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REVIEW ARTICLE

The use of flavonoids in skin cancer prevention and treatment

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Abstract

Introduction and Objective. Known for their strong antioxidant properties, flavonoids are the major polyphenolic compounds found in a wide variety of plants, vegetables, and fruits. A growing number of reports has indicated their anticancer effect. Affecting numerous cellular pathways, polyphenols suppress carcinogenesis which allows for new strategies developed to fight skin cancer. Given the high morbidity and mortality rates due to skin cancer, the aim of the review is to summarize earlier studies on the role of flavonoids in skin cancer prevention and treatment.

Review Methods. A search was conducted using the PubMed databases. Using keywords related to flavonoids and skin cancer, articles in Polish and English were manually searched. Duplicate papers were removed, and the bibliographies of selected studies as well as bibliographies from other reviews were reviewed in order to incorporate additional relevant studies into the review.

Brief description of the state of knowledge. Flavonoids are effective immunomodulators since they modulate cell growth, induce apoptosis, and reduce reactive oxygen species production. They have DNA repair abilities that can be used to prevent various skin diseases caused by excessive sun exposure. They can prevent, postpone, or completely stop photocarcinogenesis.

Summary. Because of their effect on numerous cellular pathways, flavonoids have been studied extensively to confirm their preventive and therapeutic potential in skin cancer. Flavonoids have been shown in studies to shrink cancerous tumours and prevent metastasis. Their use in prevention and anticancer therapies may contribute to lower skin cancer mortality rates.

Key words

melanoma, antioxidants, skin cancer, flavonoids, cellular pathway

INTRODUCTION

Skin tumours are divided into benign tumours, point-like malignancies and malignant tumours. Benign tumours are mainly pigmented moles, haemangiomas, neuroblastomas, epitheliomas, fibromas and adenomas. Surgical treatment by excision of the diseased tissue, together with elements of the healthy skin, leaves the margin negative and prevents further development of the disease. It is absolutely necessary to examine and remove the moles located on the hands and feet, which when exposed to mechanical trauma, can transform into melanoma. Cutaneous Malignant Melanoma (CMM) is one of the most common and aggressive skin cancers in the Caucasian population. In Poland, approximately 2,500–3,000 cases of melanoma are reported annually, of which approximately 1,500 are detected in the advanced or disseminated stage [1]. It is characterized by mortality rates highest among all skin cancers. Basal cell carcinoma (BCC), squamous cell carcinoma (SCC), adnexal tumours, cutaneous lymphomas, and Merkel cell carcinomas are all examples of non-melanoma skin cancers (NMSC). These are the most prevalent types of skin cancer, 90% of which are BCC and SCC [1].

Intense exposure to ultraviolet radiation (UV) is the primary cause of the significant rise in skin cancer incidence, which also depends on complexion, age, gender, and genetic background. It is related to the presence of melanin in the skin, where the less the melanin, the higher the risk of cancer. The mainstay of skin cancer treatment is chemotherapy applied after surgery. This regiment is frequently met with no reaction to the therapy and is related to numerous negative effects; therefore, there is a need to develop more effective anti-cancer therapies. The growing evidence has indicated the benefits of combination therapies which combine traditional chemotherapy medications with natural substances, including flavonoids. Such a combination therapy makes it possible to inhibit the development and progression of cancer cells by affecting the cell cycle, inhibiting angiogenesis, and proliferation and activation of the proapoptotic proteins [2].

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OBJECTIVE

The aim of this review is to summarize the literature on the use of flavonoids in the prevention and treatment of skin cancer.

REVIEW METHODS

A search was carried out with the use of PubMed databases for articles published between 2003 – 2022 to assess the effect of flavonoids in the prevention and therapy of skin cancer. Articles in Polish and English were searched manually. Duplicate papers were removed and the bibliographies of selected studies, as well as bibliographies from other reviews, were reviewed in order to incorporate additional relevant studies into the review.

