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REVIEW ARTICLE

Updates in clinical trial-explored chemopreventive agents for cutaneous melanoma: mechanisms affecting melanocytes

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ABSTRACT

Cutaneous melanoma is a highly aggressive skin cancer with rising incidence, driven by risk factors such as ultraviolet exposure, genetic predisposition, and immunosuppression. While surgical excision remains the primary treatment, interest in chemoprevention strategies is growing. Numerous natural and synthetic agents have shown preclinical promise, but evaluating their effectiveness is challenging due to their systemic effects on multiple cell types. This review provides a focused examination of the melanocyte-specific mechanisms of select agents that have been tested in clinical trials for melanoma chemoprevention. We discuss various molecular and cellular mechanisms driving the anti-melanoma properties of nonsteroidal anti-inflammatory drugs, statins, sulforaphane, vitamin D, and *N*-acetylcysteine. Despite promising preclinical and early clinical data, challenges remain regarding precise mechanisms, optimal dosing, long-term safety, and patient selection. Future research should focus on refining melanoma prevention strategies through well-designed clinical trials and personalized approaches integrating genetic and molecular risk factors.

ARTICLE HIGHLIGHTS

- There is a dearth of clinical trials studying chemoprevention of melanoma, particularly compared to the number examining non-melanoma skin cancers.
- To date, only NSAIDs, sulforaphane, lovastatin, atorvastatin, vitamin D, and *N*-acetylcysteine have been studied in human clinical trials specifically designed to evaluate melanoma prevention. These agents influence melanoma cells through various mechanisms:
  - NSAIDs inhibit COX-2 and NF-κB pathways, inducing cytotoxic effects through mitochondrial dysfunction, ROS generation, and immune system modulation.
  - Sulforaphane activates antioxidant and apoptotic pathways, modulating immune responses, and impairing melanoma cell migration.
  - Statins inhibit melanoma cell proliferation and induce apoptosis by disrupting IGF-1 receptor glycosylation, modulating RhoC activity, and downregulating NF-κB.
  - Vitamin D, through its active form calcitriol, regulates melanoma cell viability and apoptosis by modulating key pathways like ERK and PTEN, with its effects varying based on VDR expression and cell line characteristics.
  - *N*-acetylcysteine has antioxidant effects that can protect against UV-induced DNA damage and melanoma onset in some preclinical models.
- Continued research into both systemic effects and molecular mechanisms is essential to overcoming challenges and optimizing melanoma chemoprevention strategies.

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1. Introduction

Cutaneous melanoma arises from the malignant transformation of melanocytes in the skin. Despite accounting for a small proportion of all skin cancer diagnoses, melanoma is highly aggressive, often treatment-resistant, and represents a significant healthcare burden [1]. As with basal cell carcinoma and squamous cell carcinoma, ultraviolet (UV) exposure is a major risk factor for melanoma development.

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However, unlike these other skin cancers, melanoma frequently arises in sun-protected areas, complicating prevention and early detection efforts. Additional risk factors include immunodeficiency, atypical nevi, fair skin, and a family history of melanoma [2]. Furthermore, melanoma subtypes defined by their site of origin and tumor genotype exhibit distinct pathophysiological characteristics. For instance, acral melanoma, which arises on the palms, soles, and nail beds, more commonly harbors mutations in the *KIT* tyrosine kinase receptor gene compared to other cutaneous melanoma subtypes [3,4]. While surgical excision can be curative in some cases, the incidence of melanoma continues to rise [5,6]. In response, alongside the development of targeted therapies such as Rapidly Accelerated Fibrosarcoma (RAF) kinase inhibitors, mitogen-activated protein kinase (MEK) inhibitors, and B-RAF (BRAF) inhibitors [7], there is growing interest in prevention strategies, including chemoprevention.

Chemoprevention refers to the use of natural or synthetic compounds to lower the likelihood of cancer developing, advancing, or returning. These agents, which include vitamins, minerals, and medications, act by interfering with carcinogenic processes. Previous reviews have explored chemoprevention strategies in skin cancers broadly [8] and discussed agents with theoretical potential for melanoma prevention [9]. However, chemoprevention remains a complex field. Many agents are administered systemically and exert pleiotropic effects on various cell types, complicating their evaluation. Consequently, evidence regarding their efficacy in melanoma prevention is often inconsistent or conflicting.

To provide clarity amidst the complexity of melanoma chemoprevention, this review will focus exclusively on agents that have been evaluated in clinical trials specifically designed to study prevention of cutaneous melanoma. In this narrative review, we highlight nonsteroidal anti-inflammatory drugs, statins, sulforaphane, and vitamin D, with additional discussion of *N*-acetylcysteine (NAC) due to its investigation in the context of high-risk nevi, which can serve as precursor lesions to melanoma (Table 1). Our discussion will center on the melanocyte-specific mechanisms of these agents, rather than broader systemic effects or extrapolations from other cancer types. By offering a refined focus, we aim to clarify existing evidence, highlight key knowledge gaps, and underscore the need for further research in melanoma chemoprevention.

2. Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drug (NSAIDs) have garnered significant attention for their potential role in melanoma chemoprevention. Their primary mechanism of action is the inhibition of cyclooxygenase (COX), an enzyme critical for the synthesis of prostaglandins (PG) and thromboxane from arachidonic acid [19]. COX exists in two isoforms encoded on different chromosomes: the constitutively expressed COX-1 and the inducible COX-2 [20,21], the latter of which has also been shown to play a pivotal role regulating keratinocyte differentiation [22,23].

Table 1. Agents examined as chemopreventatives in US clinical trials for cutaneous melanoma.

