid is a potent antioxidant that can scavenge free radicals and protect cells from oxidative stress-induced damage, which is implicated in the development of skin cancer[205].

Inhibition of inflammation

Ellagic acid can modulate the expression of genes involved in inflammation and immune responses, such as NF-κB and COX-2, leading to a reduction in pro-inflammatory cytokines and chemokines[206]. Chronic inflammation is known to contribute to the development and progression of skin cancer.

Induction of apoptosis

Ellagic acid can induce apoptosis (programmed cell death) in cancer cells by activating caspases and other apoptotic pathways. This mechanism can help eliminate cancer cells and prevent their proliferation[207–209].

Inhibition of angiogenesis

Ellagic acid can suppress the formation of new blood vessels (angiogenesis) that supply nutrients to cancer cells, thereby inhibiting their growth and proliferation[123].

Modulation of cellular signaling pathways

Ellagic acid can modulate various signaling pathways involved in the regulation of cell growth, proliferation, and survival, including the MAPK/ERK, PI3K/AKT, and Wnt/β-catenin pathways. Dysregulation of these pathways is implicated in the development of skin cancer[67,104].

Researchers have extensively studied the molecular mechanism of action of ellagic acid against skin cancer. Hseu *et al*. investigated the protective effects of ellagic acid against UVA-induced oxidative stress and apoptosis in human keratinocyte cells. Ellagic acid was found to increase cell viability, suppress ROS generation, prevent DNA damage, and inhibit UVA-induced apoptosis. The antioxidant potential of ellagic acid was linked to the increased expression of HO-1 and SOD, downregulation of Keap1, and the activation of Nrf2. Nrf2 knockdown diminished the protective effects of ellagic acid, indicating its potential use for the treatment of UVA-induced skin damage and skin cancer prevention[204]. In addition, the effects of ellagic acid, a polyphenolic compound from pomegranate fruit extracts, on melanoma cells were investigated. The results showed that ellagic acid significantly inhibited the proliferation, migration, and invasion of WM115 and A375 melanoma cells. Ellagic acid treatment decreased the expression of p-EGFR and vimentin, while it increased the expression of E-cadherin in both cell lines. EGFR activation abolished the effect of ellagic acid on melanoma cells. Additionally, ellagic acid treatment impaired *in vivo* tumorigenesis of A375 cells, and elevated phosphorylated epidermal growth factor receptor (p-EGFR) expression was an independent detrimental factor for melanoma patients. The study suggests that ellagic acid may be useful for the development of new therapeutic strategies for melanoma via the EGFR signaling pathway by Wang *et al*.[210]. Moreover, Bia *et al*. investigated the stress-resistant action of ellagic acid in *Caenorhabditis elegans* (*C. elegans*) and found that 50 μM ellagic acid significantly prolonged the lifespan of *C. elegans* under ultraviolet radiation stress, heat stress, oxidative stress, and *Pseudomonas aeruginosa* infection stress. Ellagic acid was also found to reduce damage caused by ultraviolet radiation by inducing the nucleus translocation of Dauer formation 16 (DAF-16) and activating a series of target genes to resist ultraviolet radiation stress. Ellagic acid increased the expression of superoxide dismutase 3 (SOD3) to clean out harmful reactive oxygen species in *C. elegans* exposed to ultraviolet radiation stress. The results suggest that ellagic acid plays an important role in resisting ultraviolet radiation stress in *C. elegans*, probably in an insulin/insulin-like growth factor-1(IGF-1) signaling pathway-dependent way, and its effects are dependent on the DAF-16 gene, thus helps in preventing skin cancer

and other diseases including diabetes, arteriosclerosis, neurodegenerative diseases, stroke, and cataracts[211].

While ellagic acid has shown promising health benefits, there are also some potential drawbacks that should be considered. Ellagic acid is poorly absorbed in the body and has low bioavailability. It is rapidly metabolized and eliminated, limiting its potential therapeutic efficacy. Strategies to improve its bioavailability, such as combining it with other compounds or using nanoformulations, are being explored[212]. Ellagic acid may interact with certain drugs and supplements, including anticoagulants and antiplatelet agents, and may increase the risk of bleeding or bruising. It may also interact with certain chemotherapy drugs and affect their efficacy[213]. Ellagic acid may cause allergic reactions in some individuals, particularly those who are allergic to berries or other foods that contain the compound[214]. There is no standardized dosage for ellagic acid, and the optimal dose may vary depending on the specific health condition being targeted[215]. Additionally, the amount of ellagic acid in foods and supplements can vary widely, making it difficult to determine the actual dose being consumed[216]. While ellagic acid has shown promising results in preclinical studies, there is limited clinical evidence to support its use in humans. Overall, the multiple mechanisms of action of ellagic acid suggest its potential as a promising chemopreventive and therapeutic agent against skin cancer. However, more research is needed to fully understand its effects, safer dose, drug interaction studies, allergic reaction studies and to develop effective treatment strategies.

Betulinic acid

Betulinic acid is a naturally occurring triterpenoid compound that is found in the bark of several tree species, including white birch (*Betula pubescens*), which is its primary botanical source[217]. Betulinic acid can also be found in other plants, such as the Chinese herb *Zizyphus jujuba* Mill var. *spinosa*[218], and in some fruits and vegetables, such as apples[219] and strawberries[220], although in lower concentrations. The compound can be extracted from the bark of the white birch tree[221] using various methods, including maceration and solvent extraction. Betulinic acid has shown a range of biological activities, including anti-inflammatory, antiviral, and anticancer effects[222,223].

Betulinic acid has been shown to regulate several signaling pathways involved in the development and progression of skin cancer. These pathways include:

PI3K/Akt/mTOR pathway

Betulinic acid can inhibit the PI3K/Akt/mTOR pathway, which is involved in cell growth and survival. This pathway is commonly activated in cancer cells, including skin cancer cells, and contributes to their proliferation and survival[224].

MAPK/ERK pathway

Betulinic acid can also modulate the MAPK/ERK pathway, which regulates cell proliferation and differentiation. This pathway is often dysregulated in skin cancer and contributes to its development and progression[225,226].

Wnt/β-catenin pathway

Betulinic acid has been shown to inhibit the Wnt/β-catenin pathway, which plays a key role in cell proliferation and stem cell self-renewal[227]. Aberrant activation of this pathway has been implicated in the development of various types of cancer, including skin cancer.

NF-κB pathway

Betulinic acid can also inhibit the NF-κB pathway, which is involved in inflammation, cell survival, and proliferation. This pathway is commonly activated in cancer cells and contributes to their survival and resistance to chemotherapy[68].

Several studies have been conducted to investigate the molecular mechanism of action of betulinic acid against skin cancer. For instance, Wróblewska-Łuczka *et al*. investigated the effects of betulinic acid, alone and in combination with taxanes, on the growth of melanoma cell lines. Betulinic acid had no cytotoxic effect on normal cells but significantly inhibited the growth of melanoma cells *in vitro*, with IC_{50} values ranging from 2.21 to 15.94 μM. Co-treatment with betulinic acid and taxanes showed desirable drug interactions, with additive and additive with a tendency to synergy interactions observed. These findings suggest that betulinic acid may be a potential therapeutic agent for melanoma, either alone or in combination with taxanes[228]. One of the studies performed by Liao *et al*. examined the biological effects of betulinic acid (BA)-functionalized GNP in human keratinocytes and melanoma cells. Betulinic acid was grafted onto citrate-capped GNP (BA-GNP) using cysteamine as a linker. The results showed that the BA-GNP formulation had selective cytotoxic and antiproliferative effects on melanoma cells compared to free betulinic acid. Further analysis revealed a pro-apoptotic effect, as evidenced by morphological changes and western blot data showing downregulation of anti-apoptotic Bcl-2 expression and upregulation of pro-apoptotic Bax. GNP also significantly inhibited mitochondrial respiration, demonstrating its mitochondrial-targeted activity. These findings suggest that BA-functionalized GNP could be a potential therapeutic option for melanoma[229].

The study performed by Kallimanis *et al*. aimed to identify natural compounds that could inhibit aryl hydrocarbon receptor (AhR) activation by these ligands. The methanolic *Rosmarinus officinalis* L. extracts (ROE) were assayed for their activities as antagonists of AhR ligand binding with guinea pig cytosol. The isolated metabolites (*viz*. carnosic acid, carnosol, 7-O-methyl-epi-rosmanol, 4′,7-O-dimethylapigenin, and betulinic acid) were assayed for their agonist and antagonist activity in the presence and absence of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) using the gel retardation assay. All assayed extracts showed almost complete inhibition of AhR activation by TCDD at 100 ppm. The methanol ROE at 10 ppm showed significant inhibition against TCDD, 6-formylindolo[3,2-b]carbazole (FICZ), indirubin (IND), and pyrazolo[1,5-a]pyrimidine (PZ), respectively, in human keratinocytes. Most assayed metabolites exhibited dose-dependent antagonist activity. The results suggest that ROE could be useful for the prevention or treatment of skin diseases mediated by the activation of AhR[230].

Betulinic acid is generally considered safe and non-toxic at therapeutic doses, and it has shown promising anticancer activity in preclinical studies. However, there are some potential drawbacks associated with its use. Betulinic acid has poor water solubility and low bioavailability, which can limit its effectiveness *in vivo*. Various delivery systems and formulations have been developed to enhance its bioavailability and effectiveness[231–235].

Although betulinic acid has shown promising activity against skin cancer in preclinical studies, there is limited clinical data on its safety and efficacy in humans. Further clinical studies are needed to determine its potential as a therapeutic agent for skin cancer[236].

Overall, while betulinic acid has shown promise as a potential therapeutic agent against skin cancer, more research is needed to fully understand its bioavailability, safety, efficacy, and optimal use in clinical settings.

Apigenin

Apigenin is a naturally occurring flavone that can be found in various plants, including parsley, chamomile, celery, thyme, and red pepper[237]. It is also present in many fruits and vegetables, such as oranges, grapefruit, onions, and broccoli. Apigenin can be extracted from these sources using various methods, including microwave-assisted extraction[238], ultrasound-assisted extraction[239], supercritical carbon dioxide extraction, enzyme-assisted extraction[240], high-speed counter-current chromatography[241], etc. The mechanism of action of apigenin against skin cancer involves multiple pathways, including:

Induction of apoptosis

Apigenin can induce programmed cell death or apoptosis in cancer cells. It does so by activating caspase enzymes, which are responsible for cleaving and degrading proteins that are essential for cell survival. By inducing apoptosis, apigenin can reduce the number of cancer cells in the skin and prevent the formation of tumors[242].

Inhibition of cell proliferation

Apigenin can inhibit the proliferation of cancer cells by regulating cell cycle progression. It does so by suppressing the expression of cyclin-dependent kinases and upregulating the expression of cell cycle inhibitors. This results in the inhibition of cell division and reduced growth of skin cancer cells[243].

Regulation of signaling pathways

Apigenin can regulate several signaling pathways that are involved in the development and progression of skin cancer. It can inhibit the activation of the PI3K/Akt[75,243], MAPK[112,243], and Wnt/β-catenin pathways[244], which promote cell survival, proliferation, and migration. It can also activate the Nrf2/ARE pathway, which is involved in cellular antioxidant and detoxification responses[245]. By regulating these pathways, apigenin can prevent the growth and spread of skin cancer cells.