REVIEW AND DISCUSSION

The role of the skin. The skin is the largest barrier for protecting the human body. Divided into three layers – epidermis, dermis and the subcutaneous tissue – it ensures protection against mechanical injuries and has an important role in thermoregulation, absorption and excretion of substances, as well as the reception and transmission of stimuli. Blood vessels, nerve endings, mechanoreceptors, hair and glands, are all found in the dermis. The dermal extracellular matrix contains connective tissue rich in collagen and elastin, which maintains skin elasticity. The epidermis is the outermost part of the skin which is in direct contact with the external environment. It is made up of 80% keratinocytes, which are constantly renewed and divided.

In addition, the epidermis contains melanocytes, Merkel cells and immune cells – the Langerhans cells. Dysfunction of the skin as a protective barrier affects the development of multiple bacterial, fungal, viral, inflammatory and autoimmune conditions, as well as cancer [3].

The molecular aspect of carcinogenesis. A three-stage process called photocarcinogenesis involves biochemical, cellular and molecular changes that are mediated by changes in the environment. UV radiation acts directly upon the DNA, damaging it and forming cyclobutane pyrimidine dimers (CPD). In most cases, the skin is able to repair the damage by photoreactivation, using photolysis, or by nucleotide excision repair (NER), removing the dimers and closing the incisions in the DNA [1]. NER malfunction has been shown in patients with the autosomal recessively inherited disease, xeroderma pigmentosum (XP). Damage to DNA caused by UV radiation cannot be repaired. The dimers enhance cell proliferation, eventually leading to skin cancer. Radiation-induced DNA mutations are most common to affect the suppressor genes and the oncogenes [1, 4]. Such mutations occur in the form of C to T and CC to TT transitions where 90% of them have been detected in the suppressor gene p53 in human SCC and BCC [5]. The p53 gene is called the guardian of the genome because its damage causes uncontrolled cell division due to its resistance to apoptosis [1, 6]. UV radiation weakens the natural antioxidant systems of the skin resulting in overproduction of reactive oxygen species (ROS), which then leads to the oxidative damage of the DNA, proteins and lipids. From the molecular viewpoint, UVB radiation activates the nuclear factor kappa B (NFjB) and mitogen-activated protein kinase (MAPK) routs, resulting in expression of sterol messengers and the inflammatory genes, such as inducible nitric oxide synthase (iNOS), cyclooxygenase 2 (COX-2) and prostaglandin E2 (PGE2).

The first to occur is skin inflammation due to invasion of initiated macrophages and neutrophils (CD11b+) showing iNOS expression and producing NO, which has a significant effect on tumour initiation, development and progression. NO interacts with N2O2 to produce ROS and increases the expression of COX-2, an enzyme enhancing synthesis of prostaglandins mediating skin inflammation, especially PGE2. During inflammation, the leukocytes also produce the myeloperoxidase (MPO) inducing vasodilation and increased vascular permeability. Pro-inflammatory cytokines (IL-1b, IL-6, and TNF-α) are also upregulated, which aid in cancer progression. TNF-α (tumour necrosis factor-α) causes ROS to form and may contribute to tumour growth. IL-12 expression protects against tumourigenesis, whereas its absence increases COX-2 and PGE2, as well as IL-1b, IL-6 and TNF-α [7, 8]. Activation of Nrf 2 (nuclear factor erythroid 2-related factor 2) is one of the natural defence mechanisms against UV-induced inflammation in mice and humans [1]. Tumour promotion is a long and reversible process involving the clonal growth of initiated cells, resulting in premalignant lesions, basically through changes in signal transduction pathways. Pre-malignant lesions change into invasive, potentially metastatic malignant tumours as the tumour progresses [5].

