Review

Unraveling the molecular mechanisms and the potential chemopreventive/therapeutic properties of natural compounds in melanoma

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Abstract

Melanoma is the most fatal form of skin cancer. Current therapeutic approaches include surgical resection, chemotherapy, targeted therapy and immunotherapy. However, these treatment strategies are associated with development of drug resistance and severe side effects. In recent years, natural compounds have also been extensively studied for their anti-melanoma effects, including tumor growth inhibition, apoptosis induction, angiogenesis and metastasis suppression and cancer stem cell elimination. Moreover, a considerable number of studies reported the synergistic activity of phytochemicals and standard anti-melanoma agents, as well as the enhanced effectiveness of their synthetic derivatives and novel formulations. However, clinical data confirming these promising effects in patients are still scanty. This review emphasizes the anti-tumor mechanisms and potential application of the most studied natural products for melanoma prevention and treatment.

Keywords: Melanoma; Natural compounds; Phytochemicals; Chemoprevention; Novel therapeutic strategies

1 Introduction

Malignant melanoma represents the most aggressive form of skin cancer, with an increasing incidence worldwide. It derives from the transformation and uncontrolled growth of melanocytes, and it is characterized by different progression stages: early melanomas (stages 0 and I) are localized and noninvasive; stage II tumors are larger and often present ulcerations, with a high risk to metastasize; advanced melanomas (stages III and IV) have already colonized other body tissues. The staging is used to determine treatment: the main options include surgical excision, chemotherapy, targeted therapy and immunotherapy [1,2]. Unfortunately, the currently available therapeutic strategies for metastatic melanoma have a relatively low success rate, due to the development of drug resistance generally associated with changes in drug pharmacokinetics, mutation/amplification of drug targets and enhanced efflux pump-mediated drug detoxification [3–5]. Moreover, the majority of both consolidated and emerging anti-melanoma treatments is characterized by severe adverse effects [6,7]. For these reasons, in the last decade the interest in natural compounds has increased, owing to their potent and selective anti-cancer activity. In fact, a great number of studies has consistently reported that phytochemicals can exert anti-proliferative, pro-apoptotic, anti-invasive and anti-angiogenic effects in melanoma cell lines and mouse models, without significant toxicity in the latter. In particular, there are different molecular mechanisms responsible for the anti-melanoma actions of these compounds, such as inhibition of tumor-promoting proteins and activation of tumor-suppressing cascades [8]. This review attempts to summarize the recent findings about the role of various natural products in melanoma prevention and treatment.

2 N~~ATURAL COMPOUNDS TARGETING MELANOMA~~atural compounds targeting melanoma

Accumulating evidence has highlighted the ability of numerous natural compounds to specifically target different signaling molecules and pathways involved in tumorigenesis and in tumor progression. Several of these naturally occurring molecules have been tested in *in vitro*, pre-clinical and clinical studies, alone or in combination with standard anti-cancer therapies [9]. Among them, polyphenols (flavonoids, curcumin and resveratrol), organosulfur compounds (sulforaphane), terpenoids (artemisinin, oridonin and ursolic acid), saponins (ginsenosides), tocotrienols (γ- and δ-isoforms), alkaloids (berberine, harmine and capsaicin) and hydroxycinnamic acids (caffeic acid and its phenethyl ester) have shown promise as anti-melanoma agents (Fig. 1).

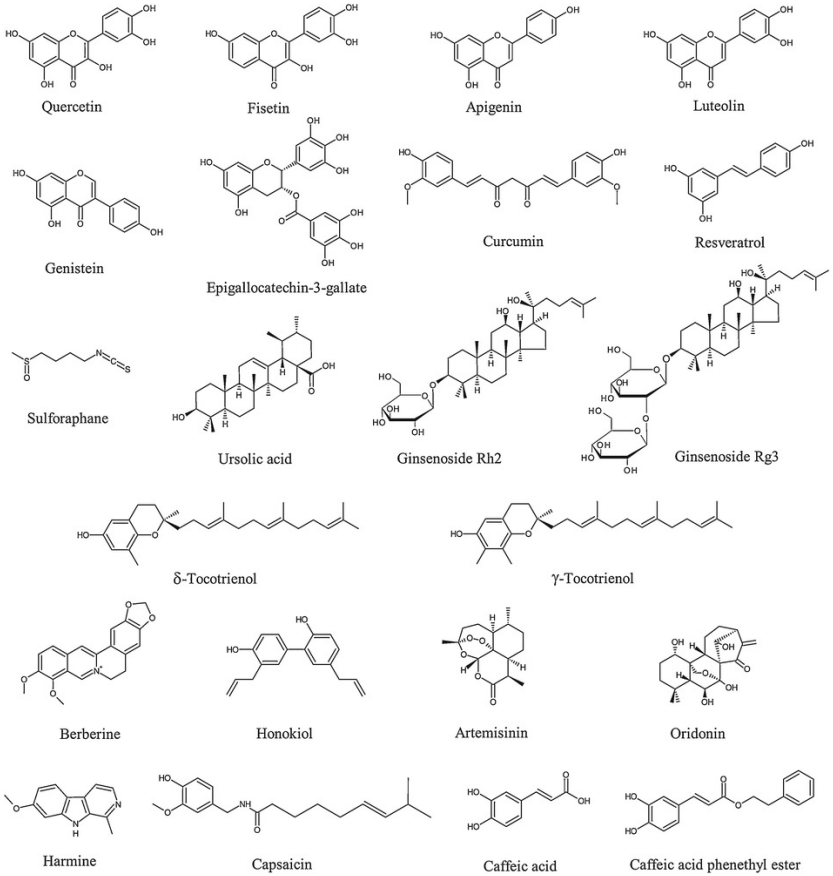

Fig. 1 Chemical structures of the main anti-melanoma natural compounds.

alt-text: Fig. 1

2.1 Quercetin

Quercetin is a penta-hydroxylated flavonol. It is particularly abundant in capers, tomatoes, apples, onions and tea, and because of this wide distribution in nature many studies have been conducted to investigate its chemopreventive and anti-tumor properties [10].