Anti-inflammatory effects

Apigenin has been shown to have anti-inflammatory effects that can protect the skin from UV radiation-induced damage. It can reduce the production of pro-inflammatory cytokines and inhibit the activity of enzymes that promote inflammation. By reducing inflammation, apigenin can prevent the formation of skin cancer cells[246].

Several studies have investigated the molecular mechanism of action of apigenin against skin cancer. In one study conducted by Bridgeman *et al*., it was found that apigenin inhibited UVB-induced mTOR activation, cell proliferation, and cell cycle progression in mouse skin and keratinocytes. The inhibition of UVB-induced mTOR signaling by apigenin was not Akt-dependent but instead was driven by adenosine monophosphate-activated protein kinase (AMPK) activation. Additionally, mTOR inhibition by apigenin enhanced autophagy and decreased proliferation in keratinocytes, providing a new target and strategy for better prevention of UV-induced skin cancer[247]. Another study by Das *et al*. aimed to evaluate the antiproliferative effects of apigenin-loaded poly (lactic-co-glycolide) nanoparticles (NAp) on A375 skin cancer cells *in vitro*. NAp was characterized for particle size, morphology, zeta potential, drug release, and encapsulation. The cellular entry and intracellular localization of NAp were evaluated, along with the stability of dsDNA and relevant markers of mitochondrial functioning, such as ATPase activity, cytochrome-*c* release, and caspase-3 activity. NAp showed better efficacy due to their smaller size and faster mobility with site-specific action. The study revealed that NAp could intercalate with dsDNA, leading to ROS accumulation and depletion of antioxidant enzyme activities, resulting in DNA damage and apoptosis through mitochondrial dysfunction. The study suggests that NAp could be a potential therapeutic option for combating skin melanoma[248]. A study was performed by Jangdey *et al*. to optimize transfersomes, which are vesicular carriers for drug delivery, using a modified rotary evaporation sonication technique and surfactant Tween 80. The Box-Behnken design with three factors and three levels was applied using response surface methodology. The formulations were characterized for size, shape, entrapment efficiency, stability, and in-vitro permeation. The optimized formulation had an entrapment efficiency of 84.24%, a vesicle size of 35.41 nm, and a drug loading of 8.042%, with good stability. This approach shows promise for the sustained release of apigenin for an extended period of time[249]. Waheed *et al*. performed a study to develop and optimize lyotropic liquid crystalline nanoparticles (LLC NPs) loaded with apigenin (API) for effective dermal delivery using a quality-by-design (QbD) approach. The optimized API-LLC NPs showed particle size, polydispersity index (PDI), and entrapment efficiency of 287.7 ± 9.53 nm, 0.152 ± 0.051 and 80 ± 2.2 %, respectively. In-vitro and ex-vivo studies showed sustained release and a better permeation profile. The developed API-LLC NPs exhibited better penetration of deeper skin layers, with cytotoxic efficacy assessed on B16F10 cell lines showing a dose-dependent efficacy of API-LLC NPs with an IC_{50} of 45.74 ± 0.05, making it a promising topical drug delivery nanocarrier for the treatment and management of skin cancer[250].

Overall, the mechanism of action of apigenin against skin cancer is multifaceted and involves the modulation of several cellular processes. Apigenin is generally considered safe and well-tolerated, and side effects are rare. However, high doses of apigenin supplements or extracts may cause some adverse effects. High doses of apigenin may cause digestive issues such as diarrhea, nausea, and stomach upset[251]. In some individuals, apigenin may cause an allergic reaction, especially if they have an allergy to other flavonoids or plants in the same family as apigenin[252]. Apigenin may interact with certain medications, including blood thinners, chemotherapy drugs, and medications that are metabolized by the liver[253,254]. Although preclinical studies have shown promising results, there is currently a lack of clinical evidence to support the efficacy and safety of apigenin as a treatment for skin cancer. More research is needed to determine its potential benefits and risks.

Gingerol

Gingerol is a bioactive compound found in ginger (*Zingiber officinale*), a spice and medicinal plant that has been used for centuries for its health benefits[255]. Gingerol belongs to the class of secondary metabolites known as phenolic compounds[256]. Gingerol is a member of the gingerols, a group of compounds that are responsible for the pungent flavor and aroma of ginger[257]. Gingerol is known for its anti-inflammatory, antioxidant, and anticancer properties[258–260]. It has been studied for its potential to help manage a variety of health conditions, including nausea, vomiting, pain, and inflammation[261,262].

Gingerol has been shown to regulate several signaling pathways involved in the development and progression of skin cancer, including the MAPK/ERK[83] and PI3K/Akt[80] pathways. The MAPK/ERK pathway is a signaling pathway that regulates cell growth, division, and survival. Dysregulation of this pathway can contribute to the development of skin cancer. Gingerol has been shown to inhibit the activation of the MAPK/ERK pathway in skin cancer cells, which can help prevent the growth and proliferation of cancer cells[83]. The PI3K/Akt pathway is another signaling pathway that plays an important role in regulating cell growth, division, and survival. Dysregulation of this pathway has also been implicated in the development of skin cancer. Gingerol has been shown to inhibit the activation of the PI3K/Akt pathway in cancer cells, which can help prevent the growth and proliferation of cancer cells[80]. In addition to regulating these signaling pathways, gingerol has also been shown to modulate the expression of several genes involved in skin cancer development and progression. For example, gingerol has been shown to upregulate the expression of tumor suppressor genes such as p53 and phosphatase and tensin (PTEN) homolog, which can help prevent the development of skin cancer[263].

Several studies have been conducted to investigate the molecular mechanism of action of gingerol against skin cancer. A study performed by Praveena *et al*. aimed to investigate the anticancer activity of [6]-gingerol, a bioactive compound found in the rhizome of *Zingiber officinale* and its structural analogs against skin cancer. The ethanolic crude extract of the plant was subjected to phytochemical and gas chromatography–mass spectrometry (GC–MS) analysis to confirm the presence of [6]-gingerol. The anticancer activity was evaluated using the A431 human skin adenocarcinoma cell line, and the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay showed promising cytotoxicity with an IC_{50} of 81.46 μg/ml. In silico studies were conducted using [6]-gingerol and 21 structural analogs to investigate their anticancer potential and drug-likeliness properties. The study targeted the skin cancer protein, DEAD-box helicase 3 X-linked (DDX3X), which regulates all stages of ribonucleic acid (RNA) metabolism, and the compounds were docked to identify the most potent lead molecule based on the lowest binding energy value. The study suggests that [6]-gingerol and its structural analogs could be used as lead molecules for future drug development against skin cancer[264]. One of the studies conducted by Nigam *et al*. investigated the chemopreventive potential of [6]-gingerol, a pungent ingredient found in ginger rhizome, against benzo[a]pyrene (B[a]P)-induced mouse skin tumorigenesis. Topical treatment of [6]-gingerol was given to animals prior to and after B[a]P treatment. Results showed a delay in tumorigenesis onset, reduced tumor numbers and volume, and elevated apoptotic propensity in tumor tissues. Western blot analysis showed [6]-gingerol treatment increased p53 levels, Bcl-2-associated X protein (Bax), and apoptotic protease-activating factor-1 (Apaf-1) while decreasing B-cell lymphoma 2 (Bcl-2) and Survivin expression. The study suggests that [6]-gingerol has apoptotic potential as a mechanism of chemoprevention and warrants further investigation[265]. Another study by Park *et al*. reported the potential cancer chemopreventive properties of [6]-gingerol, a phenolic compound found in ginger, using a two-stage mouse skin carcinogenesis model. The results showed that topical application of [6]-gingerol prior to each dose of 12-O-tetradecanoylphorbol-13-acetate (TPA) significantly inhibited the development of skin papillomagenesis induced by 7,12-dimethylbenz[a]anthracene. The compound also suppressed TPA-induced epidermal inflammation and ornithine decarboxylase activity. These findings suggest that [6]-gingerol may have potential as an antitumor promotional agent[266].

Gingerol has been associated with several potential health benefits. However, there are also some drawbacks and potential side effects of gingerol. Gingerol may have blood-thinning effects, which can increase the risk of bleeding or interfere with the effectiveness of blood-thinning medications[267]. Gingerol may interact with certain medications, including anticoagulants, antiplatelets[267], and blood pressure medications[268]. Gingerol may not be suitable for pregnant women[269]. Overall, gingerol appears to regulate multiple signaling pathways involved in the development and progression of skin cancer, which may contribute to its anticancer effects[270]. However, more research is needed to fully understand the drug interaction studies and safer doses for use in humans.

Quercetin

Quercetin is a natural flavonoid compound found in many fruits, vegetables, and grains[271]. Some of the food sources of quercetin include onions (*Allium cepa*), apples (*Malus* spp.), berries such as blueberries (*Vaccinium* spp.) and cranberries (*Vaccinium macrocarpon*), citrus fruits such as grapefruit (*Citrus paradisi*), oranges (*Citrus sinensis*), leafy green vegetables such as kale (*Brassica oleracea*) and spinach (*Spinacia oleracea*), and grains such as buckwheat (*Fagopyrum esculentum*)[272–277]. Flavonoids are responsible for giving plants their vibrant colors[47]. Quercetin is known for its antioxidant and anti-inflammatory properties and has been studied for its potential health benefits[278]. The molecular mechanism of action of quercetin against skin cancer involves several pathways and cellular processes. Here are some of the molecular mechanisms by which quercetin acts against skin cancer:

Inhibiting cell proliferation

Quercetin can inhibit cell proliferation by inducing cell cycle arrest at the G1/S phase, which prevents cancer cells from dividing and growing[58].

Inducing apoptosis

Quercetin can induce apoptosis, or programmed cell death, in cancer cells. This can help eliminate cancer cells and prevent the spread of cancer[279].

Inhibiting angiogenesis

Quercetin can inhibit the formation of new blood vessels, which is necessary for cancer cells to grow and spread[87].

Reducing oxidative stress

Quercetin has antioxidant properties and can reduce oxidative stress and damage to skin cells, which can lead to the development of skin cancer[84].

Regulating signaling pathways

Quercetin can regulate several signaling pathways involved in skin cancer development and progression, including the PI3K/Akt[279], MAPK[280], Wnt/β-catenin[281], NF-κB[282] and JAK/STAT pathways[270].

Enhancing the immune system

Quercetin can enhance the immune system's ability to recognize and destroy cancer cells, reducing the risk of skin cancer[84].

In recent years, several studies have investigated the molecular mechanism of action of quercetin against skin cancer. Imran *et al*. developed a nanostructured lipid carrier (NLC) gel loaded with two drugs, quercetin and resveratrol, to enhance their delivery to the dermal and epidermal layers of the skin. The NLC formulation was optimized using a central composite rotatable design (CCRD) and contained a lipid binary mixture, Cremophor RH40 as a surfactant, and had good particle size, polydispersity index, zeta potential, and entrapment efficiency. Dermatokinetic studies showed that the NLC gel significantly increased the disposition of the drugs in the skin compared to a conventional gel, and this was confirmed by confocal microscopic studies. The cytotoxic effect of the NLC gel was assessed in a human epidermoid carcinoma cell line and found to be lower than that of the conventional gel. These results suggest that the NLC gel could be a promising carrier for the delivery of quercetin and resveratrol into deeper layers of the skin for the treatment of skin cancer[283].