PRINCIPAL TYPES OF SKIN CANCER

Basal cell carcinoma (BCC). BBC is the most prevalent form of skin cancer. It is distinguished by its local invasiveness and low malignancy. It rarely metastasizes and sometimes grows aggressively with destruction of the surrounding tissues and involvement of the lymph nodes. There are three subtypes of BCC: nodular, superficial and morphea. It develops from keratinocytes of the basal layer of the epidermis and its appendages, due to mutations caused by UV radiation. Other risk factors are also scars, ulcers, chronic inflammation, immunosuppression, vitiligo and xeroderma pigmentosum. Located mainly in the regions mostly exposed to sunlight, especially the face and the hands, it can actually occur anywhere. The prodromal symptom is the appearance of translucent, pearly papules with telangiectasias and ulceration in the central part and a rolling raised edge. The growth of the BBC is slow. It is the most common skin cancer in Caucasians. If metastases occur, the prognosis worsens significantly and the average survival time is then between eight months and 3.6 years. The management of BCC comprises excision by Mohs microsurgery, cryosurgery, electrocoagulation and lysing [9].

Squamous cell carcinoma (SCC). SCC accounts for 20% of all skin cancers and 75% of all deaths due to NMSC. It is the most frequently diagnosed neoplasm in individuals of the black race. It develops from a rapid proliferation of epidermis cells with squamous differentiation, regional infiltration, and invasion of deeper structures. The risk factors include burns, ulcers, immune disorders, chronic inflammation and scars.

SCC may also arise against a background of actinic keratosis (*AK*) and SCC *in situ*, i.e. Bowen's disease, characterized by greater invasiveness and a tendency to form metastases mainly to the lymph nodes. The most common locations for SCC are the back of the hand, scalp, ears and midface. The characteristic symptoms are superficial, firm, erythematous papules, with well circumscribed borders on an infiltrated, raised base. They often take the form of prolonged, healing ulceration. If regional lymph node metastases are present, the 10-year survival rate is less than 20%. If metastases to distant organs are present, the 10-year survival rate is less than 10%. The treatment of SCC consists of excision by the Mohs method, electrocoagulation and lysing [3, 9].

Melanoma. Melanoma is the most malignant skin cancer with extremely aggressive growth. It is caused by the breakdown of melanocytes in the basal layer of the epidermis, which results in uncontrollable cell growth. The Clark and McGovern criteria are used to classify invasive melanoma. The most common form of melanoma is maligna, which is an asymmetric, convex pigmented lesion with irregular outline and pigment distribution in atopic or unchanged skin. It is characterized by the plaque's radial growth into profound layers of the skin. Nodular melanoma appears as small, dark, polypoid or uveitic nodules that grow quickly into the deeper layers of the skin. Lentiginous melanoma is the least common form and appears mainly in the subungual area, palmar side and back of the hand. Melanomas occur most often on the legs, back and neck.

Every year in Poland there are about 50,000 cases of new skin cancer of which about 2,500 – 3,000 are melanomas, with about 1,500 melanomas detected in the advanced or disseminated stage. The mortality rate is about 20%. The treatment assumes removal of the skin lesion along the aesthetic lines with a significant margin of the surrounding tissue. Amputation is sometimes necessary. Surgical treatment is often supported by chemotherapy, radiotherapy and immunotherapy [1, 9].

Flavonoids as anti-cancer substances. Flavonoids are natural antioxidants found in fruits, vegetables, olive oil, tea and wine. They are divided into numerous subsets involving flavanones, flavanols, flavanonols, flavones, isoflavonoids and anthocyanidins. Their health benefits are related to anti-cancer, anti-proliferative and anti-inflammatory effects. Additionally, they modulate cellular proliferation, induce cell death, reduce ROS generation, and may be useful in the prevention of cancer. They are valuable immunomodulatory compounds. They possess DNA repair capabilities that may be used to prevent various skin diseases triggered by excessive sun exposure. Flavonoids have an antioxidant mechanism because they contain a phenolic group that accepts an electron from free radicals or reactive oxygen species to form phenoxyl radicals, which are stable and interrupt the chain reaction caused by free radicals or ROS [10]. They can prevent, delay, or completely stop photocarcinogenesis.