In different human melanoma cell lines quercetin was shown to reduce cell viability at low doses and to trigger apoptosis at high doses [11]. These anti-proliferative and pro-apoptotic effects were also confirmed *in vivo* [12,13], and were associated with: decrease in the B-cell lymphoma 2 (Bcl-2) expression [14]; nitric oxide (NO) production [15]; downregulation of protein kinase C-α (PKC-α) [16]; inhibition of the signal transducer and activator of transcription 3 (STAT3) pathway [17]. Interestingly, melanoma cells overexpressing tyrosinase, the rate-limiting enzyme in melanin synthesis, were more susceptible to the apoptosis induced by quercetin: in particular, the flavonol-mediated cell

death was associated with phosphorylation of p53, inhibition of glutathione reduction and reactive oxygen species (ROS) generation [18,19]. Finally, it has been recently demonstrated that this compound can severely alter the cellular bioenergetics in murine melanoma B164A5 cells, decreasing both the oxygen consumption and extracellular acidification rates [20].

The acquisition of invasive behavior is fundamental for the transformation of *in situ* melanoma into its most aggressive counterpart. Quercetin was found to suppress the metastatic potential of melanoma cells by inhibiting the matrix metalloproteinase 9 (MMP-9) activity [21], the hepatocyte growth factor (HGF)/c-MET signaling [22], the epithelial-to-mesenchymal transition (EMT) [23] and the interactions of the tumor cells with the endothelium [24].

The role of quercetin in UV protection and melanogenesis is still a matter of debate. Yin et al. have recently demonstrated that quercitrin, a glycosylated form of quercetin, can protect skin from UVB-induced oxidative damage [25]. On the other hand, Rafiq et al. reported that UVB-irradiated B16F10 melanoma cells subsequently treated with quercetin underwent a dose dependent reduction in cell viability and increased apoptotic cell death [26]. Moreover, quercetin exerted anti-melanogenic effects in UVA-exposed B16F10 cells through downregulation of NF-E2 p45-related factor 2 (Nrf2) activity [27] and reduced oxidative stress-induced and α-melanocyte stimulating hormone (α-MSH)-mediated melanogenesis in the same cell line [28–30], while enhancing melanin synthesis in HMVII melanoma cells [31].

It is now well established that calcitriol, the active form of vitamin D, is not only involved in the regulation of bone metabolism, but it also exerts significant antitumor effects as evidenced by *in vitro* and *in vivo* studies [32]. Specifically, melanoma cells express the vitamin D receptor (VDR), and vitamin D metabolites were shown to exert antiproliferative effects on melanoma cells [33–35]. In line with these observations, melanoma development has been shown to be correlated with vitamin D deficiency and dysfunctional VDR intracellular signaling pathways [36]. Quercetin was reported to enhance VDR activity in human colorectal adenocarcinoma cells (Caco-2) by altering cofactors recruitment [37] and upregulating VDR target genes [38]. Mechanistically, quercetin was shown to bind to the VDR receptor, as evidenced by *in silico* studies [39], thus triggering its antitumor effects. However, the possible interaction of quercetin with VDR is still a matter of debate [40]. So far, there are no studies reporting the possible interaction between quercetin and VDR signaling pathways in melanoma cells.

Synergistic anti-cancer activity was shown by quercetin when given in combination with either synthetic or natural compounds: the co-treatment with dacarbazine or temozolomide sensitizes melanoma cells to the anti-tumor effects of these chemotherapeutic agents through p53 activation [19,41]; the resistance of MeWo and WM164 cells to recombinant human tumor necrosis factor-related apoptosis-inducing ligand (rhTRAIL) was completely abrogated by addition of quercetin through upregulation of rhTRAIL-binding receptors DR4 and DR5 and increased degradation of the anti-apoptotic FLICE-like inhibitory protein (FLIP) [42]; a combination of quercetin and sulforaphane caused a significant additive effect in decreasing B16F10 cell proliferation and invasion *in vitro* and *in vivo* [43]; quercetin and curcumin synergistically inhibit melanoma cell viability by downregulation of Wnt/β-catenin signaling and apoptosis induction [44]; intravenous administration of quercetin and pterostilbene to mice suppressed the migration of melanoma cells to the liver [45].

Novel quercetin synthetic derivatives have been recently developed. In particular, Yamauchi et al. observed that methylquercetins can inhibit both the proliferation and migration of melanoma cells, also stimulating melanogenesis through modulation of microphthalmia-associated transcription factor (MITF) and p38 expression [46–48]. Quercetin glycosides were demonstrated to both induce [49,50] and suppress [51] melanogenesis.

Nanosized emulsions and lipid nanosystems containing quercetin exhibited important cytotoxic effects against B16F10 cells both *in vitro* and *in vivo*, with an increased solubility and oral bioavailability in mice with respect to the standard drug [52,53].

2.2 Fisetin

Fisetin is a flavonol, chemically referred to as 3,7,3′,4′-tetrahydroxyflavone, which is commonly found in cucumbers, kiwi, onions, persimmons, apples and strawberries. It was observed to possess important neuroprotective effects, and recently its anti-cancer potential has also been investigated [54].

Different studies conducted by Syed et al. [55–57] demonstrated that fisetin can arrest melanoma cell proliferation through inhibition of the Wnt signaling pathway and direct binding to p70S6K and mTOR, and that it can activate both the intrinsic and extrinsic apoptotic pathways. Recent findings also suggest that fisetin can trigger mitochondrial apoptosis in uveal melanoma cells, while sparing normal retinal pigment epithelial cells [58], and that it can target Y-box binding protein 1 (YB-1)/ribosomal S6 kinase (RSK) axis in monolayer and 3D melanoma cultures [59].

Fisetin was reported to inhibit melanoma cell invasion through EMT reversion and suppression of mitogen-activated protein kinase (MAPK) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathways [60].

α-MSH- and 3-isobutyl-1-methylxanthine (IBMX)-induced melanosis in B16F10 melanoma cells was inhibited by fisetin treatment, which also activated the connective tissue growth factor (CTGF)/transforming growth factor β (TGFβ) signaling pathway in human skin fibroblasts and 3T3-L1 cells, thus up-regulating skin fibril-related genes and decreasing adipogenesis, respectively [61]. On the contrary, 4′-O-methylfisetin significantly promoted melanogenesis in melanoma cells via activation of mammalian target of rapamycin complex 1 (mTORC1) [62].