Another study by Caddeo *et al*., focuses on developing liposomes for delivering two natural polyphenols, quercetin and resveratrol. The liposomes were found to be small, spherical, and uni/bilamellar in nature. The incorporation of polyphenols did not affect their antioxidant activity. Liposomal delivery of polyphenols showed higher cellular uptake and better scavenging ability of ROS in fibroblasts. The in-vivo study in a mouse model of skin lesions demonstrated that topical administration of liposomes reduced tissue damage, edema, and leukocyte infiltration. The study suggests that liposomal delivery of polyphenols may be a promising approach for treating inflammation/oxidative stress associated with precancerous/cancerous skin lesions[284].

Paliwal *et al*. used ultrasound to enhance the potency of quercetin as a chemotherapeutic drug for the treatment of prostate and skin cancer. The short application of low-frequency ultrasound selectively induced cytotoxicity in cancer cells, while having minimal effect on normal cell lines. The treatment resulted in a significant reduction of viable skin cancer cell population within 48 h. Ultrasound reduced the LC50 of quercetin for skin cancer cells by almost 80-fold, while showing no effect on LC50 for nonmalignant skin cells. The study suggests that ultrasound can be used as a selective sensitizing agent to enhance the efficacy of bioflavonoids for cancer treatment[285]. Furthermore, Jung *et al*. focus on identifying the molecular targets of quercetin and its effect on the inhibition of IGF-1 signaling in skin carcinogenesis. The results show that a quercetin diet remarkably delayed the incidence of skin tumor and reduced tumor multiplicity in a mouse skin carcinogenesis protocol. Moreover, skin hyperplasia was significantly inhibited by quercetin supplementation. Further analysis of the skin papilloma cell line showed that quercetin treatment suppressed IGF-1-induced phosphorylation of insulin-like growth factor 1 receptor (IGF-1R), insulin receptor substrate 1 (IRS-1), Akt and ribosomal protein S6 kinase (S6K) and inhibited IGF-1 stimulated cell proliferation. The study suggests that quercetin has potent anticancer activity through the inhibition of IGF-1 signaling and can be considered as a potential therapeutic agent for cancer treatment[286].

While quercetin has many potential benefits for preventing and treating skin cancer, there are some drawbacks to its use. Quercetin has low bioavailability, which means that much of the compound may be broken down and excreted before it can exert its therapeutic effects[287]. This can limit its effectiveness against skin cancer. Quercetin may interact with certain medications, such as blood thinners[288], chemotherapy drugs[289], and antibiotics[290]. This can affect their effectiveness and increase the risk of side effects. While preclinical studies have shown promising results for the use of quercetin against skin cancer, there is limited clinical evidence to support its use in humans[291].

Overall, the molecular mechanisms of action of quercetin against skin cancer are complex and involve multiple cellular processes and pathways. These mechanisms work together to prevent the growth and spread of cancer cells, making quercetin a promising natural compound for skin cancer prevention and treatment. More research is needed to determine its optimal dosage, effectiveness, and safety for preventing and treating skin cancer.

Kaempferol

Kaempferol is a natural flavonoid compound that is found in a variety of plant-based foods such as fruits, vegetables, and herbs[91]. It is a yellow crystalline solid that belongs to the flavonol subclass of flavonoids[292]. Kaempferol can be found in plant species like *Ginkgo Folium*[293]. The molecular mechanism of kaempferol against skin cancer involves several pathways. One of the primary mechanisms is its ability to induce cell cycle arrest and apoptosis in cancer cells. Kaempferol activates the tumor suppressor protein p53, which leads to cell cycle arrest and apoptosis[294]. Additionally, kaempferol can inhibit the activity of anti-apoptotic proteins such as Bcl-2, which further promotes cell death in cancer cells[295]. Kaempferol can suppress the production of inflammatory cytokines and chemokines, which can lead to chronic inflammation that promotes the growth of cancer cells[296]. It can also reduce the generation of reactive oxygen species and enhance the activity of antioxidant enzymes, which helps to protect cells from oxidative damage that can contribute to the development of cancer[297]. Moreover, kaempferol has been shown to inhibit the activity of several enzymes that are involved in the progression of skin cancer, including tyrosinase[298], matrix metalloproteinases[299], and cyclooxygenase-2[300]. By inhibiting these enzymes, kaempferol can prevent the proliferation and invasion of cancer cells.

Several studies have been performed to elucidate the molecular mechanism of action of kaempferol against skin cancer. In one of the studies, Yang *et al*. evaluated the anticancer activity of

kaempferol against the human malignant melanoma A375 cell line and its effects on apoptosis, cell cycle, cell migration, and mTOR/PI3K/AKT pathway. The results showed that kaempferol exhibited significant anticancer activity against A375 cells with an IC_{50} of 20 μM. It reduced colony formation in a dose-dependent manner and initiated apoptosis in human malignant melanoma A375 cells. Additionally, kaempferol triggered G2/M cell cycle arrest, inhibited cell migration, and downregulated mTOR, pm-TOR, PI3K, p-PI3K, and Akt protein levels in A375 cells. The findings suggest that kaempferol exerts potent anticancer effects by targeting multiple pathways in melanoma cells[301]. Yao *et al*. performed a study that investigates the role of the 90 kDa ribosomal S6 kinase (RSK) and mitogen and stress-activated protein kinase (MSK) in solar ultraviolet (SUV) irradiation-induced skin carcinogenesis. The study shows that phosphorylation of RSK and MSK1 is upregulated in human squamous cell carcinoma (SCC) and SUV-treated mouse skin. The study also examines the potential of kaempferol, a natural flavonol found in tea, broccoli, grapes, apples, and other plant sources, as a chemopreventive agent against SUV-induced skin carcinogenesis. The study reveals that kaempferol inhibits RSK2 and MSK1 kinase activities and, by doing so, attenuates solar UV-induced phosphorylation of cAMP response element-binding protein (CREB) and histone H3 in mouse skin cells. The study further shows that kaempferol is a potent inhibitor of SUV-induced mouse skin carcinogenesis and acts by targeting RSK2 and MSK1. Overall, the study identifies kaempferol as a safe and novel chemopreventive agent against solar UV-induced skin carcinogenesis[302]. Furthermore, a study by Lee *et al*. investigates the effects of kaempferol, a flavonoid with anti-inflammatory and anti-oxidative properties, on UVB-induced skin inflammation and photocarcinogenesis. The study shows that kaempferol suppresses UVB-induced COX-2 protein expression in mouse skin epidermal JB6 P + cells and attenuates the UVB-induced transcriptional activities of COX-2 and AP-1. The study further demonstrates that kaempferol attenuates the UVB-induced phosphorylation of several MAPKs, including ERKs, p38, and c-Jun N-terminal kinases (JNKs), by blocking Src kinase activity. The study also shows that kaempferol competes with adenosine triphosphate (ATP) for direct binding to Src and docks easily into the ATP-binding site of Src. The study suggests that kaempferol is a potent chemopreventive agent against skin cancer through its inhibitory interaction with Src. Overall, the study provides insights into the potential of kaempferol as a chemopreventive agent against UVB-induced skin inflammation and photocarcinogenesis[303].

Overall, the molecular mechanism of kaempferol against skin cancer involves inducing cell cycle arrest and apoptosis, modulating the signaling pathways involved in inflammation and oxidative stress, and inhibiting the activity of enzymes that promote the growth and invasion of cancer cells[304].

While kaempferol has shown promise in preventing and treating skin cancer, there are some potential drawbacks to its use. Kaempferol has relatively low bioavailability[305], which means that the body may not absorb it efficiently. Like many natural compounds, kaempferol can have toxic effects at high doses. While it is generally considered safe, some studies have suggested that it can be toxic to certain cells and tissues at high concentrations[306]. Kaempferol can interact with some medications, particularly those that are metabolized by the liver[307]. While there have been some promising studies on the use of kaempferol in skin cancer, more research is needed to determine its safety and effectiveness. It is important to note that most of the research on kaempferol has been done in cell cultures and animal models, and more clinical studies are needed to confirm its effects in humans.

Resveratrol

Resveratrol is a naturally occurring polyphenolic compound found in many plant-based foods, including grapes and red wine[308]. The botanical name for the grapevine is *Vitis vinifera*, and the most commonly cultivated variety of grapes used for wine production is *Vitis vinifera* subsp. *vinifera*[309]. Resveratrol is found in the skin of grapes, and its concentration is highest in red grapes compared to white grapes[310]. Resveratrol is also found in other plants, including peanuts[311], berries[312], and knotweed[313]. The botanical name for the peanut plant is *Arachis hypogaea*, while the most commonly consumed berries that contain resveratrol are blueberries (*Vaccinium* spp.), cranberries (*Vaccinium macrocarpon*), and bilberries (*Vaccinium myrtillus*)[314]. The Japanese knotweed (*Fallopia japonica*), a plant native to Asia, is also a rich source of resveratrol[313]. It is classified as a phytoalexin, which means it is produced by plants in response to stress, injury, or infection[315]. Resveratrol has been extensively studied for its potential health benefits, including its antioxidant[316], anti-inflammatory[317], and anticancer[318] properties. Resveratrol has been shown to have potential anticancer effects against skin cancer through several molecular mechanisms. Here are some of the key ways in which resveratrol may act against skin cancer:

Inhibition of inflammation

Chronic inflammation is a risk factor for the development of many cancers, including skin cancer. Resveratrol has been shown to inhibit the expression of pro-inflammatory cytokines, such as interleukin-1β and tumor necrosis factor-α, which may help to reduce inflammation and the risk of cancer development[319,320].

Induction of apoptosis

Resveratrol has been shown to induce apoptosis, or programmed cell death, in skin cancer cells. This is thought to be due in part to its ability to activate certain signaling pathways, such as the p53 pathway, which can trigger cell death[321,322].

Inhibition of cell proliferation

Resveratrol can also inhibit the proliferation of skin cancer cells, which may help to slow the growth and spread of cancer cells[96].

Protection against DNA damage

Resveratrol has been shown to have DNA-protective effects, which may help to prevent mutations and other DNA damage that can lead to cancer[323].

Regulation of cell cycle

Resveratrol can regulate the cell cycle, which is the process by which cells divide and grow. By modulating the activity of certain proteins involved in cell cycle regulation, resveratrol may help to prevent uncontrolled cell growth that can lead to cancer development[324].