	Chemoprotective agent	Study	NCT/reference
NSAID	Aspirin	UV-protective effect of ASA in People at risk for Melanoma	NCT04066725 [10]
NSAID	Oral Aspirin	Metabolic and Inflammatory Effect of Oral Aspirin in People at Risk for Melanoma	NCT04062032 [11]
NSAID	Aspirin	ASA on Melanoma Incidence in Elderly Persons	[12]
NSAID	Sulindac	Sulindac in Preventing Melanoma in Healthy Participants Who Are at Increased Risk of Melanoma	NCT00841204 [13]
Sulforaphane	Oral broccoli sprout extract sulforaphane	Effect of Oral Sulforaphane on Atypical Nevi-Precursor Lesions	NCT01568996, [14]
Statin	Lovastatin	Lovastatin in Randomized, Double-Blind, Placebo-Controlled Phase II Clinical Trial in Patients at Risk for Melanoma	NCT00462280, [15]
Statin	Atorvastatin	Atorvastatin for Preventing Disease Metastasis in Patients With Resected High-Risk Stage IIA, IIB, or IIIA Melanoma	NCT06157099
Vitamin	Vitamin D	Effect of Vitamin D on Melanocyte Biomarkers	NCT01477463
Vitamin	Oral Vitamin D3	Vitamin D Levels in the Skin of Healthy Subjects After Oral Supplementation	NCT01447355, [16]
N-acetylcysteine	Oral NAC	Oral *N*-acetylcysteine for Protection of Human Nevi Against UV-induced Oxidative Stress	NCT01612221 [17,18]

¶ Chemopreventive agents evaluated in clinical trials for melanoma were initially identified by querying ClinicalTrials.gov using the keywords "melanoma" and either "prevention" or "chemoprevention." Studies involving behavioral interventions or cancer vaccines were excluded, as these did not meet the criteria for chemopreventive measures in the context of this review. Additional exclusions included withdrawn studies and those focused on xeroderma pigmentosum or ocular melanomas. Chemopreventive classes were retained for further analysis only if supporting literature reported results from at least one corresponding clinical trial. Following this initial screening to identify major classes of chemopreventive agents, more targeted searches for individual compounds were conducted in both ClinicalTrials.gov and PubMed.

COX-2 is notably overexpressed in human melanoma biopsies and cell lines [24,25], with immunohistochemical studies of human benign melanotic nevi, primary cutaneous melanomas, and lymph nodes containing metastatic melanoma demonstrating an increase in COX-2 expression correlates with disease progression and metastasis [25–27]. COX-2 expression is also inversely associated with patient survival [24], further supporting its role in melanoma pathogenesis. Moreover, melanoma cells produce prostaglandins such as PGE2 and PGF2α, which contribute to melanogenesis, post-inflammatory pigmentation, and support tumor growth through cancer cell survival and migration, immunosuppression, and angiogenesis [28,29].

A wide range of NSAIDs, differing in specificity and potency, are available in various formulations including capsules and topical applications. Common examples include aspirin, indomethacin, naproxen, ibuprofen, sulindac, and diclofenac. Among these, aspirin and sulindac—both nonselective NSAIDs—have been investigated in clinical trials for the chemoprevention of melanoma. Aspirin is unique amongst NSAIDs in that it irreversibly acetylates and inhibits COX [30]. While aspirin is generally considered nonselective, it preferentially inhibits COX-1 at low doses and requires higher doses to produce COX-2 effects.

Aspirin has been shown to exhibit direct cytotoxicity against melanoma cell lines, including human SK-MEL-28, MeWo, SK-MEL-5, and murine melanoma B16-F0 and B16-F10 cells [21]. This cytotoxic effect against melanoma cells is specific to those expressing tyrosinase, an enzyme that oxidizes aspirin. In experiments conducted by Vad et al., it was found that aspirin treatment led to a reduction in mitotic activity, suppressed cell proliferation, and caused a dose- and time-dependent rise in reactive oxygen species. Additionally, replenishing glutathione, an intracellular antioxidant that plays a role in the oxidation of aspirin by tyrosinase, notably reduced the cytotoxic effects of aspirin [21]. Experiments by Albano et al., using diclofenac provide evidence that in addition to the generation of intracellular reactive oxygen species, NSAIDs can exert antineoplastic effects through mitochondrial dysfunction and subsequent apoptosis of melanoma cells [31].

Briefly, COX signaling and PGs in non-melanoma cell types also influence melanoma progression, particularly through their interactions with the platelets and various immune cell populations. PGs and platelets have been shown to facilitate melanoma's ability to evade immune surveillance and promote metastasis in murine models. Platelets suppress cytotoxic T-cell immunity, thereby aiding tumor progression and metastatic dissemination [32]. However, aspirin's antiplatelet activity has been demonstrated to counteract these effects. Rachidi et al., have shown that adjuvant aspirin augments efficacy of adoptive T cell therapy of B16-F1 melanomas in C57Bl/6J mice [32]. COX-2 signaling has been linked to the inhibition of type I interferon (IFN) and T-cell-driven tumor destruction, while fostering an inflammatory profile that contributes to cancer progression [33]. Melanoma-derived prostaglandin production weakened immune responses and Zelenay et al, have shown that aspirin improves efficacy of PD-1 immunotherapy in mice [33].

Beyond its direct effects on COX and downstream prostaglandin signaling, aspirin exerts potentially chemopreventive effects through additional mechanisms, including the inhibition of nuclear factor-κB (NF-κB). NF-κB, a family of transcription factors involved in the expression of several pro-inflammatory and anti-apoptotic genes, is aberrantly activated in melanoma compared to normal melanocytes [34,35]. This activation contributes to melanoma progression by promoting cell survival and resistance to apoptosis. Interestingly, the NF-κB signaling pathway also regulates the expression of COX-2, providing NSAIDs with complementary mechanisms for inhibiting COX activity. Aspirin was the first NSAIDs shown to suppress NF-κB activation [36]. It achieves this by specifically inhibiting the β subunit of IκB kinase (IKKβ), the enzyme responsible for the phosphorylating and subsequent degradation of IκB. In the setting of inhibited IκB degradation, NF-κB remains sequestered in the cytoplasm, unable to translocation to the nucleus to exert its effects on gene expression [34]. The interaction between aspirin and IKKβ was identified as non-covalent using immunoprecipitation assays with radiolabeled aspirin [34]. Notably, NF-κB inhibition was not observed in parallel experiments with indomethacin, another COX inhibitor, providing additional evidence that aspirin's suppression of NF-κB is at least in-part independent of its COX and PG-inhibiting properties [34].

3. Sulforaphane

Sulforaphane (SFN), an isothiocyanate compound present in cruciferous vegetables like broccoli, cabbage, and Brussels sprouts, has been consistently associated with a reduced risk of various cancer types in epidemiological studies [37–40]. SFN exhibits robust anticancer properties, primarily through its activation of key signaling pathways and transcription factors involved in cellular defense and apoptosis.

Most pre-clinical animal studies on SFN's mechanisms in skin cancer have focused on non-melanoma skin cancers as summarized by Masoom et al. [41]. The general principle thought to underly the anti-skin cancer effects of SFN include: protection against oxidative stress via activation of Nrf2 [42] and Phase II Detoxification [43–45]; protection against UV-induced carcinogenesis [41,46]; and modulating growth via p53 activation and Wnt suppression [41]. While some of these likely extend to melanoma prevention as well, this review will highlight mechanistic studies with a particular focus on melanoma.