In athymic nude mice subcutaneously implanted with BRAF-mutated melanoma cells, the combination therapy with fisetin and sorafenib, a small multi-kinase inhibitor that targets both the mutated and the wild-type BRAF

kinase, more effectively reduced the tumor growth when compared to the individual agents, via enhancement of apoptosis and inhibition of MAPK and phosphoinositide 3-kinase (PI3K) pathways [63]. Moreover, fisetin was shown to potentiate the anti-metastatic effects of sorafenib, leading to a decrease in N-cadherin, vimentin, fibronectin expression and to an increase in E-cadherin levels both *in vitro* and *in vivo* [64].

The co-treatment with fisetin and melatonin also resulted in the synergistic activation of apoptosis, accompanied by suppression of cyclooxygenase-2 (COX-2), nitric oxide synthase (iNOS) and NF-κB signaling pathways [65].

2.3 Apigenin

Apigenin (4′,5,7,-trihydroxyflavone) is a flavone present in many vegetables and fruits, particularly in chamomille, parsley, celery and oranges, and possesses radical-scavenging, anti-inflammatory and anti-carcinogenic properties [66].

The anti-tumor effects of apigenin have been investigated in different types of cancer, including melanoma. The main mechanisms of action are: G2/M cell cycle arrest and p-extracellular signal-regulated kinase 1/2 (p-ERK1/2), p-Akt and p-mTOR downregulation [67]; apoptosis activation, associated with ROS accumulation, cytochrome c release, DNA fragmentation, caspase-3 and poly (ADP-ribose) polymerase (PARP) cleavage [67,68]; suppression of cell migration through STAT3 and focal adhesion kinase (FAK) inhibition [69,70]; reduced vascular endothelial growth factor (VEGF) expression and secretion [71].

PD-1/PD-L1 checkpoint blockade-based immunotherapy has shown promising results in the treatment of melanoma. Interestingly, it has been recently demonstrated that apigenin downregulates the interferon gamma (IFN-γ)-induced PD-L1 expression in melanoma cells, by inhibiting STAT1 phosphorylation. Furthermore, apigenin enhanced the T cell-mediated melanoma killing *in vitro* and suppressed the melanoma xenograft growth by increasing CD4+ and CD8 + T cell infiltration. Finally, apigenin boosted T cell immunity through downregulation of PD-L1 expression in dendritic cells [72].

Apigenin was found to overcome resistance to TRAIL and to increase TRAIL-mediated apoptosis in different cancer cell lines (such as breast cancer, colon cancer, hepatocellular carcinoma, pancreatic carcinoma cells), including melanoma cell lines [73].

Apigenin exhibited potent melanogenic activities by increasing the expression levels of MITF, tyrosinase, tyrosinase-related protein 1 (TRP-1) and TRP-2 and by activating the p38 pathway [74,75]. Similar results were obtained with apigenin-7-glucoside, which also suppressed melanoma cell proliferation [76].

Apigenin-loaded poly (lactic-co-glycolide) nanoparticles were reported to rapidly enter melanoma cancer cells, triggering mitochondrial apoptosis [77].

2.4 Luteolin

Luteolin is a common flavone that exists in a variety of plants, such as celery, broccoli, parsley, thyme and rosemary, and a growing body of evidence has suggested that it possesses potent anti-inflammatory, neuroprotective and anti-tumor activity [78,79].

The anti-melanoma activities of luteolin were found to be correlated with anti-proliferative, anti-metastatic and anti-angiogenic effects, such as cyclin-dependent kinase 1 (CDK-1) and CDK-2 inhibition, PI3K/Akt pathway downregulation, reversion of β3 integrin-mediated EMT and suppression of hypoxia-inducible factor 1-alpha (HIF1α)/VEGF signaling [80–83].

The endoplasmic reticulum (ER) stress is a cellular process occurring in different physiological and pathological conditions, as well as after treatment with various synthetic and natural agents: the prolonged accumulation of unfolded and misfolded proteins in the ER lumen can activate a set of pro-death programs, such as the double-stranded RNA-dependent protein kinase PKR-like ER kinase (PERK)/eukaryotic initiation factor 2α (eIF2α)/activating transcription factor 4 (ATF4)/C/EBP homologous protein (CHOP) pathway and the inositol-requiring enzyme 1α (IRE1α)/c-Jun N-terminal kinase (JNK)/p38 MAPK cascade. Several phytochemicals were demonstrated to trigger ER stress-related death in tumor cells [84]: among them, luteolin specifically induced this pro-apoptotic pathway in melanoma cells [85].

Glutathione S-transferase (GST) is significantly involved in the metabolism and detoxification of drugs commonly used in melanoma therapy, thus affecting treatment effectiveness. Interestingly, Balyan et al. demonstrated that luteolin can selectively inhibit GST after tyrosinase-driven conversion in luteolin-quinone and luteolin-glutathione conjugate [86].

The anti-melanogenic effects of luteolin have been reported by various studies [87,88]. Improved melanogenesis inhibitory activity has been shown by different luteolin synthetic derivatives, including 3-prenyl-luteolin [89], luteolin 7-sulfate [90] and 7-O-substituted luteolin [91], as well as by the γ-irradiated compound [92].

2.5 Genistein

Genistein (4′,5,7-trihydroxyisoflavone) is a phytoestrogen commonly found in soybeans that has been correlated with a decrease in the incidence of breast and prostate cancers [93,94].

Concerning melanoma, genistein treatment of different human and murine melanoma cell lines resulted in cell cycle arrest at G1/S and G2/M check points, accompanied by p21 upregulation, CDK1 and CDK2 inhibition and checkpoint kinase 2 (Chk2) activation [95–102]. Moreover, genistein was reported to promote morphological changes in melanoma cells, inducing a more dendritic and differentiated phenotype characterized by enhanced tyrosinase activity and melanin production [95–97].

It is well known that interleukin 8 (IL-8) synthesis can be stimulated by prostaglandin E2 (PGE2) in several pathologies, including cancer. Venza et al. demonstrated that PGE2 upregulates IL-8 expression in melanoma via the EP3 receptor and that genistein treatment can inactivate the latter, resulting in the reduction of IL-8 mRNA and protein levels and in the suppression of oral, uveal and cutaneous melanoma cell growth [103].