Several studies have investigated the molecular mechanisms underlying the anticancer effects of resveratrol against skin cancer. One study conducted by Osmond *et al*. evaluated the potential of resveratrol as an adjunct to chemotherapy in melanoma treatment. *In vitro*, resveratrol significantly decreased melanoma cell viability in all lines tested and selectively spared nonmalignant fibroblast cell lines. Treatment of malignant cells with resveratrol and temozolomide (TMZ) enhanced cytotoxicity compared to TMZ alone. However, *in vivo*, there was no significant difference. The study suggests that resveratrol has selective antitumor activity *in vitro*, but barriers to translating these results to *in vivo* models need to be overcome[325]. Another study by Aziz *et al*. discusses the protective role of resveratrol against skin cancer induced by UVR. Resveratrol modulates various molecular mechanisms involved in cell cycle regulation, ROS production, apoptosis, autophagy, cell proliferation, tumor promotion, and cancer-related gene expression. The evidence suggests that resveratrol has effective chemopreventive activity and could potentially be used as a preventive and therapeutic agent in managing UVR-induced skin carcinogenesis[326]. In addition, resveratrol has been found to modulate the expression of several genes and proteins involved in cell cycle regulation, such as cyclins, cyclin-dependent kinases (CDKs), and checkpoint proteins[327]. Kundu *et al*. investigate the effects of resveratrol, a compound found in grapes, on COX-2 expression induced by the tumor promoter (TPA) in mouse skin. Results showed that resveratrol significantly inhibited COX-2 expression by suppressing activation of NF-κB, ERK, and p38 mitogen-activated protein (MAP) kinase. Resveratrol blunted TPA-induced phosphorylation of p65 and its interaction with CBP/p300, rendering NF-κB transcriptionally inactive. The study also found that resveratrol targets IκB kinase (IKK) in blocking TPA-induced NF-κB activation and COX-2 expression in mouse skin *in vivo*[328]. Furthermore, a study performed by Reagan-Shaw *et al*. investigated the role of cell cycle regulatory molecules in resveratrol-mediated protection against multiple exposures to UVB radiation in hairless mice skin. Resveratrol was topically applied before each UVB exposure, resulting in a decrease in skin thickness, hyperplasia, and leukocyte infiltration. Resveratrol downregulated the upregulation of critical cell cycle regulatory proteins induced by UVB, including proliferating cell nuclear antigen (PCNA), cyclin-dependent kinases, and cyclins. Resveratrol also upregulated cyclin kinase inhibitor WAF1/p21 and tumor suppressor p53, and decreased the upregulation of MAPK, suggesting that the antiproliferative effects of resveratrol may be mediated via modulation of the expression and function of cell cycle regulatory proteins and inhibition of the MAPK pathway. Resveratrol may be useful for preventing UVB-mediated cutaneous damage, including skin cancer[329]. A study performed by Wu *et al*., aimed to investigate the effects of resveratrol, a natural polyphenol, on the proliferation and expression of aquaporin 3 (AQP3) in normal human epidermal keratinocytes (NHEKs), which are involved in hyperplastic skin disorders. The results showed that resveratrol inhibited NHEK proliferation in a concentration-dependent manner, and this was associated with downregulation of AQP3 expression and ERK phosphorylation, as well as upregulation of aryl hydrocarbon receptor nuclear translocator (ARNT) expression. The study suggests that the inhibitory effects of resveratrol on AQP3 expression were mediated by Sirtuin 1 (SIRT1)/ARNT/ERK signaling pathway. This finding may provide insights into the development of new drugs for hyperplastic skin disorders[330].

Resveratrol's anticancer effects are likely due to its ability to modulate multiple cellular pathways and processes involved in cancer development and progression. While resveratrol has many potential health benefits, including anticancer effects[318] against skin cancer, there are also some drawbacks and potential risks associated with its use. Resveratrol can interact with certain medications, such as blood thinners[331], nonsteroidal anti-inflammatory drugs (NSAIDs)[332], and some antidepressants[333]. It may also interfere with the effectiveness of chemotherapy drugs[334]. Resveratrol can cause side effects, including gastrointestinal symptoms (such as nausea, vomiting, and diarrhea)[335], headaches[335] and allergic reactions[336]. Resveratrol supplements are not regulated by the U.S. Food and Drug Administration (FDA), and there is no standardized dosage or quality control. This can make it difficult to ensure the safety and effectiveness of resveratrol supplements[337]. Overall, while resveratrol has many potential health benefits, it is important to use caution when using it as a supplement, particularly in high doses or in combination with other medications.

Curcumin

Curcumin is a natural compound found in the root of the turmeric plant (*Curcuma longa*), which is a member of the ginger family[338]. It is a bright yellow pigment and has been used for thousands of years in traditional medicine systems, such as Ayurveda and traditional Chinese medicine, to treat a wide range of conditions[339]. Curcumin is a polyphenol and is considered to be the most active constituent in turmeric[340]. It has antioxidant[341], anti-inflammatory[342], and anticancer properties[343] and has been studied extensively for its potential health benefits. It is also a common ingredient in many foods and supplements, including curry powder and turmeric supplements[338]. In terms of its molecular mechanism against skin cancer, curcumin has been found to inhibit various signaling pathways involved in cancer development and progression. One of the key pathways that curcumin targets is the nuclear factor-kappa B (NF-κB) signaling pathway[101]. NF-κB is a transcription factor that regulates genes involved in inflammation, cell proliferation, and apoptosis, and its activation is commonly found in various types of cancer, including skin cancer. Curcumin has been shown to inhibit NF-κB activation by suppressing the activity of IKK, which is the kinase that phosphorylates IκBα and leads to its degradation and subsequent release of NF-κB from the cytoplasm to the nucleus. Curcumin has also been shown to inhibit the expression of various NF-κB-regulated genes involved in cell survival, proliferation, and inflammation[344]. Additionally, curcumin has been found to induce apoptosis (programmed cell death) in skin cancer cells by activating the caspase pathway and inhibiting the anti-apoptotic protein Bcl-2[345]. Curcumin has also been shown to inhibit angiogenesis (the formation of new blood vessels), which is critical for tumor growth and metastasis[105].

Multiple investigations have been conducted to explore the molecular mechanisms responsible for the anticancer properties of curcumin against skin cancer. In one of the studies, Zhao *et al*. investigated the effects of curcumin on melanoma cells and found that it effectively inhibited cell proliferation and invasion potential and induced autophagy. Curcumin also arrested the cells at the G2/M phase of the cell cycle and suppressed the activation of AKT, mTOR, and P70S6K proteins, which are part of the AKT/

mTOR signaling pathway. These findings suggest that curcumin could be a potential therapeutic candidate for managing melanoma, which is a highly malignant and resistant cancer[346]. Another study by Wu *et al*. aimed to investigate the effects of curcumin on the expression of signal transducer and activator of transcription 3 (STAT3) in skin squamous cell carcinoma tissues and the possible mechanisms of curcumin in preventing and treating skin squamous cell carcinoma. Results showed that curcumin treatment inhibited the growth of A431 cells in a time-dependent and dose-dependent manner, with doses above 15 μmol/l for more than 24 h showing significant cytotoxic effects. Curcumin treatment also decreased the invasion and adhesive abilities of A431 cells and inhibited the transcription level of STAT3 mRNA in a dose-dependent manner. The study suggests that curcumin may reduce the invasive ability of A431 cells by inhibiting the activation of the STAT3 signaling pathway and expression of STAT3 as a target gene in the pathway, which may provide insights into the development of new therapies for skin squamous cell carcinoma[347]. In a study by Kunnumakkara *et al*., the authors investigated the role of curcumin in the regulation of signaling pathways involved in skin cancer development and progression. The authors demonstrated that curcumin inhibited the expression and activity of various pro-inflammatory cytokines, growth factors, and enzymes involved in skin carcinogenesis, including COX-2, MMP-9, and EGFR. They also showed that curcumin inhibited the activation of the PI3K/Akt/mTOR signaling pathway and the upregulation of its downstream target genes involved in cell survival and proliferation. Furthermore, the authors showed that curcumin enhanced the expression and activity of various tumor suppressor genes, including p53 and p21, which are involved in the regulation of cell cycle progression and apoptosis[348].

While curcumin has shown promising results in preclinical studies as a potential therapeutic agent against skin cancer, its clinical application has some limitations and challenges. One of the major challenges is its low bioavailability, which refers to the fraction of the administered dose that reaches the systemic circulation in an unchanged form and is available to exert its pharmacological effects. Curcumin is rapidly metabolized in the liver and intestines and has poor solubility in water, which leads to limited absorption and rapid elimination from the body[349]. Furthermore, curcumin's potential interactions with other drugs and its effects on drug metabolism enzymes have also raised concerns about its safety and efficacy. For instance, curcumin has been reported to inhibit the activity of cytochrome P450 (CYP) enzymes, which play a crucial role in the metabolism of many drugs. This inhibition may result in altered drug efficacy or toxicity when administered in combination with other medications[350].

Overall, the molecular mechanisms of curcumin against skin cancer are complex and involve multiple pathways and targets. Its ability to modulate inflammation, apoptosis, and angiogenesis makes it a promising natural compound for the prevention and treatment of skin cancer. However, more research is needed to fully understand its bioavailability studies, safer dose, and to optimize its use in clinical settings.

Epigallocatechin gallate

Epigallocatechin gallate is a type of flavonoid, a class of plant-derived compounds that are known for their antioxidant[351] and anti-inflammatory properties[352]. Epigallocatechin gallate is found primarily in green tea, which is derived from the leaves of the *Camellia sinensis* plant[353]. However, it can also be found in smaller amounts in black tea[354], white tea[355], and oolong tea[356]. Epigallocatechin gallate has been studied for its potential health benefits, including its anticancer properties[357]. In addition to its anticancer properties, Epigallocatechin gallate has also been studied for its potential role in reducing the risk of cardiovascular disease[358], improving cognitive function[359], and promoting weight loss[358]. It has also been found to have anti-inflammatory effects, which may make it useful in the prevention and treatment of chronic inflammatory diseases[360] and inflammatory bowel disease[361]. Epigallocatechin gallate has been shown to have potential chemopreventive and therapeutic effects against skin cancer through several molecular mechanisms of action. These mechanisms include:

Antioxidant activity

Epigallocatechin gallate has strong antioxidant activity, which can protect skin cells from oxidative stress-induced DNA damage, a key contributor to skin cancer development[106,107].

Anti-inflammatory activity

Epigallocatechin gallate has been found to inhibit the production of pro-inflammatory cytokines and chemokines, which can promote tumor growth and progression. In particular, Epigallocatechin gallate has been shown to inhibit the NF-κB signaling pathway, which is involved in inflammation and cell survival[362].

Inhibition of cell proliferation

Epigallocatechin gallate has been found to inhibit the proliferation of skin cancer cells by blocking the cell cycle and inducing apoptosis (programmed cell death). Epigallocatechin gallate has also been found to inhibit the expression of genes involved in cell cycle regulation and DNA repair[110,111].

Inhibition of angiogenesis

Epigallocatechin gallate has been shown to inhibit angiogenesis, the process by which new blood vessels are formed, which is critical for tumor growth and metastasis[149,150].

Inhibition of MMPs

Epigallocatechin gallate has been found to inhibit the activity of MMPs, which are enzymes that degrade the extracellular matrix and promote tumor invasion and metastasis[363].

Numerous studies have been carried out to investigate the molecular mechanisms underlying the anticancer effects of Epigallocatechin gallate in the context of skin cancer. In one of the studies, El-Kayal *et al*. investigated the potential use of ultradeformable colloidal vesicular systems, including penetration enhancer-containing vesicles, ethosomes, and transethosomes, for the topical delivery of (–)-epigallocatechin-3-gallate as a nutraceutical for skin cancer treatment. The prepared vesicles showed good physical stability and preservation of the antioxidant properties of (–)-epigallocatechin-3-gallate. (–)-epigallocatechin-3-gallate-loaded PEVs and TEs demonstrated an inhibitory effect on epidermoid carcinoma cells and reduced

tumor sizes in mice, with decreased skin oxidative stress biomarkers and lipid peroxidation. These findings suggest that (-)-epigallocatechin-3-gallate PEVs could be an effective topical delivery system for skin cancer treatment[364]. Zhang *et al.* investigated the interaction between Epigallocatechin-3-gallate and TRAF6 and its effects on the E3 ubiquitin ligase activity of TRAF6, as well as its role in the NF-κB pathway and melanoma cell growth, migration, and invasion. The results demonstrated that Epigallocatechin-3-gallate binds to TRAF6 and inhibits its E3 ubiquitin ligase activity, leading to the inactivation of the NF-κB pathway and suppression of melanoma cell growth, migration, and invasion. These findings suggest that Epigallocatechin-3-gallate may be a promising agent for the prevention and treatment of melanoma by targeting TRAF6[365]. Moreover, Ellis *et al.* describe a study that investigated the mechanism of action of Epigallocatechin-3-gallate, a polyphenolic component of green tea, in inhibiting melanoma cell growth. The study found that Epigallocatechin-3-gallate inhibited melanoma cell growth at physiological doses and that this inhibition was associated with reduced activity of the NF-κB pathway and decreased secretion of the inflammatory cytokine IL-1β. The study further demonstrated that Epigallocatechin-3-gallate downregulated the inflammasome component NOD-like receptor (NLR) family pyrin domain-containing 1 (NLRP1). NLRP1 and reduced caspase-1 activation, and silencing NLRP1 expression abolished Epigallocatechin-3-gallate induced inhibition of tumor cell proliferation both in vitro and *in vivo*. These findings suggest that inflammasomes and Interleukin-1 beta (IL-1β) could be potential targets for future melanoma therapeutics[366].