In vitro, SFN induces apoptosis of human melanoma ME-18 [47] and inhibits growth of B16-F10 melanoma cell lines [48]. Treatment of B16F-10 melanoma cells with SFN induces apoptosis, evidenced by cell blebbing, DNA condensation, and caspase 3 activation and associated downregulation of NF-kB subunits p50 and p65 [49]. One study [50] showed that SFN-mediated apoptosis can be augmented if combined with inhibition of Akt, which is upregulated in a large portion of melanomas [51]. RNA-seq of primary human malignant melanoma A375 has shown upregulation of pro-apoptotic genes, *p53*, Bcl-2-associated X protein (*BAX*), p53 upregulated modulator of apoptosis (PUMA) and *FAS*, and cell-cycle arrest genes Early Growth Response *1 (EGR1)*, Growth Arrest And DNA Damage Inducible Beta (*GADD45B*), and Cyclin Dependent Kinase Inhibitor 1 A (*CDKN1A)* [52]. Furthermore, sulforaphane has been identified as a powerful epigenetic regulator, affecting histone acetylation and methylation in malignant melanoma [53].

Notably, in vitro experiments have provided evidence that SFN treatment can induce apoptosis or morphological changes to primary human epidermal melanocyte (HEMa) cells as it does in malignant melanoma cell lines A375 and 501MEL [52]. Differences in susceptibility to SFN-induced cytotoxicity have been shown by others as well, [53] but the mechanisms underpinning these differences remain to be understood and are likely multifactorial. Possible explanations include differences in baseline NRF2 or NF-kB gene expression, BRAF mutational status, or basal glutathione (GSH) metabolism [53].

In murine studies, oral administration of SFN-containing radish extracts, mitigated pulmonary metastasis of melanoma [48]. Later studies provided evidence that this may be attributable to enhanced natural killer (NK) cell activity, upregulation of interleukin-2 (IL-2) and IFN-γ, and downregulation of proinflammatory cytokines IL-1β, IL-6, Tumor Necrosis Factor (TNF-α), and Granulocyte-macrophage colony-stimulating facto (GM-CSF) [54]. This reduced metastatic potential parallels the reduced migratory capacity of B16-F10 cells and [55] and wound closure in A375 [52] cells cultured in the presence of SFN. Mechanistically, SFN-induced inhibition of metalloproteinase activation likely contributes to this impaired cell migration [55].

The clinical trial conducted by Tahata et al. furthers our understanding of the chemoprotective mechanisms of SFN. The safety and feasibility of broccoli sprout extract (BSE), which contains SFN, was evaluated in patients with a history of melanoma and at least two clinically atypical nevi measuring 4 mm or larger in diameter [14]. The study utilized an oral formulation of BSE-SFN extracted from *Brassica oleracea*, administered as gel capsules at doses up to 3 x 200 µmol. Participants had no history of antineoplastic treatment for melanoma within the past year. Results demonstrated a dose-dependent increase in SFN concentrations in plasma and skin, along with reduced levels of pro-inflammatory cytokines, including Interferon gamma-induced protein 1(IP-10/CXCL10), Monocyte chemoattractant protein-1 (MCP-1/CCL2), Monokine induced by gamma (MIG CXCL9), and Macrophage Inflammatory Proteins (MIP-1β/CCL4), between days 1 and 28. These cytokines, which function as chemoattractants for immune cells such as monocytes, T cells, and natural killer cells, decreased independently of the administered dose. The intervention was well-tolerated and showed promising tumor-suppressive effects, although further efficacy studies are required to definitively establish its role in melanoma prevention.

4. Statins

Statins, or 3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductase inhibitors, are commonly prescribed to reduce cholesterol levels by blocking the conversion of HMG-CoA to mevalonate (MVA), a key precursor in cholesterol synthesis. Beyond cholesterol, MVA is essential for synthesizing isoprenoid intermediates that play a role in the posttranslational modification of critical proteins such as Rho, Rac, and Ras GTPases, which are involved in cellular proliferation and motility [56].

Statins exhibit a range of antitumor activities in melanoma cells. Lovastatin, for example, reduces MVA levels, which in turn arrests the growth of SK-MEL-2 human melanoma cells [57]. This growth-inhibitory effect can be partially reversed by the addition of exogenous insulin-like growth factor-1 (IGF-1). Melanoma cells express IGF-1 receptors (IGF-1R) on their surface [58], and blocking this receptor has been demonstrated to inhibit

both the proliferation and motility of cultured melanoma cells [58,59]. MVA is critical for the glycosylation and translocation of IGF-1R to cell surface, so the depletion of MVA leads to a decrease in the number of IGF-1R available on the cell membrane [57]. When lovastatin depletes MVA, it results in decreased glycosylation of IGF-1R, reduced expression on the cell membrane, and consequently inhibited DNA synthesis, ultimately leading to the growth arrest of SK-MEL-2 cells [60].

Statins, particularly lipophilic statins such as lovastatin and simvastatin, have been shown to reduce proliferation and induce cytotoxicity of murine melanoma cell cultures [61]. That being said, hydrophilic rosuvastatin has also been shown to reduce viability and proliferation of human melanoma cell lines in vitro [62]. Lovastatin induces apoptosis in both human and murine melanoma cell lines, evidenced by increased caspase-3 activity and Annexin V staining [63]. In vivo, high-dose oral simvastatin administered to C57Bl/6J mice before and after inoculation with B16-F10 murine melanoma cells significantly impairs tumor growth [64]. Notably, comparing BRAFV600E and wild type melanoma lines in vivo suggests that at high-doses statin-induced apoptosis is independent of BRAF mutation status [65]. Lovastatin-treated human melanoma cells exhibit altered, rounded morphology, and the addition of geranylgeranyl pyrophosphate partially rescues cells from apoptosis, suggesting a geranylation-specific mechanism [63]. Similarly, simvastatin inhibits cell proliferation, arrests cells in the G1 phase, and induces apoptosis in murine B16-F10 and human SK-Mel-3 and A375 melanoma cell lines [66,67]. Like lovastatin, the pro-apoptotic effects of simvastatin could be reversed by geranylgeranyl pyrophosphate [66]. Additionally, simvastatin downregulates NF-κB p65 expression, which augments apoptotic effect [65].