MicroRNAs (miRNAs) are endogenous, ˜22 nucleotide, non-coding RNAs implicated in RNA silencing and post-transcriptional control of gene expression. miRNAs may function as either oncogenes or tumor suppressors (oncomirs), depending on the specific cancer type. Sun et al. reported that genistein can inhibit human uveal melanoma cell growth via downregulation of miR-27a and of its target gene zinc finger and BTB domain containing 10 (ZBTB10) [104].

Genistein suppressed the invasive potential of melanoma cells via the FAK/paxillin pathway *in vitro* [105–107] and significantly decreased the number and size of liver and lung metastases in C57BL/6 mice [108–110].

Vasculogenic mimicry (VM) describes the ability of aggressive melanoma cells to form vascular-like structures in the absence of endothelial cells. Genistein not only exhibited anti-angiogenic properties in mouse models of melanoma [111] but also inhibited VM of uveal melanoma cells both *in vitro* and *in vivo* [112].

The effects of genistein on the immune system were evaluated by Guo et al. in adult female B6C3F1 mice injected with B16F10 cells. In particular, they observed that genistein could enhance host resistance to tumor formation, by increasing the activity of cytotoxic T and NK cells [113].

Synergistic anti-melanoma effects were shown by genistein when given in combination with standard chemotherapeutic agents, such as cyclophosphamide [114] and cisplatin [115]. Moreover, a recent study by Ji et al. has suggested that increasing the intracellular levels of ceramide can sensitize melanoma cells to the growth-suppressing activity of genistein [116].

5,7,4′-Trihydroxy-3′-methoxyisoflavone, obtained through biotransformation of genistein by two recombinant *Escherichia coli* strains, significantly reduced the proliferation of murine melanoma cells, without affecting the growth of normal murine fibroblasts [117].

In an interesting study conducted by Danciu et al., a lamellar lyotropic liquid crystal genistein-based formulation (LLC-Gen) was obtained in order to enhance the aqueous solubility of this compound. The formulation was applied locally, in a murine model of melanoma, with or without electroporation: the tumor volume, the amount of melanin and the degree of erythema were significantly reduced after 21 days of treatment, with an even better prognosis after electroporation [118].

2.6 Epigallocatechin-3-gallate

Epigallocatechin gallate (EGCG), the ester of epigallocatechin and gallic acid, belongs to the catechin subclass of flavonoids. It is the major component of green tea and is a potent free-radical scavenger and antioxidant. In addition, it is under study as a potential chemopreventive agent [119].

In melanoma cells, EGCG was found to exert both anti-proliferative and pro-apoptotic activities, inducing cyclin D1 and CDK2 downregulation, p16INK4a, p21CIP1/WAF1 and p27KIP1 activation, Bcl-2-associated X protein (Bax)/Bcl-2 ratio modulation and caspase-3, -7 and -9 cleavage [120]. Interestingly, these anti-cancer effects have been associated with inhibition of glucosidase II, a key enzyme involved in the glycoprotein synthesis in the ER, and with inflammasome downregulation, followed by reduced IL-1β secretion and NF-κB activity [121,122]. Furthermore, EGCG was demonstrated to act as an agonist of 67-kDa laminin receptor (67LR), a cell surface receptor highly expressed in melanoma cells, leading to mTOR pathway inhibition, merlin tumor suppressor activation and increased miRNA-let-7b expression [123,124].

EGCG treatment resulted in the suppression of melanoma cell migration and invasion, correlated with E-cadherin upregulation, HGF/SF-Met signaling dysregulation, MMP-2 inhibition and TNF receptor-associated factor 6 (TRAF6) inactivation [125–129].

In co-cultures of F10-OVA melanoma cells and tumor-specific CD3 + T cells, EGCG reduced PD-L1 mRNA expression of 30% in the tumor cells and restored IL-2 mRNA expression in the lymphocytes, indicating that it can function as an immune checkpoint inhibitor [130].

EGCG was shown to possess anti-melanogenic activity, associated with decreased MITF production and tyrosinase expression [131,132].

Synergistic anti-melanoma effects of EGCG with different synthetic and natural anti-cancer agents have been observed: the co-treatment with dacarbazine significantly reduced the primary tumor growth and the number of

lung metastases in melanoma-bearing mice [133]; the addition of TRAIL to the EGCG treatment enhanced the apoptosis rate in human melanoma A375 cells [134]; EGCG sensitized melanoma cells to IFN-α-induced growth suppression [135]; with respect to monotherapy, the combination treatment with EGCG and vorinostat, a histone deacetylase (HDAC) inhibitor, resulted in significantly greater inhibition of cell proliferation and activation of apoptosis [136]; vitamin A increased the expression of the 67-kDa laminin receptor 67LR in B16 melanoma cells, potentiating the anti-proliferative activity of EGCG [137]. Moreover, EGCG was reported to overcome resistance to the BRAF inhibitor vemurafenib by activating 67LR-dependent protein phosphatase2A pathway in melanoma cells [138].

Novel EGCG synthetic derivatives have been recently developed: a 3,4,5-trimethoxybenzoyl ester analogue of EGCG was reported to bind to human dihydrofolate reductase and disrupt the folate cycle in melanoma cells, leading to cancer cell death [139]; although EGCG methylation generally reduces its anti-tumor properties, the anti-proliferative effects exerted by 7-OMe EGCGs on B16 cells were similar to those of EGCG [140]; 4-(S)-(2,4,6-trimethylthiobenzyl)-EGCG triggered apoptosis in melanoma cells via ROS-mediated autophagy induction [141].

Transferrin receptors are generally overexpressed in cancer cells and therefore can be exploited for the anti-tumor drug transport across cell membranes. Lemarié et al. reported that the intravenous administration of transferrin-bearing vesicles entrapping EGCG to mice bearing B16-F10 tumors successfully inhibited cancer progression [142].

Improved anti-melanoma efficacy was shown by EGCG when encapsulated in gold and chitosan nanoparticles [143,144], as well as in nanoethosomes [145], in *in vitro* and *in vivo* experiments.

2.7 Curcumin

Curcumin is a polyphenol obtained from *Curcuma longa*, commonly known as turmeric. It is nontoxic and characterized by many therapeutic properties, particularly by antioxidant, anti-inflammatory and anti-microbial activities [146,147].