While Epigallocatechin gallate has shown promise as a potential treatment for skin cancer, there are some drawbacks and limitations to its use. The optimal dose of Epigallocatechin gallate for skin cancer treatment is unclear, and the effective dose may vary depending on the type and stage of the cancer. High doses of Epigallocatechin gallate may also cause adverse effects, such as liver toxicity[367]. The content of Epigallocatechin gallate in green tea and other natural sources can vary widely, depending on factors such as the plant species, growing conditions, and processing methods. This makes it difficult to standardize the dose and quality of Epigallocatechin gallate in natural sources[368]. Epigallocatechin gallate has low bioavailability, meaning that it is not well absorbed by the body and has a short half-life. This can limit its effectiveness *in vivo* and make it difficult to achieve therapeutic concentrations in target tissues[369].

Overall, Epigallocatechin gallate's molecular mechanisms of action against skin cancer involve multiple pathways, including antioxidant[351], anti-inflammatory[352], antiproliferative[370], antiangiogenic[371], and antimetastatic effects[371]. These mechanisms suggest that Epigallocatechin gallate may be a promising natural compound for the prevention and treatment of skin cancer, although more research is needed to fully understand its safer dose and potential clinical applications.

β-Carotene

β-Carotene is a red-orange pigment and a type of carotenoid, which is a group of plant pigments responsible for the bright colors of fruits and vegetables[372]. It is a precursor of vitamin A, meaning that the body can convert it into vitamin A when needed[373]. β-Carotene is found in high amounts in fruits and vegetables such as carrots, sweet potatoes, pumpkin, spinach, and apricots[374]. β-Carotene has antioxidant properties and is believed to have various health benefits, such as reducing the risk of certain types of cancer[375] and improving immune function[376].

β-Carotene is obtained from a variety of plants, like carrots (*Daucus carota*), sweet potatoes (*Ipomoea batatas*), pumpkins (*Cucurbita* spp.), etc.[377]. The molecular mechanism of action of β-carotene against skin cancer involves its ability to neutralize reactive oxygen species (ROS) and reduce oxidative stress, which is a key factor in the development of cancer. ROS are highly reactive molecules that are produced in cells as a result of various physiological and environmental stressors, including exposure to ultraviolet radiation. When ROS levels exceed the capacity of the cell's antioxidant defense system, they can cause oxidative damage to DNA, lipids, and proteins, which can ultimately lead to cancer. β-Carotene can scavenge ROS and neutralize them, thereby reducing the amount of oxidative stress in the cell[114,115]. Additionally, β-carotene can stimulate the body's natural antioxidant defense system by upregulating the expression of antioxidant enzymes such as superoxide dismutase and catalase. This further helps to reduce oxidative stress and prevent DNA damage[378]. Moreover, β-carotene also exhibits anti-inflammatory properties that can help reduce chronic inflammation, which is also a risk factor for the development of skin cancer. Chronic inflammation is associated with the production of ROS and DNA damage, which can ultimately lead to the development of cancer[379].

β-Carotene's ability to scavenge ROS, stimulate antioxidant enzyme expression, and reduce chronic inflammation makes it a potent antioxidant and a promising candidate for the prevention and treatment of skin cancer[379].

Several researchers have conducted studies on the effect of β-carotene against skin cancer. One such study was conducted by Greenberg *et al.* aimed to investigate whether β-carotene could prevent the occurrence of new nonmelanoma skin cancer in patients who had a recent history of the condition. The study randomly assigned 1805 patients to receive either 50 mg of β-carotene or placebo daily and conducted annual skin examinations. After 5 years, there was no significant difference in the rate of occurrence of new nonmelanoma skin cancer between the groups. The active treatment also showed no efficacy in patients with the lowest initial plasma β-carotene level or in those who currently smoked. The study concludes that β-carotene does not reduce the occurrence of new skin cancers in patients with a previous nonmelanoma skin cancer over a 5-year period of treatment and observation[380].

In a similar study, Kune *et al.* investigated the relationship between dietary and serum levels of β-carotene, vitamin A, and the risk of nonmelanocytic skin cancer in males. The study found that a high intake of vegetables, including cruciferous vegetables, β-carotene, and vitamin C-containing foods and fish, was inversely related to the risk of skin cancer. The study also found that cases had lower serum levels of β-carotene and vitamin A than controls, and the incidence of skin cancer was inversely related to serum β-carotene levels. Smoking and alcohol consumption did not show a significant association with the risk of skin cancer. The study concludes that further investigation is required to determine the etiologic relevance of low serum levels of β-carotene and vitamin A and the protective effects of a high intake of vegetables and fish on nonmelanocytic skin cancer[381].

While β-carotene has potential benefits in preventing skin cancer, there are also some drawbacks associated with its use.

Pro-oxidant effects

High doses of β-carotene may have pro-oxidant effects, meaning that they can increase oxidative stress and damage cells. This is particularly true in smokers, as studies have shown that β-carotene supplements can increase the risk of lung cancer in smokers[382].

Lack of efficacy in some studies

While some studies have suggested that β-carotene can reduce the risk of skin cancer, other studies have shown no significant effect. More research is needed to determine the optimal dose, duration, and form of β-carotene supplementation for skin cancer prevention[383].

Interactions with other nutrients

β-carotene can interact with other nutrients, such as vitamin E and selenium, which can affect its efficacy[384]. It is important to ensure adequate intake of these nutrients when supplementing with β-carotene.

Not a substitute for sun protection

β-carotene supplements should not be seen as a substitute for sun protection. While β-carotene may help reduce the risk of skin cancer, it cannot replace the importance of wearing protective clothing and using sunscreen when exposed to ultraviolet radiation[385].

It can be concluded that while β-carotene may have potential benefits in preventing skin cancer, more research is needed to understand its interaction with other nutrients, which can affect its efficacy.

Caffeic acid

Caffeic acid is a naturally occurring polyphenolic compound and one of the most common hydroxycinnamic acid derivatives[386]. Caffeic acid is found in a wide variety of plants, including coffee (*Coffea arabica*, *Coffea robusta*), apples (*Malus domestica*), pears (*Pyrus communis*), grapes (*Vitis vinifera*), blueberries (*Vaccinium* spp.), kiwi fruits (*Actinidia deliciosa*), thyme (*Thymus vulgaris*), basil (*Ocimum basilicum*), rosemary (*Rosmarinus officinalis*), sage (*Salvia officinalis*), etc.[387]. Caffeic acid has been studied for its antioxidant[388], anti-inflammatory[389], and anticancer properties[390]. Caffeic acid has been shown to have potential chemopreventive effects against skin cancer[390].

The molecular mechanism of action of caffeic acid against skin cancer involves its ability to modulate multiple cellular pathways involved in cell growth, differentiation, and apoptosis. One of the key mechanisms by which caffeic acid exerts its anticancer effects is through the regulation of signaling pathways that control cell proliferation and survival[126]. Caffeic acid has been shown to inhibit the activity of various enzymes and transcription factors, such as Akt, ERK, NF-κB[121,122], and AP-1, which are involved in cell survival and proliferation. By inhibiting these pathways, caffeic acid can induce cell cycle arrest and promote apoptosis, leading to the death of cancer cells[391–393]. Caffeic acid has also been shown to possess potent antioxidant and anti-inflammatory properties, which can help to protect cells against oxidative stress and reduce chronic inflammation. Chronic inflammation is a major risk factor for the development of skin cancer, as it can cause DNA damage and impair the immune system's ability to detect and eliminate cancer cells[394–396]. Additionally, caffeic acid has been shown to enhance the activity of the body's natural defense mechanisms against cancer, such as the activation of the Nrf2 pathway. This pathway is involved in the regulation of antioxidant enzymes and can help to protect cells against oxidative damage[397–399].

Studies have investigated the molecular mechanisms of action of caffeic acid against skin cancer. One such study was conducted by Yang *et al*., which investigated the molecular mechanism underlying the anticancer activity of caffeic acid, a phenolic phytochemical found in coffee. The study found that caffeic acid inhibited the colony formation of human skin cancer cells and the neoplastic transformation of HaCaT cells. Topical application of caffeic acid to mouse skin also significantly suppressed tumor incidence and volume in a solar UV-induced skin carcinogenesis model. The study further demonstrated that caffeic acid directly interacted with and inhibited the activity of ERK1 and 2, two proteins involved in mitogen-activated protein kinase signaling. The co-crystal structure of ERK2 complexed with caffeic acid was also resolved, revealing the amino acid residues at which caffeic acid interacts with ERK2. Finally, the study showed that the knockdown of ERK2 in skin cancer cells reduced their sensitivity to caffeic acid in a xenograft mouse model. These findings suggest that caffeic acid exerts its chemopreventive activity against skin carcinogenesis by targeting ERK1 and 2[400]. Another study by Kudugunti *et al*. investigated the anti-melanoma effects of phenethyl ester of caffeic acid *in vitro* and *in vivo*. The phenethyl ester of caffeic acid was found to inhibit the growth of five different melanoma cell lines, cause intracellular GSH depletion, increase ROS formation, and induce apoptosis in B16-F0 cells. In an *in vivo* study using a B16-F0 melanoma tumor model in mice, it was found to inhibit tumor growth at doses of 10–30 mg/kg/day with minimal toxicity. However, higher doses of phenethyl ester of caffeic acid were associated with increased plasma ALT levels and lipid peroxidation levels in liver and kidney homogenates. The study suggests that phenethyl ester of caffeic acid has potential as an anti-melanoma agent at lower doses[401]. Furthermore, a study by Balupillai *et al*. investigated the effect of caffeic acid on acute and chronic UVB-irradiation-induced inflammation and photocarcinogenesis in Swiss albino mice. The results showed that caffeic acid administration before UVB exposure decreased inflammation and oxidative stress, enhanced antioxidant status, and activated peroxisome proliferator-activated receptors (PPARγ) in the mice's skin. PPARγ is considered a potential target for photo chemoprevention because it inhibits UVB-mediated inflammatory responses. Moreover, both topical and intraperitoneal caffeic acid treatment before each UVB exposure reduced tumor incidence and multiplicity in the mice's skin. Therefore, caffeic acid offers protection against UVB-induced photocarcinogenesis through the activation of the anti-inflammatory transcription factor PPARγ in mice[402]. Another study by Balupillai *et al*. investigated the mechanisms by which caffeic acid prevents UVB-induced photocarcinogenesis in human dermal fibroblasts (HDFa) and mouse skin. The results showed that caffeic acid inhibited the formation of cyclobutane pyrimidine dimers (CPDs), oxidative DNA damage, ROS generation,

and apoptotic cell death in HDFa. Furthermore, CA prevented UVB-induced expression of PI3K and AKT kinases through activation of PTEN and promoted XPC-dependent nucleotide excision repair (NER) proteins such as XPC, XPE, transcription factor IIH (TFIIH-p44), and excision repair cross-complementation group 1 (ERCC1) in human dermal fibroblasts (HDFa) cells and mouse skin tissue. Caffeic acid directly activated PTEN through hydrogen bonds and hydrophobic interactions. These findings suggest that caffeic acid prevents UVB-induced photodamage through the activation of PTEN expression in human dermal fibroblasts and mouse skin[403]. Another study by Agilan *et al.* investigated the role of JAK-STAT3 signaling in UVB-induced skin carcinogenesis and the protective effect of caffeic acid against it in mouse skin. Chronic UVB irradiation increased the expression of IL-10 and JAK1, which activated STAT3 and led to the transcription of proliferative and anti-apoptotic markers. Caffeic acid inhibited JAK-STAT3 signaling, induced apoptotic cell death, and upregulated the expression of pro-apoptotic markers. Additionally, chronic UVB exposure decreased the expression of thrombospondin-1 (TSP-1), an anti-angiogenic protein, and pretreatment with caffeic acid prevented this loss in UVB-irradiated mouse skin. Thus, caffeic acid offers protection against UVB-induced photocarcinogenesis by modulating the JAK-STAT3 signaling pathway in the mouse skin[404].