Polyphenols in green tea (*PGI*). Green tea *(Camellia sinensis)* leaves have a significant amount of polyphenols, including flavanols, flavandiols, and phenolic acids. Green tea leaves contain four major flavonoids: (-)-epigallocatechin gallate (EGCG), (-)-epigallocatechin (EGC), (-)-epicatechin gallate (ECG) and (-)-epicatechin (EC). According to epidemiological data, drinking green tea on a regular basis lowers the risk of multiple cancers. ECG and EGCG are antioxidants with antimutagenic, anti-inflammatory, and anticancer properties [5]. By modulating the cyclin-dependent kinase pathways and Bcl-2 (B-cell lymphoma 2) family proteins, EGCG inhibits growth, encourages cell cycle inhibition, and induces apoptosis in melanoma cells. It was found that oral administration of green tea or injection of PG and EGCG fractions into mice inhibited growth and induced regression of benign cutaneous papilloma in mice [11]. Histopathological analysis of skin tumours indicated that green tea has a significant inhibitory impact on the development of UVB-induced keratoses and tumours [12]. Meeran et al. conducted a study to clarify whether induction of IL-12 by EGCG was related to its photocarcinogenesis preventive role. Topical use of EGCG in wild-type mice reduced the number of UVB-induced skin tumours [13]. Topical application of PGs to the skin of mice reduced UVB-induced MAPK phosphorylation, IKKα (Inhibitor kappaB kinase alpha) activation and IαBα (Inhibitor αBα) phosphorylation and degradation. PGs also inhibited UVB-induced NF-κB/p65 nuclear translocation and NF-κB/p65 DNA binding activity. It is the effect on these cellular pathways that determines the photoprotective properties of PGs, including EGCG, and protects against photocarcinogenesis [14]. Topical application of PG or EGCG as a hydrophilic ointment markedly inhibits UVB exposure-induced phosphorylation of ERK1/2, JNK and p38 MAPK family proteins [15]. UVB-induced significant increase in matrix metalloproteinases MMP-2 and MMP-9, CD31 (biomarker of neovascularization), vascular endothelial growth factor and proliferating cell nuclear antigen (PCNA) were all diminished when PG was added to mice's drinking water. Furthermore, more cytotoxic CD8+ T cells and higher caspase-3 activation were found in PG-treated mice tumours, indicating tumour cell death following PG treatment [16]. By focusing on the NFκB signalling pathways, the combination of EGCG with interferon / vorinostat therapy increases its effectiveness against melanoma. Through the activation of cell cycle inhibitory proteins, modification of Bcl-2 family proteins, and the NFκB signalling pathway, the combination of EGCG with vorinostat greatly reduces melanoma cell proliferation and enhances apoptosis. The latest report discovered that melanoma growth was inhibited by NFκB activity when treated with EGCG [17]. Singh and Katiyar found that EGCG inhibited melanoma cell growth by decreasing the expression of COX-2, PGE2 and PGE2 receptors in melanoma cells [18]. EGCG with its antioxidant, anti-inflammatory and anti-cancer potential, is undoubtedly a good applicant for the prevention and therapy of skin cancer

Polyphenols of pomegranate fruit extract (*PFE*). Pomegranate fruit extract (PFE) is a great source of flavonoids, such as epigallocatechin gallate, quercetin, kaempferol, and luteolin. It possesses potent antioxidant activity [5]. When PFE was administered orally to UVB-exposed SKH-1 mice, the frequency and prevalence of tumours was lower than in control animals that were not given PFE and UVB radiation [19]. PFE inhibits UVB-induced phosphorylation of ERK1/2, JNK1/2 and p38 proteins, as well as inactivation and phosphorylation of IκBα, initiation of IKKα, nuclear translocation and phosphorylation of the NF-κB/p65 at Ser536 position [20]. PFE can inhibit UVB-induced initiation of MAPKs and NF-κB signalling routes. Additionally, UVB-

treated skin and tumours showed decreased levels of hypoxia-inducible factor-1α, and concurrently decreased production of the inducible nitric oxide synthase and cyclooxygenase-2 (*COX-2*) [19].