As regards its anti-melanoma effects, curcumin was shown to arrest cell proliferation and to trigger both extrinsic and intrinsic apoptosis *in vitro* and *in vivo* [148–155]. In particular, it was reported to inhibit the NF-κB [156–158], STAT3 [159], Akt/mTOR [160] and Wnt/β-catenin [44] signaling pathways, to induce ER stress [161], to activate mammalian Sterile 20-like kinase 1 (MST1)/JNK cascade [162] and to enhance ROS production [163,164] in melanoma cells.

Curcumin exhibited anti-invasive properties, correlated with modulation of FAK and MMP-2 activity and of integrin receptor, nonmetastatic gene 23 (Nm23) and E-cadherin expression [165,166]. Moreover, curcumin selectively downregulated the levels of phosphatase of regenerating liver-3 (PRL-3), an oncogene involved in tumor metastasis, in B16F10 cells [167]. Interestingly, pulmonary administration of this compound resulted in a significant decrease in the number of lung metastatic nodules in melanoma mouse models [168].

Different curcumin-based combination therapies have been proposed for the treatment of melanoma: C6 ceramide and homoserine based C8-ceramide analogues promoted curcumin-mediated anti-proliferative and anti-angiogenic effects [169,170]; the co-treatment with tamoxifen and curcumin resulted in synergistic induction of apoptosis in G361 chemo-resistant cells [171]; fibroblast activation protein α (FAPα) vaccine combined with curcumin elicited the anti-cancer response to the natural compound via inhibition of indolamine-2,3-dioxygenase and of EMT [172]; 1-phenyl-2-decanoylamino-3-morpholino-1-propanol (PDMP) facilitated curcumin-induced apoptotic cell death by enhancing ceramide accumulation and c-Jun N-terminal kinase (JNK) phosphorylation whilst suppressing Akt/mTOR signaling pathway [173]; ABT-737, a novel Bcl-2 inhibitor, potentiated the pro-apoptotic activity of curcumin in WM-115 and B16 cell lines [174]; a combination of curcumin and NC10, a synthetic nitrosyl-iron complex, improved the anti-tumor efficacy of the monotherapy with the polyphenol [175]; borneol, a terpene derivative commonly used in Chinese medicine, effectively synergized with curcumin, by activating the caspase cascade in A375 cells [176]; the red united blue light irradiation greatly enhanced the oxidative stress-mediated cell death induced by curcumin [177].

Many recent studies have focused on the synthesis of anti-melanoma curcumin derivatives: the curcumin analog DM-1 triggered apoptotic cell death, alone or in combination with dacarbazine, both *in vitro* and *in vivo* [178–181]; the analog D6 significantly upregulated the p53 expression and inhibited the PI3K/Akt and NF-κB pathways, inducing mitochondrial apoptosis in different melanoma cell lines [182–184]; treatment with the FLLL32 and FLLL62 analogues resulted in STAT3 inhibition, ultimately leading to melanoma cell death [185,186]; the curcuminoid EF24 exhibited potent anti-proliferative, anti-metastatic and anti-angiogenic effects, also modulating miRNA-21 and miRNA-33b expression [187–189]; ferrocenyl curcuminoid derivatives showed improved anti-melanoma activity compared to the corresponding organic compounds [190]; different curcumin-like diarylpentanoid analogues were demonstrated to suppress the melanogenesis in B16 cells [191]; tetrahydricyrcumin, salicyl curcumin and curcumin-III greatly reduced the neo-vascularization in mouse melanoma models [192].

Micelles and liposomes are vesicles in which drugs can be trapped and administered more efficiently. Different curcumin-loaded micellar systems (chitosan-cholesterol-, poly(D,L-lactide)-, cholesterol-conjugated poly(D,L-lactide)-, PEG-, cholesterol- and vitamin E-conjugated PEG-based micelles) exhibited higher cytotoxicity with respect to the free compound in 2D and 3D melanoma cell cultures and in melanoma-bearing mice, successfully solubilizing and stabilizing the drug and promoting its controlled release to the tumor cells [193–199]; liposomal delivery of curcumin, alone or in combination with anti-cancer agents and molecules such as paclitaxel or STAT3 siRNA, resulted in growth-suppressing and anti-angiogenic effects in *in vitro* and *in vivo* melanoma models [200–204].

Nanoparticles and cyclodextrin-based carriers can also be used to encapsulate curcumin and its analogues, and have been recently proposed as promising new formulations for melanoma treatment [205–223].

An anti-Muc18 antibody-coupled curcumin more efficiently reduced the brain metastasis formation in mice inoculated with B16F10 cells [224].

2.8 Resveratrol

Resveratrol (trans-3,4′,5-trihydroxystilbene) is a grape-derived polyphenol that has been intensively studied for its chemopreventive potential [225].

In the case of melanoma, resveratrol was found to inhibit cell growth by inducing S phase arrest, with cyclins A, E, and B1 upregulation, dihydronicotinamide riboside quinone reductase 2 (NQO2)-mediated p53 overexpression, ERK1/2 pathway suppression, NF-κB inactivation and oncogenic miR-221 downregulation [226–230]. Moreover, it was shown to trigger mitochondrial apoptosis via Bax/Bcl-2 ratio modulation, caspase-3 cleavage, STAT3/β-catenin and survivin suppression, ROS production and ER stress activation [231–239]. Finally, it was observed to induce phenotype changes and to affect melanin synthesis in melanoma cells [240–243].

In addition to the above mentioned anti-cancer effects, resveratrol exhibited important anti-angiogenic and anti-invasive activities, associated with αvβ3 integrin inhibition, VEGF downregulation, increased thrombospondin 1 (TSP1) expression and Akt and FAK pathways inactivation [244–248]. Notably, in mice injected with B16 M cells resveratrol successfully prevented liver metastases by reducing IL-18-dependent expression of vascular cell adhesion protein 1 (VCAM-1) in tumor-activated hepatic sinusoidal endothelium, thus inhibiting melanoma cell adhesion to the microvasculature [249,250].

Cellular senescence is a tumor-suppressive mechanism generally associated with DNA damaging cancer therapies. In particular, it can be followed by deleterious effects in the tumor microenvironment, such as the acquisition of a senescence-associated secretory phenotype (SASP) which is responsible for the conversion of fibroblasts into pro-inflammatory cells capable of promoting cancer progression. In a recent study by Menicacci et al., chronic resveratrol treatment significantly inhibited MRC5 fibroblast SASP-related pro-tumor effects on melanoma cells, reducing the expression of EMT markers correlated with malignant features [251].