Simvastatin has been shown to induce heme oxygenase-1 (HO-1) protein expression in human melanoma cell lines. HO-1, a protein that protects cells against oxidative stress, appears to act as a defense mechanism against statin-induced apoptosis. When statin treatment was combined with pharmacologic inhibition of HO-1, the apoptotic effects of the statin were significantly augmented, suggesting that HO-1 expression may partially counteract the pro-apoptotic activity of statins [65]. Exogenous tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) also works synergistically with statins to induce apoptosis, through a mechanism thought to involve suppression of NF-κB- and STAT-3-dependent transcription [65].

Furthermore, simvastatin has been shown to destabilize transcriptional machinery in the murine B16-F10 melanoma cell line through downregulation of non-POU-domain-containing octamer binding protein (nonO), a nuclear $p54^{nrb}$ protein required for normal cell survival [67]. Additionally, lipophilic statins lovastatin and simvastatin suppress expression of hypoxia-inducible factor 1α (HIF-1α) [61], which correlates with metastatic potential of human melanoma cell lines [68], and reduce the concentration of nonenzymatic antioxidants (i.e., vitamins, glutathione, etc) in tumor lysates [61].

Statins also modulate immune evasion mechanisms and the tumor microenvironment through multiple pathways. A critical mechanism involves the inhibition of RhoC activation through suppression of post-translational geranylgeranylation. RhoC, a GTPase overexpressed in melanoma cell lines and metastatic samples, drives metastasis by regulating actin cytoskeleton dynamics and gene transcription [69,70]. Atorvastatin blocks RhoC activity, leading to depolymerization of F-actin and altered morphology in amelanotic melanoma cells (e.g., A375M). This disruption of cytoskeletal integrity significantly inhibits melanoma cell invasion, as demonstrated in matrigel invasion assays [69]. Additionally, in vivo studies reveal that statins suppress the expression and activity of matrix metalloproteinases (MMPs) and very late antigens (VLAs) which are critical mediators of extracellular matrix degradation and tumor invasion [71].

In murine models, atorvastatin enhances the membrane localization of FasL on melanoma cells, increasing their ability to induce apoptosis in Fas-sensitive lymphocytes via the RhoA/ROCK signaling pathway [72]. This activity highlights the role of statins in reducing immune surveillance evasion. Moreover, coculture experiments with human dermal fibroblasts and endothelial cells demonstrate that lovastatin can reduce the angiogenic potential of human melanoma cell lines, further inhibiting tumor progression [73].

5. Vitamin D

Vitamin D is a fat soluble vitamin which is classically thought of as a major regulator of calcium and phosphate metabolism, has several pleotropic affects throughout the body including immune modulation, cell cycle regulation, and angiogenesis, all of which play important roles in the development and progression of malignancy [74,75]. Vitamin D can be sourced from dietary intake or synthesized in the body. The canonical biosynthesis from cholesterol involves several organs. In the setting of UV-exposure, 7-dehydrocholesterol is converted into

cholecalciferol (Vitamin D3) in the stratum basale of the skin. Vitamin D3 is then converted to calcidiol (25-hydroxycholecalciferol D3) in the liver. Lastly, calcidiol is converted into its biologically active form, calcitriol (1,25-dihydroxycholecalciferol D3) in the kidney [74]. The sequential hydroxylation reactions of this canonical pathway typically involve CYP27 enzymes. Active calcitriol can exert its biological effects through both the genomic vitamin-D-receptor (VDR) pathway and the non-genomic endoplasmic reticulum protein 57 (ERp57) pathway [76]. Notably, several non-canonical pathways of vitamin D metabolism and vitamin D analogs have been described in the skin [77–79]. Szyszka et al., have reviewed the therapeutic potential of vitamin D analogs in melanoma, but these agents have yet to be tested as chemotherapeutic agents in clinical trials [80].

The VDR is found on the nuclear membrane of many cell types [81], including melanocytes and keratinocytes [82,83]. Ligand-bound VDR forms a heterodimer with the retinoid X receptor and leads to transcriptional modulation of hundreds of genes [75,84–86]. Defects in vitamin D signaling—whether due to reduced receptor levels, lower precursor metabolite concentrations, or impaired activation—are linked to melanoma growth and progression [87]. Clinically, serum calcidiol levels decline as melanoma advances [88] correlating with poorer prognoses in advanced disease [89]. Beyond reduced serum vitamin D levels, metastatic melanomas also exhibit decreased VDR receptor expression, further diminishing the functional impact of circulating vitamin D [90,91].

Vitamin D exerts complex and variable effects on melanocytes and melanoma cells through multiple mechanisms. In vitro studies have shown that calcitriol can inhibit DNA replication in human melanoma MM96 cells [92] and reduce adhesion of murine melanoma B16 cells to the extracellular matrix by inhibiting type IV collagenase activity, suggesting roles in limiting invasion or altering cell-environment interactions [93]. Calcitriol also influences viability of melanoma cell lines through induction of apoptosis, as indicated by increased caspase-3 expression [94]. However, responses to vitamin D vary between melanoma cell lines; while some undergo apoptosis upon treatment, others, such as MeWo human melanoma cells, exhibit resistance to apoptosis induced by calcitriol or vitamin D analog EB1089, despite being susceptible to the antiproliferative effects of both [95–98]. Shariev et al., provide evidence that this variability may be partially dependent on VDR expression and phosphatase and tensin homolog (PTEN), a key regulator of apoptosis. Normal cell survival, proliferation, and melanogenesis depends on Ras-mediated activation of the Raf/extracellular signal-regulated kinase (ERK) and Phosphatidylinositol 3-Kinase (PI3K)/AKT/Mechanistic Target of Rapamycin (mTOR) pathways. Calcitriol binding to VDR regulates these pathways by activating ERK, and upregulating PTEN, which suppresses AKT, mTOR. This ultimately reduces melanoma cell viability and promotes apoptosis. By examining human melanoma cell lines with different baseline expression of VDR and ERp57, Shariev et al., found that calcitriol-induced apoptosis was most significant in cell lines in which calcitriol induced VDR expression. Furthermore, siRNA silencing of PTEN impaired calcitriol-mediated melanoma apoptosis [94].

6. *N*-acetylcysteine

N-acetylcysteine (NAC), which is converted to glutathione—a powerful antioxidant, is available in topical and oral formulations. The therapeutic benefit of NAC is thought to come largely from the effect of glutathione which acts to counteractive oxidative stress. In a preclinical study, incubation with NAC reduced the formation of UV-induced peroxide in mouse melan-a cells in a dose-dependent manner and mitigated ROS-induced DNA damage as measured by 8-oxoguanine (8-OG) staining. NAC did not significantly prevent formation of CPDs, which are thought to represent oxidation-independent DNA damage induced directly by UV [99].