In addition, in studies on reconstructed human skin, PFE reduced UVB-induced c-Fos protein expression and c-Jun phosphorylation, and inhibited the expression of collagenase (MMP-1), gelatinase (MMP-2, MMP-9), stromelysin (MMP-3), marilysin (MMP-7) and elastase (MMP-12). Furthermore, administration of PFE to human skin fibroblasts reduces UVB-induced cell death by decreasing NF-κB activation, downregulating proapoptotic caspase-3 and accumulating cells in the G0/G1 phase of the cell cycle [21, 22]. Due to the photoprotective effect, pomegranate fruit extract has applications in the prevention as well as supportive treatment of skin cancer.

Silymarin and silibinin. Silymarin is a flavonoid extracted from milk thistle (*Silybum marianum).* Topical application of this compound to the skin of hairless SKH-1 mice greatly reduced the frequency and mean volume of UVB-induced tumours, compared to mice not treated with silymarin. Silymarin effectively protects the skin from all stages of photocarcinogenesis [23]. When applied topically, silibinin, the main component of Silymarin, induces MAPK cascades in UVB-induced skin cancers, thereby enhancing apoptotic death of the skin cancer cells [24]. Through its effect, Silymarin may prevent promotion of skin cancer by inhibiting photoaging and inducing apoptosis of the cancer cells [25].

Genistein. Genistein (4',5,7-trihydroxyisoflavone) is a soybean isoflavone and phytoestrogen that is structurally and functionally similar to estrogen. It is characterized by its anti-inflammatory and antioxidant effects. Additionally, it inhibits angiogenesis, promotes apoptosis, reduces cancer metastasis and decreases cancer cell proliferation. The C57BL/6J mouse model has demonstrated that genistein inhibits cell cycle progression, induces apoptosis, and inhibits tumour formation by melanoma cells with the B164A5 mutation's ability to metastasize [26, 27]. Tyrosine kinase is essential for the increase in prostaglandin *(PG)* synthesis when keratinocytes are exposed to UVB light. Genistein treatment lowers EGFR tyrosine phosphorylation caused by UVB exposure and lowers PGE2 generation in the cells. In addition, topical genistein administration to mouse skin decreases UVB-induced expression of c-fos and c-jun in mouse skin, which may be a result of EGFR phosphorylation and protein tyrosine kinase activity inhibition. Treatment with genistein inhibits UVB-induced phosphorylation of p66Shc on Ser36 and FKHRL1 on Thr32 in human dermal fibroblasts [27]. Genistein also inhibits invasion, adhesion, angiogenesis and metastasis of melanoma cells in mice, thus raising hopes for skin cancer treatment [28].

Fisetin. Fisetin (3,3′,4′,7-Tetrahydroxyflavone) is a flavonoid naturally found in mango, kiwi, grapes and cucumbers which shows antioxidant, anti-inflammatory and antiproliferative properties. The skin cancer inhibitory effects of fisetin involve phosphorylation of MEK1/2 and ERK1/2 and inhibition of the nuclear factor kappaB (*NFκB*) signaling pathway [28]. Syed et al. observed that fisetin downregulates Wnt/β-catenin, PI3K/AKT, mTOR (mammalian target of rapamycin) and microphthalmia-associated transcription factor (MITF) signalling proteins in melanoma cell lines [29]. Fisetin exhibits antitumour effects by reducing cell migration and invasion, decreasing the expression of mesenchymal proteins (N-cadherin, vimentin and fibronectin) and the proteins Snail1, Twist1, Slug and ZEB1, and increasing the expression of E-cadherin. In advanced cancer, it protects against lung metastasis. It shows strong synergism with sorafenib [10].