It is well documented that NO can participate to melanoma progression. Yang et al. demonstrated that NO can enhance melanoma metastatic potential via an apurinic/apyrimidinic endonuclease-1 (APE)/redox factor-1 (Ref-1)-driven feedback loop, which is suppressed by resveratrol [252].

Resveratrol was shown to potentiate the activity of different anti-melanoma agents: it sensitized melanoma cells to TRAIL pro-apoptotic effects [253,254]; the natural compound-mediated APE/Ref-1 inhibition increased the dacarbazine-induced cell death [255]; resveratrol addition rendered melanoma cells more sensitive to temozolomide treatment [255]; capsaicin and resveratrol synergistically triggered apoptosis through NO elevation in A375 cells [256]; melanoma sensitivity to cisplatin was enhanced by resveratrol via connexin 43 upregulation [257]; vemurafenib resistance was reversed by resveratrol treatment via Akt inactivation in BRAF-mutated melanoma cells [258]; synergistic anti-proliferative effects, correlated with AMP-activated protein kinase (AMPK), vasodilator-stimulated phosphoprotein (VASP) and VEGF modulation, were shown by a combination of resveratrol and 5-fluorouracil [259,260]; chloroquine synergized with the polyphenol to induce cytotoxicity in melanoma cells [261]; resveratrol improved the efficacy of high-dose IL-2 immunotherapy in B16F10 melanoma mouse models, also preventing the endothelial cell injury and inhibiting the development vascular leak syndrome [262]; resveratrol was demonstrated to act as radiotherapy sensitizer in radioresistant melanoma cell lines [263].

In the last decade, several resveratrol analogues have been produced in order to improve the pharmacokinetic properties and to increase the pharmacological potency of this compound for melanoma treatment [264–274].

2.9 Sulforaphane

Sulforaphane is an organic isothiocyanate with several health benefits. It is obtained from cruciferous plants, such as broccoli, cabbage and cauliflower [275].

In melanoma setting, sulforaphane was shown to trigger cell growth arrest and apoptosis, accompanied by the upregulation of early growth response protein 1 (EGR1), growth arrest and DNA-damage-inducible beta (GADD45B), ATF3 and CDKN1A, by the activation of caspase-3 and -9, Bax, p53, p53 upregulated modulator of apoptosis (PUMA), Fas and mouse double minute 2 homolog (MDM2) and by the downregulation of Bcl-2, BH3 interacting domain death agonist (Bid) and NF-κB [276–279]. Furthermore, it induced oxidative stress and modulated the expression of nerve growth factor receptors TrKA and p75NTR, shifting their ratio from pro-survival to pro-apoptotic [278–280].

Sulforaphane reduced the invasive potential of B16F10 melanoma cells by inhibiting MMPs activity, thereby suppressing lung metastases [281]. Moreover, it inhibited the spread of B16F10 cells through the stimulation of cell-mediated immune response, upregulation of IL-2 and IFN-γ and downregulation of proinflammatory cytokines IL-1β, IL-6, TNF-α and granulocyte-macrophage colony-stimulating factor (GM-CSF) [282].

Cancer stem cells (CSCs) are widely recognized as a small subpopulation of cancer cells within the tumor mass responsible for the resistance to standard anti-cancer therapies. In particular, they possess self-renewal ability, as well as the capacity to give rise to the entire tumor cell bulk through differentiation, thus representing important therapeutic targets. Several phytochemicals were demonstrated to target CSCs, and sulforaphane was found to specifically eliminate the melanoma CSC subpopulation, by suppressing enhancer of zeste homolog 2 (Ezh2) function [283].

Sulforaphane-encapsulated microspheres exhibited potent anti-melanoma activity both *in vitro* and *in vivo* [284,285].

Tahata et al. investigated sulforaphane efficacy and safety in 17 patients with at least 2 atypical nevi and a prior history of melanoma. The patients were given three different oral doses of the compound (50, 100 or 200 µmol) daily for 28 days. Sulforaphane was well tolerated even at the higher dose and achieved dose-dependent levels in plasma and skin. Importantly, plasma levels of proinflammatory cytokines decreased, while the expression of the tumor suppressor decorin increased from day 1 to 28 [286].

2.10 Ursolic acid

Ursolic acid is a triterpenoid exhibiting a wide spectrum of pharmacological properties, including anti-inflammatory and anti-microbial features. It is present in a variety of plants and herbs, such as thyme and rosemary, as well as in fruit peels [287].

Many studies have pointed out that ursolic acid possesses potent anti-melanoma activity, correlated with modulation of different pathways, including NF-κB, p53, Akt and ERK1/2 proteins, and with caspase cascade activation [288–292]. Notably, it has also been demonstrated that tyrosinase- and TRP-1-mediated melanogenesis and COX-2/PGE2 pathway are implicated in the resistance of melanoma cells to the ursolic acid cytotoxicity [293,294].

In addition to the above forenamed anti-melanoma effects, ursolic acid was observed to reduce the levels of VEGF, NO and proinflammatory cytokines in the serum of melanoma mouse models [295]. Furthermore, it significantly suppressed lung metastasis formation [296].

It should be noted that ursolic acid sensitized melanoma cells both to UV irradiation [297] and radiotherapy [298].

Novel derivatives and nanoformulations have been recently developed [299–302]; interestingly, the administration of low molecular weight heparin-conjugated ursolic acid and of inclusion complexes formed by the acid and cyclodextrins to melanoma-bearing mice resulted in a significant tumor growth inhibition [303–305].

2.11 Ginsenosides

Ginsenosides are triterpene saponins and are the major pharmacologically active components of ginseng root [306].

In melanoma cells, ginsenoside Rh2 was found to exert a G1 phase-specific suppressive effect on the Cdk2 activity and to induce caspase-3 and -8 dependent apoptosis [307,308]. Similar anti-proliferative and pro-apoptotic effects were also shown by other members of the ginsenoside group: ginsenoside Rg3 decreased HDAC3 expression, increased p53 acetylation, downregulated NF-κB-mediated fucosyltransferase 4 (FUT4) expression and inactivated epidermal growth factor receptor (EGFR)/MAPK pathway, leading to melanoma cell death both *in vitro* and *in vivo* [309–312]; upregulation of Fas, FasL and Bax protein expression and downregulation of procaspase-8, procaspase-3, mutant p53 and Bcl-2 protein expression were observed in SK-MEL-2 human melanoma cells after ginsenoside Rk1 treatment [313]; a major metabolite of the red ginseng ginsenoside Rb1, called 20-O-β-D-glucopyranosyl-20(S)-protopanaxadiol, suppressed melanoma cell growth by inducing autophagy and apoptosis via AMPK/JNK signaling activation [314].