Oral NAC has demonstrated a protective effect against UV-induced melanoma in double hepatocyte growth factor-survivin transgenic mice, delaying tumor onset; however, this benefit has not been sustained over time in vivo [99]. Goodson et al. found that nevi collected and irradiated ex vivo from a subset of patients who were pretreated with oral NAC were protected against UV-induced glutathione depletion [17]. However, a pilot Phase 2 trial failed to demonstrate any benefit when nevi were irradiated in vivo following the same oral NAC dose. One proposed explanation for this discrepancy involves differences in melanocortin 1 receptor (MC1R) and cyclin-dependent kinase inhibitor 2 (CDKN2A) polymorphisms between patients [18]. Furthermore, additional preclinical studies have raised concerns that oral NAC may promote melanoma metastasis, as evidenced by increased metastasis in BRAFV600E-transgenic mice [100] and patient-derived xenograft melanoma models [101]. Given these conflicting findings, the mechanisms underlying NAC's influence on melanoma progression and glutathione metabolism in vivo require further elucidation before chemoprevention trials can be confidently and safely designed.

7. Conclusions

Despite advances in targeted therapies and immunotherapy, cutaneous melanoma remains a significant public health challenge due to its rising incidence, aggressive nature, and limited preventive strategies. Chemoprevention offers a promising avenue for reducing melanoma risk and a handful of agents—aspirin, statins, sulforaphane, vitamin D, and NAC—have already begun to be studied in clinical trial. However, the field faces many challenges (as reviewed by Elmets et al. [102]) and remains in its early stages, with many unanswered questions regarding optimal dosing, patient selection, and long-term safety.

In this review, we highlighted the melanocyte-specific mechanisms of select chemopreventative agents that have been, or are being tested in clinical trials for melanoma. These agents each influence melanocyte growth, metabolism, gene expression, and interactions with the extracellular matrix through unique, sometimes overlapping, mechanisms. Focusing on melanocyte-specific mechanisms provides a framework for understanding melanocytes in the broader context of the skin and body that ultimately dictates the pathophysiology of melanoma. Studies have shown that even in highly controlled in vitro settings responses can be variable, influenced by factors such as genetics, gene expression, and other yet-to-be-identified factors. As such, optimal chemoprevention may require a personalized approach, considering individual variables like VDR polymorphisms and genetic risk factors. Target populations, duration of prophylaxis, feasibility with regards to route of administration, side effect profiles, and cost must also all be considered.

8. Future perspectives

Improving our understanding of the basic mechanisms underlying melanoma prevention is essential for supporting future in vivo experiments and clinical trials. Additionally, it is important to recognize that effects that are beneficial in a therapeutic context may not necessarily be advantageous for prevention, furthering the need for clinical trials specifically designed to examine efficacy and safety of preventative agents. Given the challenges of conducting chemoprevention trials—such as long study durations and the need for large numbers of participants—we encourage considering cutaneous findings across a broader range of clinical trials. For instance, including melanoma development as a supplementary readout in trials focused on non-melanoma skin cancers would provide valuable insights and greatly benefit the field. In conclusion, while chemoprevention holds great promise for reducing melanoma risk, continued research is essential to overcome current challenges and optimize prevention strategies. As more studies investigate the systemic effects of these interventions in vivo, it remains crucial to carefully interrogate the underlying molecular and cellular mechanisms, as these insights are vital for understanding the full impact of chemoprevention and improving outcomes.

Disclosure statement

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

[1] Arnold M, Singh D, Laversanne M, et al. Global burden of cutaneous melanoma in 2020 and projections to 2040. JAMA Dermatol. 2022;158(5):495–503. doi: 10.1001/jamadermatol.2022.0160

[2] Conforti C, Zalaudek I. Epidemiology and risk factors of melanoma: a review. Dermatol Pract Concept. 2021;11(Suppl 1):e2021161S. doi: 10.5826/dpc.11S1a161S

[3] Handolias D, Salemi R, Murray W, et al. Mutations in KIT occur at low frequency in melanomas arising from anatomical sites associated with chronic and intermittent sun exposure. Pigment Cell Melanoma Res. 2010;23(2):210–215. doi: 10.1111/j.1755-148X.2010.00671.x

[4] Beadling C, Jacobson-Dunlop E, Hodi FS, et al. KIT gene mutations and copy number in melanoma subtypes. Clin Cancer Res. 2008;14(21):6821–6828. doi: 10.1158/1078-0432.CCR-08-0575

[5] Ross MI, Gershenwald JE. Evidence-based treatment of early-stage melanoma. J Surg Oncol. 2011;104(4):341–353. doi: 10.1002/jso.21962