Curcumin. Curcumin, a polyphenol derived from Curcuma longa L., exhibits numerous biological activities including anti-inflammatory, antioxidant and anticancer properties [14, 15]. This compound has been shown to be chemopreventive for many cancers due to induction of apoptosis, increased cell adhesion, and inhibition of angiogenesis in cancer cells. The effects on AKT (protein kinase B), NFκB, AP-1 (Activator Protein-1) and N-terminal c-Jun kinase have been reported [10, 28, 29]. Curcumin induces apoptosis by upregulating p53, p21 (Cip1), p27 (Kip1) and checkpoint kinase 2. By downregulating NFκB, iNOS expression and the catalytic subunit of DNA-dependent protein kinase, it shortens the survival of cancer cells [30]. Reducing the tumour size is also possible by blocking glutathione S-transferase, initiating apoptosis via Fas receptor / caspase-8, reducing COX enzymes and inhibiting NFκB signaling [31]. Curcumin activates the tumour cell death pathways by cleaving p23 and reducing the anti-apoptotic protein Mcl-1 in melanoma cells. Furthermore, the antimetastatic potential of curcumin acts by decreasing the activity of collagenase, expression of FAK (focal adhesion kinase) and function of MMP-2 (matrix metalloproteinase-2). Curcumin inhibits osteopontin (OPN) -induced IκBα phosphorylation and degradation by inhibiting IKK (I-kB kinase) activity in B16F10 mouse melanoma cells. Additionally, by inhibiting the NFκB signalling pathway, it triggers apoptosis by lowering the cell proliferation, migration, and invasion caused by OPN [32].

Apigenin. Apigenin (4',5,7-trihydroxyflavone) is a flavonoid found in parsley, celery, chamomile and artichokes. It is characterized by broad antioxidant, antimutagenic, anti-inflammatory and antiproliferative properties [28]. Its main action is based on inhibiting IL-6 and modulating the expression of IL-6 signal transducing receptor (IL-6Rα) and suppressor of cytokine signalling protein (SOCS3). By inhibiting the expression and secretion of matrix metalloproteinase-2 (MMP- 2), it regulates the STAT3 pathway by inhibiting its phosphorylation at the tyrosine 705 site. It also inhibits the phosphorylation of JAK2 and Src. Furthermore, by reducing the expression of VCAM-1 (vascular cell adhesion molecule 1) induced by TNF-α and by decreasing tumour cell adhesion, it reduces tumour growth and decreases the likelihood of lung metastasis [10]. It has also been proven to reduce skin cancer development by inhibiting VEGF (vascular endothelial growth factor) secretion resulting from inhibition of ERK1/2 and PI3K/AKT signalling [33]. Apigenin has also been observed to inhibit cell proliferation and induce cell death in A375 melanoma cells without harming peripheral blood cells [34]. Skin malignancies, including melanoma in particular, seem to respond well to apigenin treatment.

Luteolin. Luteolin is a flavonoid found mainly in carrots, olives, thyme and oregano. It is characterized by antioxidant,

anti-inflammatory and anticancer activities, inhibiting angiogenesis by modulating multiple signaling pathways and miRNAs, promoting apoptosis by inhibiting PI3K/Akt and activating FOXO3a (Forkhead box protein O3), and sensitizing cells to the anticancer therapy by activating JNK (c-Jun N-terminal kinase) [35]. Studies have proven the ability to stimulate melanogenesis, decrease the invasive capacity of B16F10 melanoma cells and decrease EMT (epithelial-mesenchymal transition) by inhibiting the β3 integrin/FAK signalling pathway [36]. A recent study examined the effectiveness of luteolin against A375 melanoma cells both *in vivo* and *in vitro*. It was demonstrated that luteolin reduced the expression of MMP-2 and MMP-9 through the PI3K / AKT pathway, which hindered growth and caused apoptosis in the test cells [37]. In conclusion, luteolin reduces tumour cell proliferation and migration, stimulates apoptosis and reduces tumour invasiveness and growth.