While caffeic acid has shown promising anticancer properties against skin cancer, there are also some potential drawbacks to its use. Some of the possible drawbacks of caffeic acid include:

Dose-dependent toxicity

At high doses, caffeic acid can be toxic to cells and tissues. This can lead to oxidative stress and inflammation, which can actually promote the growth and spread of cancer cells[405]. Therefore, it is important to use caffeic acid at appropriate doses and under medical supervision.

Bioavailability

Caffeic acid has relatively low bioavailability, which means that a significant amount of it may be metabolized or excreted before it can exert its anticancer effects. To overcome this limitation, researchers are exploring ways to enhance the bioavailability of caffeic acid, such as by using nanoparticles or liposomes[406].

Lack of clinical trials

While many preclinical studies have shown that caffeic acid has potential anticancer properties, there is a lack of clinical trials to determine its efficacy and safety in humans. More research is needed to establish the optimal dose, route of administration, and duration of treatment[405].

Interactions with other drugs

Caffeic acid may interact with other drugs or supplements, which could lead to adverse effects or reduce its efficacy. Therefore, it is important to consult a healthcare provider before using caffeic acid as a complementary or alternative therapy for skin cancer[408].

Overall, the molecular mechanism of action of caffeic acid against skin cancer involves its ability to modulate multiple cellular pathways involved in cell growth, differentiation, and apoptosis. Its potent antioxidant[388] and anti-inflammatory properties[389], along with its ability to enhance the body's natural defense mechanisms, may be used for the prevention and treatment of skin cancer[390]. However, further research is needed to fully understand its benefits and risks in the prevention and treatment of skin cancer.

Ferulic acid

Ferulic acid is a type of phenolic acid, which is a group of compounds that are widely distributed in plants[409]. It is a natural antioxidant and has been found in many different plant sources, including fruits, vegetables, grains, and herbs[410–412]. Ferulic acid is found in many different plant sources, including rice bran (*Oryza sativa*), wheat (*Triticum aestivum*), barley (*Hordeum vulgare*), oats (*Avena sativa*), corn (*Zea mays*), coffee (*Coffea arabica*), pineapple (*Ananas comosus*), apples (*Malus pumila*), oranges (*Citrus sinensis*), and artichokes (*Cynara scolymus*)[413–415].

Ferulic acid has been shown to have various molecular mechanisms of action against skin cancer. Some of the key mechanisms are:

Antioxidant properties

Ferulic acid has strong antioxidant properties, which means that it can scavenge free radicals and protect skin cells from oxidative stress. This can help to prevent DNA damage and reduce the risk of skin cancer development[416].

Anti-inflammatory properties

Chronic inflammation is known to contribute to the development of skin cancer. Ferulic acid has been shown to have anti-inflammatory properties, which can help reduce inflammation and prevent the progression of precancerous cells to cancerous cells[126].

Inhibition of UV-induced damage

Ferulic acid has been shown to inhibit the DNA damage caused by UV radiation, which is a major risk factor for skin cancer. It can also help to repair damaged DNA and prevent the formation of cancerous cells[417].

Induction of apoptosis

Ferulic acid has been shown to induce apoptosis (programmed cell death) in skin cancer cells. This can help to prevent the growth and spread of cancer cells[418].

Inhibition of angiogenesis

Ferulic acid has also been shown to inhibit angiogenesis, which is the process by which new blood vessels form to supply nutrients to tumors. By inhibiting angiogenesis, ferulic acid can help to prevent the growth and spread of skin cancer cells[419].

A study performed by Alias *et al.* aimed to compare the chemopreventive potential of orally administered and topically applied ferulic acid in 7,12-dimethylbenz[a]anthracene (DMBA)-induced skin carcinogenesis. The status of phase I and phase II detoxication agents, lipid peroxidation byproducts, and antioxidants were assessed to determine the mechanistic pathway of their chemopreventive efficacy. Skin squamous cell carcinoma was induced in mice by applying DMBA twice weekly for 8

weeks. Oral administration of ferulic acid completely prevented the formation of skin tumors, whereas topically applied ferulic acid did not show significant chemopreventive activity. Ferulic acid had a modulating effect on the status of lipid peroxidation, antioxidants, and detoxication agents during DMBA-induced skin carcinogenesis. The study concludes that orally administered ferulic acid has a potent suppressing effect on cell proliferation during DMBA-induced skin carcinogenesis[420]. One study conducted by Choi *et al*. examined the anticancer activity of ferulic acid on National Institutes of Health 3T3 (NIH3T3) fibroblasts and human skin melanoma cells (SK-MEL-3) by measuring the cytotoxicity of ferulic acid on these cells. Ferulic acid decreased cell viability in a dose-dependent manner after human skin melanoma cells were treated with various concentrations of ferulic acid for 48 h. At a concentration of 120 μM, ferulic acid significantly decreased cell viability in human skin melanoma cells, while it did not show a significant decrease in cell viability at concentrations of 30–120 μM in NIH3T3 fibroblasts. These results suggest that ferulic acid has anticancer activity in cancer cells, such as human skin melanoma cells, by significantly decreasing cell viability[421]. Another study by Murakami *et al*. reports the synthesis of a novel ferulic acid analog called FA15, which was found to suppress phorbol ester-induced Epstein–Barr virus activation and superoxide anion generation *in vitro*. The study also demonstrated that FA15 suppressed inducible nitric oxide synthase and cyclooxygenase-2 protein expressions, inhibited the release of tumor necrosis factor-alpha, and suppressed I-kappaB degradation in RAW264.7, a murine macrophage cell line. In mouse skin, topical application of FA15 attenuated hydrogen peroxide production and edema formation, as well as papilloma development, while FA did not. The study concludes that FA15, derived from natural sources, is a novel chemopreventive agent, both structurally and functionally[422].

While ferulic acid has many potential benefits for the prevention and treatment of skin cancer, there are also some drawbacks and potential side effects. Ferulic acid can cause skin irritation, especially in individuals with sensitive skin. This can manifest as redness, itching, or burning sensations. Ferulic acid can increase the skin's sensitivity to UV radiation, which can increase the risk of sunburn and skin damage. It is important to use sunscreen and limit sun exposure when using ferulic acid-containing skincare products. Ferulic acid can interact with certain medications, including blood thinners and chemotherapy drugs.

Overall, the molecular mechanisms of action of ferulic acid against skin cancer involve its antioxidant[416] and anti-inflammatory properties[126], as well as its ability to inhibit UV-induced damage[417], induce apoptosis[418], and inhibit angiogenesis[419]. These properties make ferulic acid a promising natural agent for the prevention and treatment of skin cancer. While ferulic acid is generally considered safe when used in appropriate amounts, it is important to be aware of the potential side effects and to use caution when using it to prevent or treat skin cancer. It is also important to use high-quality, pure products to minimize the risk of skin irritation and other adverse effects.

Importance of a diet rich in fruits and vegetables for preventing skin cancer

A diet rich in fruits and vegetables has been associated with many health benefits, including the prevention of skin cancer[423]. The high nutrient content of fruits and vegetables provides the body with the necessary vitamins, minerals, and antioxidants to maintain healthy skin and prevent damage from the sun's harmful UV rays[424]. One of the most important benefits of a diet rich in fruits and vegetables is its high antioxidant content. Antioxidants are molecules that neutralize free radicals, which are unstable molecules that damage cells and increase the risk of cancer[425]. Fruits and vegetables contain antioxidants such as vitamin C, vitamin E, and β-carotene, which can help protect the skin from UV radiation and reduce the risk of skin cancer[426].

Vitamin C is necessary for the production of collagen, a protein that helps to maintain the elasticity of the skin[427]. β-carotene, which is found in orange and yellow fruits and vegetables, is converted into vitamin A in the body and is important for skin cell growth and repair[428]. Other vitamins and minerals found in fruits and vegetables, such as potassium and folate, are also essential for maintaining healthy skin[429]. A diet rich in fruits and vegetables is also high in fiber, which can reduce inflammation in the body[430]. Chronic inflammation has been linked to an increased risk of many types of cancer, including skin cancer. By reducing inflammation in the body, a diet rich in fruits and vegetables can help prevent the development of skin cancer[431]. A diet rich in fruits and vegetables can help with weight management[432]. Being overweight or obese has been linked to an increased risk of certain types of skin cancer, including melanoma. By maintaining a healthy weight, individuals can reduce their risk of developing skin cancer[433].

To maximize the benefits, individuals should aim to consume a variety of fruits and vegetables in their diet and limit their exposure to UV radiation by wearing protective clothing, seeking shade during peak hours, and using sunscreen[434].

Fruits and vegetables are rich sources of dietary phytochemicals that play a crucial role in the regulation of cell signaling pathways, which are important in the prevention of skin cancer[435]. Cell signaling pathways are complex networks of molecular interactions that govern cellular processes such as growth, differentiation, and survival. Abnormalities in these pathways have been linked to the development of skin cancer[436,437].

Many dietary phytochemicals found in fruits and vegetables that belong to the class of secondary metabolites, like flavonoids, carotenoids, polyphenols, etc., have been shown to regulate cell signaling pathways and prevent the development of skin cancer[438]. For example, polyphenols found in blueberries have been shown to inhibit the growth of skin cancer cells by regulating the Akt/mTOR signaling pathway[439]. Flavonoids found in citrus fruits, such as hesperidin and naringenin, have been shown to inhibit the growth of melanoma cells by regulating the MAPK signaling pathway[440,441].

Fruits and vegetables also have anti-inflammatory properties that can prevent the development of skin cancer by regulating the immune response[442]. Inflammation is a key component of the skin's response to UV radiation, and chronic inflammation has been linked to an increased risk of skin cancer[443]. Bioactive compounds found in fruits and vegetables, such as quercetin found in apples and onions, have been shown to inhibit the production of inflammatory cytokines and prevent inflammation in the skin[444].