[6] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70(1):7–30. doi: 10.3322/caac.21590
[7] Leonardi GC, Falzone L, Salemi R, et al. Cutaneous melanoma: from pathogenesis to therapy (review). Int J Oncol. 2018;52(4):1071–1080. doi: 10.3892/ijo.2018.4287
[8] Tow R, Hanoun S, Andresen B, et al. Recent advances in clinical research for skin cancer chemoprevention. Cancers (Basel). 2023;15(15):3819. doi: 10.3390/cancers15153819
[9] Jeter JM, Bowles TL, Curiel-Lewandrowski C, et al. Chemoprevention agents for melanoma: a path forward into phase 3 clinical trials. Cancer. 2019;125(1):18–44. doi: 10.1002/cncr.31719
[10] Okwundu N, Rahman H, Liu T, et al. A randomized double-blind placebo-controlled trial of oral aspirin for protection of melanocytic nevi against UV-induced DNA damage. Cancer Prev Res (Phila). 2022;15(2):129–138. doi: 10.1158/1940-6207.CAPR-21-0399
[11] Varedi A, Rahman H, Kumar D, et al. ASA suppresses PGE(2) in plasma and melanocytic nevi of human subjects at increased risk for melanoma. Pharmaceuticals (Basel). 2020;13(1):7. doi: 10.3390/ph13010007
[12] Yan MK, Orchard SG, Adler NR, et al. Effect of aspirin on melanoma incidence in older persons: extended follow-up of a large randomized double-blind placebo-controlled trial. Cancer Prev Res (Phila). 2022;15(6):365–375. doi: 10.1158/1940-6207.CAPR-21-0244
[13] Curiel-Lewandrowski C, Swetter SM, Einspahr JG, et al. Randomized, double-blind, placebo-controlled trial of sulindac in individuals at risk for melanoma: evaluation of potential chemopreventive activity. Cancer. 2012;118(23):5848–5856. doi: 10.1002/cncr.27540
[14] Tahata S, Singh SV, Lin Y, et al. Evaluation of biodistribution of sulforaphane after administration of oral broccoli sprout extract in melanoma patients with multiple atypical nevi. Cancer Prev Res (Phila). 2018;11(7):429–438. doi: 10.1158/1940-6207.CAPR-17-0268
[15] Linden KG, Leachman SA, Zager JS, et al. A randomized, double-blind, placebo-controlled phase II clinical trial of lovastatin for various endpoints of melanoma pathobiology. Cancer Prev Res (Phila). 2014;7(5):496–504. doi: 10.1158/1940-6207.CAPR-13-0189
[16] Curiel-Lewandrowski C, Tang JY, Einspahr JG, et al. Pilot study on the bioactivity of vitamin d in the skin after oral supplementation. Cancer Prev Res (Phila). 2015;8(6):563–569. doi: 10.1158/1940-6207.CAPR-14-0280
[17] Goodson AG, Cotter MA, Cassidy P, et al. Use of oral *N*-acetylcysteine for protection of melanocytic nevi against UV-induced oxidative stress: towards a novel paradigm for melanoma chemoprevention. Clin Cancer Res. 2009;15(23):7434–7440. doi: 10.1158/1078-0432.CCR-09-1890
[18] Cassidy PB, Liu T, Florell SR, et al. A phase II randomized placebo-controlled trial of oral *N*-acetylcysteine for protection of melanocytic nevi against UV-induced oxidative stress in vivo. Cancer Prev Res (Phila). 2017;10(1):36–44. doi: 10.1158/1940-6207.CAPR-16-0162
[19] Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nat New Biol. 1971;231(25):232–235. doi: 10.1038/newbio231232a0
[20] Tanabe T, Tohnai N. Cyclooxygenase isozymes and their gene structures and expression. Prostaglandins Other Lipid Mediat. 2002;68–69:95–114. doi: 10.1016/s0090-6980(02)00024-2
[21] Morita I. Distinct functions of COX-1 and COX-2. Prostaglandins Other Lipid Mediat. 2002;68–69:165–175. doi: 10.1016/s0090-6980(02)00029-1
[22] Leong J, Hughes-Fulford M, Rakhlin N, et al. Cyclooxygenases in human and mouse skin and cultured human keratinocytes: association of COX-2 expression with human keratinocyte differentiation. Exp Cell Res. 1996;224(1):79–87. doi: 10.1006/excr.1996.0113
[23] Goldyne ME. Cyclooxygenase isoforms in human skin. Prostaglandins Other Lipid Mediat. 2000;63(1–2):15–23. doi: 10.1016/s0090-6980(00)00094-0
[24] Becker MR, Siegelin MD, Rompel R, et al. COX-2 expression in malignant melanoma: a novel prognostic marker? Melanoma Res. 2009;19(1):8–16. doi: 10.1097/CMR.0b013e32831d7f52
[25] Kuźbicki L, Sarnecka A, Chwirot BW. Expression of cyclooxygenase-2 in benign naevi and during human cutaneous melanoma progression. Melanoma Res. 2006;16(1):29–36. doi: 10.1097/01.cmr.0000194430.77643.a0
[26] Denkert C, Kobel M, Berger S, et al. Expression of cyclooxygenase 2 in human malignant melanoma. Cancer Res. 2001;61(1):303–308.
[27] Kuźbicki Ł, Lange D, Strączyńska-Niemiec A, et al. The value of cyclooxygenase-2 expression in differentiating between early melanomas and histopathologically difficult types of benign human skin lesions. Melanoma Res. 2012;22(1):70–76. doi: 10.1097/CMR.0b013e32834defec
[28] Tomita Y, Maeda K, Tagami H. Melanocyte-stimulating properties of arachidonic acid metabolites: possible role in postinflammatory pigmentation. Pigment Cell Res. 1992;5(5 Pt 2):357–361. doi: 10.1111/j.1600-0749.1992.tb00562.x
[29] Wang D, Dubois RN. Eicosanoids and cancer. Nat Rev Cancer. 2010;10(3):181–193. doi: 10.1038/nrc2809
[30] Simmons DL, Botting RM, Hla T. Cyclooxygenase isozymes: the biology of prostaglandin synthesis and inhibition. Pharmacol Rev. 2004;56(3):387–437. doi: 10.1124/pr.56.3.3
[31] Albano F, Arcucci A, Granato G, et al. Markers of mitochondrial dysfunction during the diclofenac-induced apoptosis in melanoma cell lines. Biochimie. 2013;95(4):934–945. doi: 10.1016/j.biochi.2012.12.012
[32] Rachidi S, Metelli A, Riesenberg B, et al. Platelets subvert T cell immunity against cancer via GARP-TGFbeta axis. Sci Immunol. 2017;2(11):eaai7911. doi: 10.1126/sciimmunol.aai7911
[33] Zelenay S, van der Veen AG, Bottcher JP, et al. Cyclooxygenase-dependent tumor growth through evasion of immunity. Cell. 2015;162(6):1257–1270. doi: 10.1016/j.cell.2015.08.015