Ginsenosides have been recently proposed as skin-whitening agents, owing to their ability to affect melanin synthesis via tyrosinase inhibition [315–318]. Notably, Kim et al. have also suggested that ginsenoside F1 may attenuate B16F10 melanoma cell hyperpigmentation via Ras homologous (Rho) signaling activation and subsequent dendrite retraction [319]. However, the role of ginsenosides in altering melanoma cell morphology is still unclear, since a recent study by Jiang et al. has demonstrated that ginsenoside Rh2 can induce dendrite formation by changing the physical properties of cholesterol-regulated membrane lipid bilayers [320].

Promising anti-angiogenic and anti-metastatic potential in melanoma treatment was shown by ginsenosides Rb2, Rg3 and Rp1 [321–325].

Ginsenoside Rh2 treatment enhanced the anti-cancer immunological response in melanoma mouse models, by increasing T-lymphocyte infiltration in the tumor and by triggering cytotoxicity in spleen lymphocytes [326]. Similarly, ginsenoside Rg3 induced immunogenic cell death in B16F10 melanoma cells, as evidenced by upregulated surface expression of calreticulin and heat shock proteins; moreover, the proportion of dendritic CRT^{+} $CD11c^{+}$ cells was increased in the Rg3-treated group, which also secreted IFN-γ, an effector molecule for anti-tumor activity in T cells [327].

Oral administration of ginsenoside Rh2 to C57BL/6 mice bearing B16 melanoma synergistically enhanced the anti-tumor activity of cyclophosphamide in a dose-dependent manner. Furthermore, it decreased the micronucleus formation in polychromatic erythrocytes and DNA strand breaks in white blood cells, suggesting that it not only increases the anti-melanoma efficacy of cyclophosphamide but also reduces its genotoxic effects [328].

New synthetic ginsenoside derivatives have been recently obtained, showing considerable cytotoxicity against melanoma cells [329]. Interestingly, Cui et al. cloned and characterized a novel ginsenoside-transforming β-glucosidase (BglG167b) derived from *Microbacterium* sp. Gsoil 167 that can efficiently hydrolyze gypenoside XVII, a deglycosylated product of major ginsenoside Rb1, into gypenoside LXXV, which displayed an enhanced anti-melanoma effect compared to the original compound [330].

In a study by Zare-Zardini et al., novel drug delivery systems based on ginsenoside Rh2-treated highly porous graphene were produced in order to improve the compound cytotoxic effects on different cancer cell lines, including

melanoma A375 cells [331].

2.12 Tocotrienols

Tocotrienols (TTs) are hydrophobic compounds which belong to the vitamin E family. They are composed of a chromanol ring linked to an unsaturated isoprenoid side chain; the number and the position of methyl substitutes on the chromanol ring identify α-, β-, γ- and δ-TT isoforms. Natural sources containing high levels of tocotrienols are annatto (*Bixa orellana* L.) seeds, red palm oil, rice bran and other vegetable oils. In several studies TTs were reported to exert health promoting effects based on their neuroprotective, cardioprotective, antioxidant, anti-inflammatory and cholesterol-lowering properties [332]. In addition, anti-proliferative, pro-apoptotic and anti-metastatic activities have been demonstrated in a wide range of cancer cells *in vitro* and *in vivo* [333–337].

We demonstrated that δ-TT exerts pro-apoptotic effects in human melanoma A375 and BLM cell lines, by triggering the activation of the PERK/p-eIF2α/ATF4/CHOP, IRE1α and caspase-4 ER stress-related pathways [338,339]. We also showed that, unlike vemurafenib, δ-TT specifically targets the ABCG2-positive CSCs subpopulation in the A375 cell line, preventing the formation of melanospheres and inducing their disaggregation [340].

In malignant melanoma cells, γ-TT-induced cell death was found to be associated with the cleavage of procaspases, the activation of JNK signaling pathway and the suppression of NF-κB, EGFR and inhibitor of DNA-binding (Id) family proteins. Moreover, γ-TT significantly suppressed melanoma cell invasion capability, by downregulating mesenchymal markers and restoring E- and γ-cadherin expression [341].

A synergistic tumor-suppressing activity was observed by combining TTs with standard anti-cancer agents or other natural compounds. In particular, TTs were reported to potentiate lovastatin-mediated growth inhibition of murine melanoma B16 cells, by dysregulating HMG-CoA reductase activity both *in vitro* and *in vivo* [342]. Moreover, in the same cell line γ-TT was found to upregulate the aryl hydrocarbon receptor (AhR) expression, enhancing the anti-proliferative activity of baicalein, a flavone isolated from the roots of *Scutellaria baicalensis* and *Scutellaria lateriflor* [343].

Despite the many anti-cancer properties, TTs fail to reach the tumor mass after intravenous administration, and melanoma-targeted vesicles bearing transferrin have been proposed to overcome bioavailability limitations [344].

2.13 Berberine

Berberine is a benzylisoquinoline alkaloid extracted from various plants, particularly from those belonging to the genus *Berberis*. Ongoing experimental and clinical studies have pointed out great potential of this compound in the regulation of glucose and lipid homeostasis, inflammation and cancer growth [345].

Serafim et al. demonstrated that in melanoma cells berberine is concentrated in mitochondria at low doses, promoting G1 phase arrest, while it accumulates in the cytoplasm and in the nucleus at higher doses, inducing G2 arrest [346]. Importantly, berberine was also shown to trigger apoptosis [347] and necrosis [348] and to inhibit melanin synthesis [349] in different melanoma cell lines.

Melanoma cell migration was significantly affected by berberine treatment through modulation of PI3K/Akt, FAK and NF-kB pathways *in vitro* [350,351]. Furthermore, the alkaloid successfully enhanced the survival of melanoma-bearing mice, by reducing pulmonary metastases via MMP downregulation and AMPK-mediated suppression of ERK activity and COX-2 expression [352,353].