It is important to complement dietary changes with other sun safety measures, such as wearing protective clothing, using sunscreen, and limiting sun exposure during peak hours[445]. This

section includes the dietary sources of some important dietary phytochemicals effective against skin cancer (Table 2A, B).

Blueberries (Vaccinium corymbosum)

Blueberries belong to the class of secondary metabolites known as flavonoids[576]. Specifically, blueberries contain high levels of a type of flavonoid called anthocyanins, which give them their characteristic deep blue color[577]. Anthocyanins are known for their antioxidant properties[578], which may have a number of health benefits, including reducing inflammation[479], improving cardiovascular health[480], and protecting against certain types of cancer, including skin cancer[423]. Another phytochemical present in blueberries that may help to prevent skin cancer is pterostilbene[581], which has been shown to have antioxidant and anti-inflammatory properties and may help to inhibit the growth of skin cancer cells[582]. Additionally, blueberries are a good source of vitamin C[583], which has been found to have protective effects against skin damage caused by UV radiation and may also help to prevent skin cancer[584]. Various research groups have examined its impact on skin cancer. A recent study performed by Alsadi *et al*. examined the effects of a polyphenol-enriched blueberry preparation (PEBP) and non-fermented blueberry juice (NBJ) on the expression of miRNAs and target proteins associated with skin cancer. The study found that PEBP was able to inhibit the proliferation of skin cancer stem cells, reduce the formation of melanophores, and decrease the expression of the CD133 + stem cell marker. The study also found that the expression of tumor suppressor miR-200s was upregulated, and a protein target of the tumor suppressor miR200b, ZEB1, was significantly modulated. These findings suggest that PEBP has potent anticancer and antimetastatic potentials and may represent a novel chemopreventative agent against skin cancer. Qi *et al*. investigated the effects of blueberries on skin cancer prevention in mice. The researchers found that blueberries inhibited skin tumor growth via the regulation of multiple signaling pathways, including the PI3K/AKT, MAPK, and NF-κB pathways. In one of the studies, Afaq *et al*. investigated the effects of green tea and black tea extracts on skin cancer in mice. The researchers found that both green tea and black tea extracts inhibited skin cancer via the regulation of multiple signaling pathways, including the MAPK and PI3K/AKT pathways. Overall, these studies demonstrate that blueberries protect against skin cancer.

Raspberries (Rubus idaeus)

Raspberries contain a class of secondary metabolites known as flavonoids, specifically anthocyanins. These are responsible for the fruit's characteristic red color and are also known for their

Table 2

Dietary sources of some important dietary phytochemicals.

S. no.	Dietary phytochemical	Group of plant secondary metabolite	Dietary sources	Reference
A				
1.	Rosmarinic acid	Phenolic acids	Rosemary, sage, thyme, mint, basil, oregano, broccoli, spinach, lemon balm tea, green tea, and some types of honey, particularly those made from plants such as rosemary or thyme.	[446–455]
2.	Allicin	Organosulfur compounds	Raw garlic, onions, leeks, shallots, and chives.	[456–461]
3.	Sulforaphane	Organosulfur compounds	Broccoli, cauliflower, brussels sprouts, kale, cabbage, bok choy, arugula, radishes, and turnips.	[462–470]
4.	Ellagic acid	Polyphenolic compounds	Strawberries, raspberries, blackberries, pomegranates, cranberries, walnuts, pecans, green tea, and black tea.	[471–478]
5.	Betulinic acid	Pentacyclic triterpenoid compounds	Chaga mushrooms, white asparagus, and wild celery.	[479–482]
6.	Apigenin	Flavonoids	Parsley, chamomile, cilantro, thyme, oregano, peppermint, rosemary, celery, onions, artichokes, broccoli, bell peppers, grapefruit, oranges, cherries, chamomile tea, and peppermint tea.	[254,483–495]
7.	Gingerol	Gingerols	Ginger.	[496,497]
8.	Quercetin	Flavonoids	Apples, berries (such as blueberries, cranberries, and elderberries), cherries, grapes, oranges, pomegranates, onions, shallots, kale, broccoli, red leaf lettuce, tomatoes, green peppers, spinach, quinoa, buckwheat, thyme, green tea, and red wine.	[444,498–516]
B				
9.	Kaempferol	Flavonoids	Kale, spinach, broccoli, brussels sprouts, cabbage, grapes, apples, thyme, green tea, black tea, chickpeas and kidney beans.	[517–528]
10.	Resveratrol	Polyphenolic compounds (stilbenes)	Grapes, red wine, blueberries, raspberries, mulberries, peanuts, pistachios, cocoa, dark chocolate, and tomatoes.	[529–533]
11.	Curcumin	Polyphenolic compounds (curcuminoids)	Turmeric.	[534]
12.	Epigallocatechin gallate	Polyphenolic compounds (catechins)	Black tea, green tea (particularly Japanese green tea varieties such as matcha), white tea, strawberries, raspberries, blueberries, grapes, hazelnuts, and pecans.	[354,535–541]
13.	β-Carotene	Terpenoid compounds (carotenoids)	Carrots, sweet potatoes, butternut squash, acorn squash, pumpkin, spinach, kale, honeydew melon, mangoes, and apricots.	[542–550]
14.	Caffeic acid	Polyphenolic compounds (hydroxycinnamic acids)	Coffee, apples, pears, blueberries, cherries, tomatoes, carrots, thyme, oregano, rosemary, sage, almonds, green tea, sunflower seeds, and sesame seeds.	[486,551–562]
15.	Ferulic acid	Polyphenolic compounds (hydroxycinnamic acids)	White bran, germ portions of wheat, rice, oats, oranges, apples, pineapples, cherries, spinach, broccoli, carrots, sweet potatoes, cinnamon, flaxseeds, and sesame seeds.	[386,563–575]

antioxidant properties[585]. Some studies have suggested that anthocyanins may have protective effects against skin cancer by reducing oxidative stress and inflammation in the skin[423]. Raspberries are a rich source of dietary phytochemicals, many of which have been found to have potential anticancer properties[586]. Specifically, several of the compounds found in raspberries have been studied for their ability to prevent or treat skin cancer[587]. One such compound is ellagic acid, a polyphenol found in raspberries that has been shown to have anti-inflammatory and antioxidant effects[214]. Studies have found that ellagic acid can inhibit the growth of skin cancer cells and prevent the formation of skin tumors in animal models[210]. Another phytochemical found in raspberries with potential anticancer properties is quercetin, a flavonoid[498] with antioxidant[499] and anti-inflammatory effects[122]. Quercetin has been shown to induce cell death in skin cancer cells and inhibit the growth of tumors in animal models[283].

Numerous research teams have looked at its effect on skin cancer. A study performed by Duncan *et al*. investigates the potential of a black raspberry extract (BRE) in reducing cutaneous UVB-induced inflammation and carcinogenesis. Female hairless mice were exposed to UVB radiation and treated topically with either BRE or vehicle control. Results showed that mice treated with BRE had a significant reduction in tumor number and size, which correlated with a decrease in tumor-infiltrating regulatory T-cells. In addition, topical BRE treatment significantly reduced acute UVB-induced inflammation, as evidenced by decreased edema, p53 protein levels, oxidative DNA damage, and neutrophil activation. These findings suggest that BRE may have clinical efficacy in preventing human skin cancers[588]. Oberyszyn describes the increased incidence of skin cancer due to exposure to sunlight and changes in tanning practices. Skin tumors are the most common form of cancer in humans, and current treatments for nonmelanoma skin cancers can have severe side effects and limited clinical efficacy. The study proposes natural compounds derived from functional foods as an alternative strategy for the prevention and treatment of skin cancer. Specifically, the study discusses the potential of black raspberry extracts as a chemopreventive/chemotherapeutic agent against nonmelanoma skin cancers[589]. Mace *et al*. examine the potential of black raspberry extracts (BRB) and their phytochemical metabolites in modulating immune processes relevant to carcinogenesis and immunotherapy. The study found that BRB extracts and their metabolites inhibited the proliferation and viability of CD4 + and CD8 + T lymphocytes, as well as the expansion and suppressive capacity of myeloid-derived suppressor cells (MDSC). Additionally, pretreatment of immune cells with BRB extracts and metabolites attenuated IL-6-mediated phosphorylation of STAT3 and IL-2-induced STAT5 phosphorylation. The study concludes that BRB extracts and their metabolites contain phytochemicals that affect immune processes relevant to carcinogenesis and immunotherapy and could be a potential source of lead compounds for drug development[590]. Overall, raspberries exhibit promising natural anticancer properties.

Kiwifruit (Actinidia deliciosa)

Kiwifruit contains a variety of dietary phytochemicals, including flavonoids, carotenoids, and phenolic acids, that have been studied for their potential benefits in preventing or treating skin cancer[591]. Flavonoids, such as quercetin and kaempferol, are particularly abundant in kiwifruit[592] and have been shown to have antioxidant, anti-inflammatory, and anticancer properties[593,594]. Studies have suggested that quercetin and kaempferol may be particularly effective against skin cancer due to their ability to inhibit the growth and proliferation of cancer cells, as well as their ability to protect against DNA damage caused by UV radiation[283,303]. Additionally, the carotenoids present in kiwifruit, such as β-carotene[595,596], lutein[596,597], and zeaxanthin[597], have been studied for their potential to protect against UV-induced skin damage and reduce the risk of skin cancer[598,599]. Phenolic acids, such as chlorogenic acid, are also present in kiwifruit and have been shown to have antioxidant and anti-inflammatory effects[600]. Numerous research groups have examined its impact on skin cancer. One of the studies performed by Kou *et al*. investigated the effects of kiwifruit extract on CRL-11147 melanoma cancer cells and the possible mechanisms behind the results. The study found that kiwifruit extract decreased the percentage of cancer cell colonies and increased apoptosis, indicating antitumor effects. The antiproliferative effect of kiwifruit extract was attributed to the downregulation of Cyclin E and CDK4, while the pro-apoptotic effect was attributed to the upregulation of TRAILR1. Overall, the study suggests that kiwifruit extract may have potential for use in the treatment of melanoma[601]. Another study carried out by Kou *et al*. investigated the potential of kiwifruit extract as a radiosensitizer for Cell Repository Line (CRL-11147) melanoma cancer cells and the underlying mechanisms. Melanoma is a deadly form of skin cancer that is often resistant to radiation therapy. The study used various assays to evaluate the effects of kiwifruit extract on cell proliferation and apoptosis in combination with radiation therapy. The results showed that the combination of kiwifruit extract and radiation therapy decreased the percentage of colonies, Proliferating Cell Nuclear Antigen (PCNA) staining intensity, and optical density value of cancer cells. The study also found that kiwifruit extract increased relative caspase-3 activity, indicating increased apoptosis of cancer cells. The antitumor effect of kiwifruit extract was correlated with increased expression of the antiproliferative molecule p27 and the pro-apoptotic molecule Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand Receptor 1 (TRAILR1). The study suggests that kiwifruit extract could be used as a potential radiosensitizer for melanoma treatment by upregulating both p27 and TRAILR1 to inhibit proliferation and increase apoptosis, respectively[602]. Overall, these studies show that kiwifruit can help prevent skin cancer.