Quercetin. Quercetin is a flavonoid naturally found in onions, grapes, nigella and tarragon. It is characterized by strong antioxidant, anti-inflammatory and anticancer activity. Its anticancer effects affect mainly the A375SM melanoma cells. Quercetin reduces the viability and proliferation of A375SM and induces apoptosis. Kim et al. observed reduction in tumour volume under the influence of quercetin, making this polyphenol effective against melanoma [38]. In addition, quercetin inhibits STAT3 (Signal transducer and activator of transcription 3) activation by IL-6 by decreasing cyclin D1 levels and MMP-2 secretion, resulting in inhibition of cell proliferation and migration by accumulating cells in the proliferative S and G2/M phases of the cell cycle [39, 40]. By acting on B16-BL6 cell lines, it reduces tumour invasiveness, decreases proliferation, decreases the rate of cells in the S and G2/M phases of the cell cycle, decreases the frequency of lung metastasis, and increases apoptosis. By affecting the A2058 and A375 cell lines it inhibits cell migration and tumour invasiveness. Finally, it reduces tumour growth by affecting the K1735M2 cell line.

SUMMARY

Multiple studies have been carried out to confirm the preventive and therapeutic potential of flavonoids in skin cancer due to their effect on many cellular pathways. This review brings together the relevant studies reporting the use of flavonoids in the skin cancer therapies, their antiproliferative, anti-inflammatory, proapoptotic, cytotoxic and antioxidant effects. It has been shown that flavonoids are able to shrink cancerous tumours and to prevent metastasis. Their use in prevention and in anticancer therapies may contribute to reduced mortality rates from skin cancer. It is worth supplementing the diet with products rich in flavonoids and using them as adjuvants to sunscreens and anti-cancer therapy. It seems that the combination of nanotechnology, together with phytochemicals, could be a viable form of future anti-cancer therapy.

Table 1. The use of flavonoids in skin cancer prevention and treatment

Flavonoids	Anti-cancer effect	References
(-)-epigallo-catechin gallate	Positive effect resulting from growth inhibition, cell cycle arrest and apoptosis induction of melanoma cells.	[5]
	Positive effect resulting from inhibition of UVB exposure.	[15]
	Positive effect when combined with interferon/vinostat therapy.	[17]
	Positive effect resulting from inhibition of melanoma cell invasion.	[18]
Kaempferol	Positive effect resulting from inhibition of UVB-induced signalling pathways activation.	[19]
	Positive effect resulting from inhibition of UVB-induced protein phosphorylation.	[20]
	Positive effect resulting from reduction of UVB-induced cell death.	[22]
Silymarin, Silibinin	Positive effect resulting from induction of MAPK cascades in UVB-induced skin cancers.	[24]
Genistein	Positive effect resulting from apoptosis induction, tumour growth suppression and reduction of UVB-induced protein phosphorylation.	[26, 27]
Fisetin	Positive effect resulting from kinases phosphorylation and signalling pathway inhibition.	[28]
	Positive effect resulting from cell migration reduction and inhibition of protein expression.	[10]
Curcumin	Positive effect resulting from apoptosis induction.	[30]
	Positive effect resulting from glutathione S-transferase inhibition and apoptosis induction.	[31]
	Positive effect resulting from inhibition of osteopontin (OPN)-induced IκBα phosphorylation.	[32]
Apigenin	Positive effect resulting from IL-6 inhibition and modulation of its expression.	[10]
	Positive effect resulting from growth factors and signalling pathways inhibition.	[33]
Luteolin	Positive effect resulting from signalling pathways and miRNAs modulation and apoptosis promotion.	[35]
	Positive effect resulting from proliferation inhibition and apoptosis induction.	[37]
Quercetin	Positive effect resulting from apoptosis induction, cell proliferation and migration inhibition.	[39, 40]

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