[34] Yin MJ, Yamamoto Y, Gaynor RB. The anti-inflammatory agents aspirin and salicylate inhibit the activity of I(kappa)B kinase-beta. Nature. 1998;396(6706):77–80. doi: 10.1038/23948
[35] McNulty SE, del Rosario R, Cen D, et al. Comparative expression of NFkappaB proteins in melanocytes of normal skin vs. benign intradermal naevus and human metastatic melanoma biopsies. Pigment Cell Res. 2004;17(2):173–180. doi: 10.1111/j.1600-0749.2004.00128.x
[36] Kopp E, Ghosh S. Inhibition of NF-kappa B by sodium salicylate and aspirin. Science. 1994;265(5174):956–959. doi: 10.1126/science.8052854
[37] Verhoeven DT, Goldbohm RA, van Poppel G, et al. Epidemiological studies on brassica vegetables and cancer risk. Cancer Epidemiol Biomarkers Prev. 1996;5(9):733–748.
[38] van Poppel G, Verhoeven DT, Verhagen H, et al. Brassica vegetables and cancer prevention. Epidemiology and mechanisms. Adv Exp Med Biol. 1999;472:159–168. doi: 10.1007/978-1-4757-3230-6_14
[39] Steinmetz KA, Potter JD. Vegetables, fruit, and cancer prevention: a review. J Am Diet Assoc. 1996;96(10):1027–1039. doi: 10.1016/S0002-8223(96)00273-8
[40] Beecher CW. Cancer preventive properties of varieties of *Brassica oleracea*: a review. Am J Clin Nutr. 1994;59(5 Suppl):1166S–1170S. doi: 10.1093/ajcn/59.5.1166S
[41] Masoom M, Khan MA. Efficacy of sulforaphane in skin cancer animal models: a systematic review. Polim Med. 2024;54(2):105–111. doi: 10.17219/pim/189406
[42] Houghton CA, Fassett RG, Coombes JS. Sulforaphane and other nutrigenomic Nrf2 activators: can the clinician's expectation be matched by the reality? Oxid Med Cell Longev. 2016;2016(1):7857186. doi: 10.1155/2016/7857186
[43] Ma Q. Role of nrf2 in oxidative stress and toxicity. Annu Rev Pharmacol Toxicol. 2013;53(1):401–426. doi: 10.1146/annurev-pharmtox-011112-140320
[44] Malakoutikhah Z, Mohajeri Z, Dana N, et al. The dual role of Nrf2 in melanoma: a systematic review. BMC Mol Cell Biol. 2023;24(1):5. doi: 10.1186/s12860-023-00466-5
[45] Dinkova-Kostova AT, Jenkins SN, Fahey JW, et al. Protection against UV-light-induced skin carcinogenesis in SKH-1 high-risk mice by sulforaphane-containing broccoli sprout extracts. Cancer Lett. 2006;240(2):243–252. doi: 10.1016/j.canlet.2005.09.012
[46] Li S, Yang Y, Sargsyan D, et al. Epigenome, transcriptome, and protection by sulforaphane at different stages of UVB-induced skin carcinogenesis. Cancer Prev Res (Phila). 2020;13(6):551–562. doi: 10.1158/1940-6207.CAPR-19-0522
[47] Misiewicz I, Skupinska K, Kasprzycka-Guttman T. Sulforaphane and 2-oxohexyl isothiocyanate induce cell growth arrest and apoptosis in L-1210 leukemia and ME-18 melanoma cells. Oncol Rep. 2003;10(6):2045–2050. doi: 10.3892/or.10.6.2045
[48] Kim SJ, Kim BS, Kyung TW, et al. Suppressive effects of young radish cultivated with sulfur on growth and metastasis of B16-F10 melanoma cells. Arch Pharm Res. 2006;29(3):235–240. doi: 10.1007/BF02969399
[49] Hamsa TP, Thejass P, Kuttan G. Induction of apoptosis by sulforaphane in highly metastatic B16F-10 melanoma cells. Drug Chem Toxicol. 2011;34(3):332–340. doi: 10.3109/01480545.2010.538694
[50] Rudolf K, Cervinka M, Rudolf E. Sulforaphane-induced apoptosis involves p53 and p38 in melanoma cells. Apoptosis. 2014;19(4):734–747. doi: 10.1007/s10495-013-0959-7
[51] Ng LL. Psychological aspects of rheumatic diseases. Singapore Med J. 1992;33(1):79–81.
[52] Arcidiacono P, Ragonese F, Stabile A, et al. Antitumor activity and expression profiles of genes induced by sulforaphane in human melanoma cells. Eur J Nutr. 2018;57(7):2547–2569. doi: 10.1007/s00394-017-1527-7
[53] Mitsiogianni M, Trafalis DT, Franco R, et al. Sulforaphane and iberin are potent epigenetic modulators of histone acetylation and methylation in malignant melanoma. Eur J Nutr. 2021;60(1):147–158. doi: 10.1007/s00394-020-02227-y
[54] Thejass P, Kuttan G. Modulation of cell-mediated immune response in B16F-10 melanoma-induced metastatic tumor-bearing C57BL/6 mice by sulforaphane. Immunopharmacol Immunotoxicol. 2007;29(2):173–186. doi: 10.1080/08923970701511728
[55] Thejass P, Kuttan G. Antimetastatic activity of sulforaphane. Life Sci. 2006;78(26):3043–3050. doi: 10.1016/j.lfs.2005.12.038
[56] Etienne-Manneville S, Hall A. Rho GTPases in cell biology. Nature. 2002;420(6916):629–635. doi: 10.1038/nature01148
[57] Carlberg M, Dricu A, Blegen H, et al. Mevalonic acid is limiting for N-linked glycosylation and translocation of the insulin-like growth factor-1 receptor to the cell surface. Evidence for a new link between 3-hydroxy-3-methylglutaryl-coenzyme a reductase and cell growth. J Biol Chem. 1996;271(29):17453–17462. doi: 10.1074/jbc.271.29.17453
[58] Resnicoff M, Coppola D, Sell C, et al. Growth inhibition of human melanoma cells in nude mice by antisense strategies to the type 1 insulin-like growth factor receptor. Cancer Res. 1994;54(18):4848–4850.
[59] Stracke ML, Kohn EC, Aznavoorian SA, et al. Insulin-like growth factors stimulate chemotaxis in human melanoma cells. Biochem Biophys Res Commun. 1988;153(3):1076–1083. doi: 10.1016/s0006-291x(88)81338-x
[60] Dricu A, Wang M, Hjertman M, et al. Mevalonate-regulated mechanisms in cell growth control: role of dolichyl phosphate in expression of the insulin-like growth factor-1 receptor (IGF-1R) in comparison to Ras prenylation and expression of c-myc. Glycobiology. 1997;7(5):625–633. doi: 10.1093/glycob/7.5.625
[61] Alupei MC, Licarete E, Cristian FB, et al. Cytotoxicity of lipophilic statins depends on their combined actions on HIF-1alpha expression and redox status in B16.F10 melanoma cells. Anticancer Drugs. 2014;25(4):393–405. doi: 10.1097/CAD.0000000000000065
[62] Maj M, Czajkowski R, Zegarska B, et al. Anti-proliferative and cytotoxic activity of rosuvastatin against melanoma cells. Postepy Dermatol Alergol. 2016;33(4):257–262. doi: 10.5114/ada.2016.61601