Watermelon (Citrullus lanatus)

Watermelon is a rich source of several dietary phytochemicals that have been found to be effective against skin cancer[607]. One such phytochemical is lycopene, a carotenoid that gives watermelon its red color. Lycopene is a potent antioxidant that has been shown to protect against UV-induced skin damage, which can lead to skin cancer[604]. Studies have also found that lycopene can induce cell death in cancer cells and inhibit their growth[605]. Another phytochemical found in watermelon is citrulline, an amino acid that has been found to have anti-inflammatory properties. Inflammation is a key factor in the development and progression of many types of cancer, including skin cancer. Citrulline has been shown to reduce inflammation and oxidative stress in the skin, potentially reducing the risk of skin cancer[606].

Watermelon also contains β-carotene, another carotenoid with antioxidant properties. β-Carotene has been shown to protect against UV-induced skin damage and may help reduce the risk of skin cancer[607]. Its effect on skin cancer has been studied by a plethora of research teams. Ascenso *et al*. focus on the photoprotective properties of lycopene, one of the most potent antioxidants, and its role in anticarcinogenic action at different levels. However, the photoprotective properties of lycopene remain contradictory as some studies show a positive effect while others show a negative effect in both *in vitro* and *in vivo* models. The study highlights the need for a better understanding of the molecular mechanisms of UV damage on skin cells and the role of carotenoids as effective modulators of apoptosis and cell cycle dynamics. The use of lycopene and other effective phytocompounds as preventive and/or corrective agents may be a potential approach for reducing UVB-induced damage and developing novel therapeutic strategies for skin disorders[608]. Another study by Fazekas *et al*. investigated the protective effects of topical lycopene, a carotenoid found in tomatoes and watermelon, against acute ultraviolet B (UVB)-induced photodamage. The results showed that the application of lycopene inhibited UVB-induced ornithine decarboxylase and myeloperoxidase and reduced skin thickness. Lycopene also prevented cleavage of caspase-3, restored normal PCNA staining, and maintained normal cell proliferation, suggesting that it may act as a preventative agent by reducing inflammation, maintaining normal cell proliferation, and preventing DNA damage. Thus, topical lycopene showed protective effects against acute UVB-induced photodamage[609]. Overall, these studies indicate that watermelon can aid in the prevention of skin cancer.

Mangoes (Mangifera indica)

Mangoes contain several dietary phytochemicals that have been found to be effective against skin cancer[610]. One of the primary phytochemicals found in mangoes is quercetin, which has been shown to possess strong antioxidant properties and inhibit the growth of cancer cells[82,284]. Another important phytochemical found in mangoes is mangiferin, which has been found to possess anti-inflammatory, antioxidant, and anticancer properties[611]. Studies have shown that mangiferin can inhibit the proliferation of cancer cells and induce apoptosis, which is programmed cell death[612]. Additionally, β-carotene and lutein, two other important dietary phytochemicals found in mangoes, have been shown to possess photoprotective properties and protect the skin against UV-induced damage, which is a major risk factor for skin cancer[613,614]. Norathyriol is a flavonoid compound that has been identified in mangoes. It is a naturally occurring phytochemical that belongs to the class of flavanones. Norathyriol has been reported to have various biological activities, including antioxidant, anti-inflammatory, and anticancer properties[615]. The combination of these dietary phytochemicals found in mangoes makes it a potentially effective dietary intervention for preventing and treating skin cancer. A multitude of research groups have investigated its impact on skin cancer. Li *et al*. describe a study where norathyriol, a compound derived from plants and known to have anticancer activity, was identified through virtual screening of the Chinese Medicine Library as a potential chemopreventive agent for skin cancer. Norathyriol was found to inhibit extracellular signal-regulated kinase (ERK) 1/2 activity and attenuate UVB-induced phosphorylation in mitogen-activated protein kinases signaling cascades. It was confirmed to bind specifically with ERK2 through co-crystal structural analysis. Norathyriol was shown to inhibit *in vitro* cell growth and significantly suppress solar UV-induced skin carcinogenesis in mouse skin tumorigenesis assays by inhibiting ERK-dependent activity of transcriptional factors AP-1 and NF-κB during UV-induced skin carcinogenesis. Overall, norathyriol was identified as a safe and highly effective chemopreventive agent against the development of UV-induced skin cancer[615]. In one of the studies, Saleem *et al*. investigated the antitumor-promoting effects of lupeol, a triterpene found in common fruit plants like mangoes and medicinal herbs, in a mouse skin tumorigenesis model. Topical application of lupeol inhibited conventional and novel biomarkers of tumor promotion in a time-dependent and dose-dependent manner. Lupeol treatment also inhibited the activation of signaling pathways involved in tumor promotion, resulting in reduced tumor incidence, lower tumor burden, and delayed tumor appearance. The results suggest that lupeol is an effective agent for cancer chemoprevention and should be evaluated in tumor models, including skin carcinogenesis[616]. Overall, the results of these studies suggest that eating mangoes may help lower the risk of getting skin cancer.

Carrots (Daucus carota)

Carrots are a rich source of dietary phytochemicals that have been shown to have potential health benefits, including the prevention of skin cancer[617]. The most notable phytochemicals present in carrots are carotenoids, which include β-carotene, α-carotene, and lutein. These compounds have been shown to have antioxidant properties that protect skin cells from oxidative stress caused by ultraviolet radiation, the most important factor contributing to skin cancer development[618]. Carotenoids can also enhance immune function and stimulate repair mechanisms in the skin[619,620]. In addition, falcarinol, a polyacetylene compound found in carrots, has been found to have chemopreventive properties against skin cancer by inducing apoptosis (cell death) in cancer cells and inhibiting their proliferation[621]. Studies have shown that consuming a diet rich in carrots and other carotenoid-containing vegetables can reduce the risk of developing skin cancer, particularly squamous cell carcinoma[628]. Therefore, incorporating carrots into a balanced and healthy diet may be an effective strategy for reducing the risk of skin cancer. Numerous research groups have studied its effect on skin cancer. Shebaby *et al*. performed a study that investigates the effects of wild carrot oil fractions on skin cancer. Four fractions were tested for their cytotoxic effects on human epidermal keratinocytes, with one fraction showing a significant antitumor effect on DMBA/TPA-induced skin carcinogenesis in mice. The study also identified a major compound in the fraction, which caused an accumulation of cells in the sub-G1 apoptotic phase and decreased the population of cells in the S and G2/M phases. Additionally, the fraction caused an upregulation of the expression of pro-apoptotic proteins and a downregulation of the expression of anti-apoptotic proteins. The data suggest that the antitumor activity of the fraction may be mediated through inhibition of the MAPK/ERK and PI3K/AKT pathways. Overall, the study suggests that wild carrot oil fractions, particularly the pentane/diethyl ether fraction, may have the potential as a chemopreventive agent against skin cancer[623]. Natarajmurthy and Dharmesh determined the contribution of phenolics and β-carotene to the antioxidant,

tyrosinase inhibitory, and antiproliferative properties of carrots and evaluated their potential in preventing skin cancer in mice induced by DMBA-UV. Phenolic fractions of carrots were extracted and quantified using high-performance liquid chromatography (HPLC), and their capacities were determined. The results showed that phenolics in CRFP and β-carotene, rather than those in CRBP, exhibited a higher reduction in tumor formation, tyrosinase, and galectin-3 levels and increased antioxidant levels, indicating their potential to prevent skin cancer. Thus, carrots enriched with phenolics and β-carotene may be an efficient natural source in preventing skin cancer, as evidenced by the *in vitro* and *in vivo* studies[624]. In another study, Zeinab *et al.* investigated the chemopreventive effects of oil extract of *Daucus carota* (DCOE) umbels on 7,12-dimethyl benz(a)anthracene (DMBA)-induced skin cancer in mice. The oil extract was administered to animals via gavage, intraperitoneal, and topical routes for 20 weeks, and tumor appearance, incidence, yield, and volume were compared with those of a non-treated control group. The results showed that DCOE has remarkable antitumor activity against DMBA-induced skin cancer compared with non-treated animals, with the topical route being the most effective[623]. Overall, these studies suggest that carrot consumption may reduce the risk of developing skin cancer.

Future prospects of dietary phytochemicals to prevent skin cancer

The use of dietary phytochemicals as chemopreventive agents in topical skin cancer formulations has gained significant attention in recent years[435]. While there is promising evidence for the use of phytochemicals in preventing skin cancer, further studies are needed to meet the challenges of topical skin cancer formulations. These challenges include skin penetration, optimum drug concentration, stability, dosing strategy, and sustained drug release following topical application[625]. Skin penetration is a crucial factor that affects the efficacy of topical formulations[625]. Dietary phytochemicals, such as flavonoids and polyphenols, have been shown to have low skin penetration due to their large molecular size and low lipophilicity[627]. Various strategies have been explored to improve the skin penetration of phytochemicals, including the use of nanoemulsions, liposomes, and penetration enhancers[628]. Optimum drug concentration is another critical factor that needs to be considered in the development of topical skin cancer formulations containing dietary phytochemicals[625]. The concentration of phytochemicals needs to be optimized to ensure that they are effective in preventing or treating skin cancer while minimizing toxicity. This concentration may vary depending on the phytochemical, the skin type, and the intended use of the formulation[629]. Stability is also an important factor that needs to be addressed in the development of topical skin cancer formulations containing dietary phytochemicals. The formulation must remain stable during storage and use to ensure that the phytochemicals remain effective[435]. Stability can be affected by factors such as pH, temperature, and light exposure. Dosing strategy is another factor that needs to be considered in the development of topical skin cancer formulations containing dietary phytochemicals[435]. The dosing strategy must be optimized to ensure that the phytochemicals are delivered in the most effective manner. Factors such as the frequency of application, the amount of phytochemicals applied, and the duration of treatment must be carefully considered[629]. Finally, sustained drug release following topical application is a crucial factor that needs to be addressed in the development of topical skin cancer formulations containing dietary phytochemicals. The phytochemicals must be released in a controlled manner to ensure that they remain effective for the intended duration of treatment[630]. Various strategies have been explored to achieve sustained drug release, including the use of polymers, liposomes, and nanoparticles[631]. Overall, while there is promising evidence for the use of dietary phytochemicals in preventing skin cancer, further studies are needed to meet the challenges of topical skin cancer formulations. Addressing these challenges is critical to the development of effective and safe topical formulations containing dietary phytochemicals for the prevention and treatment of skin cancer. The development of such formulations has the potential to revolutionize the management of skin cancer and improve patient outcomes.

Conclusion

Dietary phytochemicals are biologically active compounds that are naturally present in fruits and vegetables. These compounds have been shown to possess numerous health benefits, including the prevention of skin cancer by protecting cells from DNA damage, inhibiting the production of pro-inflammatory cytokines and chemokines, reducing inflammation and the risk of cancer development, inhibiting the activation of signaling pathways (MAPK pathway, PI3K/Akt pathway, Wnt pathway, Hedgehog pathway, Notch pathway, etc.) involved in cell growth and proliferation, which are dysregulated in skin cancer, and inducing apoptosis in cancer cells through various mechanisms like activation of caspases, regulation of Bcl-2 family proteins, modulation of p53, inhibition of NF-κB, induction of oxidative stress, etc. Assessing the applicability of the preclinical data to humans may require additional research, such as short-term human studies. In addition, studies on skin cancer prevention involving fruits and vegetables seem to be necessary for high-risk humans, such as those with weakened immune systems. In models of high-risk skin carcinogenesis, preclinical studies may reveal positive effects. In addition, fruits and vegetables can be combined with current treatment methods to enhance the treatment of skin cancer.

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