Berberine exhibited antiangiogenic activity associated with the inhibition of HIF, VEGF, NO and proinflammatory cytokines [354].

Finally, it should be underlined that increased anti-melanoma effects were shown by berberine when given in combination with doxorubicin [355].

2.14 Other compounds

Honokiol is a lignan occurring in several species of the genus *Magnolia*. It exerted cytostatic and cytotoxic effects in melanoma cells, by reducing cyclin D1, CDK1 and CDK2 levels, attenuating Akt/mTOR signaling, suppressing HIF-1 pathway, disrupting mitochondrial electron transport chain (ETC) function and inducing caspase/PARP cleavage [356–360]. In addition, it activated ER stress via direct binding to GRP78 ATPase domain and Calpain-10 and CHOP/GADD153 cascade [361,362]. Furthermore, it affected the migration ability of Hs294t and SK-Mel28 cells through inhibition of NADPH oxidase 1 (Nox1) and blockade of the interactions between the enzyme subunits p22 and p47 [363]. It also specifically targeted and eliminated melanoma CSCs via AMPK activation and Notch-2 downregulation [364,365], while its bis-dichloroacetate derivative demonstrated enhanced activity in vemurafenib-resistant melanoma *in vivo* [366].

Artemisinin and its derivatives, such as artenusate, artemison and dihydoartemisinin, are well known antimalarial drugs. Interestingly, in melanoma cell lines they were shown to exert potent anti-proliferative and pro-apoptotic effects, associated with Wnt/β-catenin signaling inhibition and oxidative stress induction, and to suppress cell migration through downregulation of MMP-2 and αvβ3 integrin expression [367–372].

Oridonin, a diterpenoid isolated from *Rabdosia rubescens*, was found to induce G2/M phase arrest and differentiation of melanoma cells, and to activate p53 and ERK pathways, to suppress IGF-1R signaling and fatty acid

synthase (FAS) activity, to modulate Bax/Bcl-xL ratio and Bim expression and to promote cytochrome c release from mitochondria, ultimately triggering apoptosis [373–377]. Moreover, it was reported to affect melanoma cell invasive potential and TGF-β1-mediated EMT via PI3K/Akt downregulation [378].

Harmine is a β-carboline alkaloid from the plant *Peganum harmala*. Hamsa et al. reported that in B16F10 cells it can activate both intrinsic and extrinsic apoptosis, suppress angiogenesis through modulation of VEGF, NO and pro-inflammatory cytokines, and inhibit invasion via MMP-9 and ERK downregulation [379–381]. Notably, harmine analogues have also shown promising anti-melanoma effects both *in vitro* and *in vivo* [382,383].

Capsaicin is an alkaloid derived from chili peppers of the genus *Capsicum*. Morré et al. correlated its anti-melanoma activity with the inhibition of cell surface NADH oxidase [384]. More recently, in melanoma cells capsaicin was demonstrated to inhibit NF-κB-driven proliferation [385], to trigger Bcl-2 dependent apoptosis [386] and to suppress PI3K/Akt signaling-mediated migration [387].

Caffeic acid and its phenetyl ester (CAPE) are bioactive compounds from the propolis extract. They were observed to reduce p-Akt, p-mTOR and X-linked inhibitor of apoptosis protein (XIAP) levels [388] and to trigger ROS formation, GSH depletion and mitochondrial apoptosis [389–392], as well as to inhibit VEGFR-2-driven neovascularization [393] and tyrosinase dependent melanin synthesis [394,395] in melanoma cells and mouse models.

The molecular mechanisms underlying the anti-melanoma effects of the natural compounds here discussed are summarized in Fig. 2.

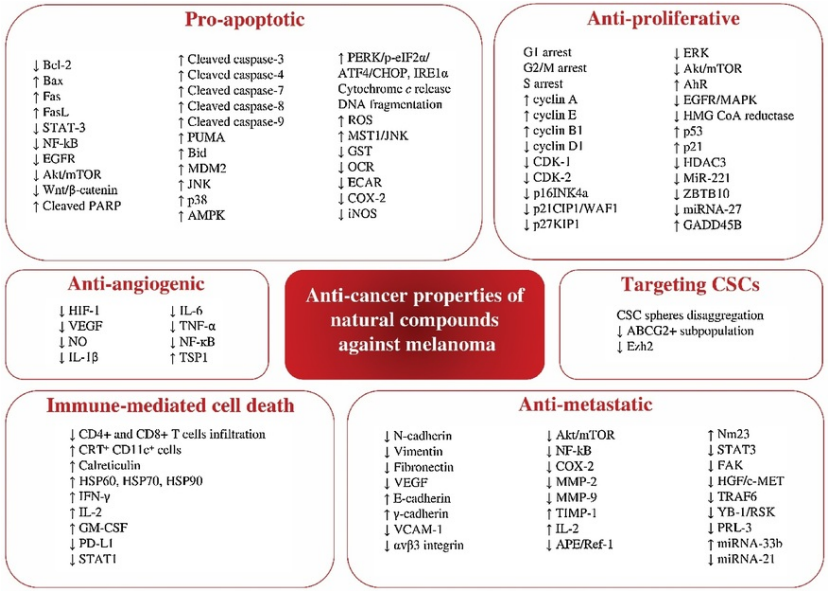

Fig. 2 Molecular mechanisms underlying the anti-melanoma effects of natural compounds. Phytochemicals modulate several key pathways involved in apoptosis, proliferation, metastasis, angiogenesis, cancer stemness and immune response.

alt-text: Fig. 2

3 C~~ONCLUDING REMARKS~~oncluding remarks

The present article gives an overview of recent evidence about the anti-melanoma effects of various natural products.

Nutraceuticals present numerous advantages since they are usually nontoxic and their cost is highly affordable around the world. It is now well established that they can exert anti-melanoma properties, and many *in vitro* and pre-clinical studies have been conducted to clarify the molecular mechanisms underlying these activities. Moreover, recent studies focused on the development of new synthetic derivatives, formulations and combinations with standard drugs, have clearly suggested that these compounds hold promise for melanoma prevention and treatment. However, the relevance of these findings still needs to be confirmed in patients, and clinical trials aimed at validating nutraceuticals effectiveness are urgently required.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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