[63] Shellman YG, Ribble D, Miller L, et al. Lovastatin-induced apoptosis in human melanoma cell lines. Melanoma Res. 2005;15(2):83–89. doi: 10.1097/00008390-200504000-00001
[64] Favero GM, M FO, Oliveira KA, et al. Simvastatin impairs murine melanoma growth. Lipids Health Dis. 2010;9(1):142. doi: 10.1186/1476-511X-9-142
[65] Ivanov VN, Hei TK. Regulation of apoptosis in human melanoma and neuroblastoma cells by statins, sodium arsenite and TRAIL: a role of combined treatment versus monotherapy. Apoptosis. 2011;16(12):1268–1284. doi: 10.1007/s10495-011-0649-2
[66] Saito A, Saito N, Mol W, et al. Simvastatin inhibits growth via apoptosis and the induction of cell cycle arrest in human melanoma cells. Melanoma Res. 2008;18(2):85–94. doi: 10.1097/CMR.0b013e3282f60097
[67] Zanfardino M, Spampanato C, De Cicco R, et al. Simvastatin reduces melanoma progression in a murine model. Int J Oncol. 2013;43(6):1763–1770. doi: 10.3892/ijo.2013.2126
[68] Mills CN, Joshi SS, Niles RM. Expression and function of hypoxia inducible factor-1 alpha in human melanoma under non-hypoxic conditions. Mol Cancer. 2009;8(1):104. 17 doi: 10.1186/1476-4598-8-104
[69] Collisson EA, Kleer C, Wu M, et al. Atorvastatin prevents RhoC isoprenylation, invasion, and metastasis in human melanoma cells. Mol Cancer Ther. 2003;2(10):941–948.
[70] Clark EA, Golub TR, Lander ES, et al. Genomic analysis of metastasis reveals an essential role for RhoC. Nature. 2000;406(6795):532–535. doi: 10.1038/35020106
[71] Tsubaki M, Takeda T, Kino T, et al. Statins improve survival by inhibiting spontaneous metastasis and tumor growth in a mouse melanoma model. Am J Cancer Res. 2015;5(10):3186–3197.
[72] Sarrabayrouse G, Synaeve C, Leveque K, et al. Statins stimulate in vitro membrane FasL expression and lymphocyte apoptosis through RhoA/ROCK pathway in murine melanoma cells. Neoplasia. 2007;9(12):1078–1090. doi: 10.1593/neo.07727
[73] Depasquale I, Wheatley DN. Action of Lovastatin (Mevinolin) on an in vitro model of angiogenesis and its co-culture with malignant melanoma cell lines. Cancer Cell Int. 2006;6(1):9. doi: 10.1186/1475-2867-6-9
[74] Holick MF. Vitamin D deficiency. N Engl J Med. 2007;357(3):266–281. doi: 10.1056/NEJMra070553
[75] Ebert R, Schütze N, Adamski J, et al. Vitamin D signaling is modulated on multiple levels in health and disease. Mol Cell Endocrinol. 2006;248(1–2):149–159. doi: 10.1016/j.mce.2005.11.039
[76] Mizwicki MT, Bula CM, Bishop JE, et al. New insights into Vitamin D sterol-VDR proteolysis, allostery, structure-function from the perspective of a conformational ensemble model. J Steroid Biochem Mol Biol. 2007;103(3-5):243–262. doi: 10.1016/j.jsbmb.2006.12.004
[77] Slominski AT, Kim TK, Shehabi HZ, et al. In vivo production of novel vitamin D2 hydroxy-derivatives by human placentas, epidermal keratinocytes, Caco-2 colon cells and the adrenal gland. Mol Cell Endocrinol. 2014;383(1–2):181–192. doi: 10.1016/j.mce.2013.12.012
[78] Slominski AT, Kim TK, Shehabi HZ, et al. In vivo evidence for a novel pathway of vitamin D(3) metabolism initiated by P450scc and modified by CYP27B1. Faseb J. 2012;26(9):3901–3915. doi: 10.1096/fj.12-208975
[79] Slominski AT, Kim TK, Li W, et al. The role of CYP11A1 in the production of vitamin D metabolites and their role in the regulation of epidermal functions. J Steroid Biochem Mol Biol. 2014;144(Pt A):28–39. doi: 10.1016/j.jsbmb.2013.10.012
[80] Szyszka P, Zmijewski MA, Slominski AT. New vitamin D analogs as potential therapeutics in melanoma. Expert Rev Anticancer Ther. 2012;12(5):585–599. doi: 10.1586/era.12.40
[81] Stumpf WE, Sar M, Reid FA, et al. Target cells for 1,25-dihydroxyvitamin D3 in intestinal tract, stomach, kidney, skin, pituitary, and parathyroid. Science. 1979;206(4423):1188–1190. 7 doi: 10.1126/science.505004
[82] Colston K, Colston MJ, Feldman D. 1,25-Dihydroxyvitamin D3 and malignant melanoma: the presence of receptors and inhibition of cell growth in culture. Endocrinology. 1981;108(3):1083–1086. doi: 10.1210/endo-108-3-1083
[83] Milde P, Hauser U, Simon T, et al. Expression of 1,25-dihydroxyvitamin D3 receptors in normal and psoriatic skin. J Invest Dermatol. 1991;97(2):230–239. doi: 10.1111/1523-1747.ep12480255
[84] White JH. Profiling 1,25-dihydroxyvitamin D3-regulated gene expression by microarray analysis. J Steroid Biochem Mol Biol. 2004;89–90(1–5):239–244. doi: 10.1016/j.jsbmb.2004.03.074
[85] Lehmann B. Role of the vitamin D3 pathway in healthy and diseased skin–facts, contradictions and hypotheses. Exp Dermatol. 2009;18(2):97–108. doi: 10.1111/j.1600-0625.2008.00810.x
[86] Bikle D. Nonclassic actions of vitamin D. J Clin Endocrinol Metab. 2009;94(1):26–34. doi: 10.1210/jc.2008-1454
[87] Brozyna AA, Jozwicki W, Janjetovic Z, et al. Expression of the vitamin D-activating enzyme 1alpha-hydroxylase (CYP27B1) decreases during melanoma progression. Hum Pathol. 2013;44(3):374–387.
[88] Newton-Bishop JA, Davies JR, Latheef F, et al. 25-Hydroxyvitamin D2/D3 levels and factors associated with systemic inflammation and melanoma survival in the Leeds Melanoma Cohort. Int J Cancer. 2015;136(12):2890–2899.
[89] Timerman D, McEnery-Stonelake M, Joyce CJ, et al. Vitamin D deficiency is associated with a worse prognosis in metastatic melanoma. Oncotarget. 2017;8(4):6873–6882. 24 doi: 10.18632/oncotarget.14316
[90] Brożyna AA, Jozwicki W, Janjetovic Z, et al. Expression of vitamin D receptor decreases during progression of pigmented skin lesions. Hum Pathol. 2011;42(5):618–631. doi: 10.1016/j.humpath.2010.09.014
[91] Brożyna AA, Jóźwicki W, Slominski AT. Decreased VDR expression in cutaneous melanomas as marker of tumor progression: new data and analyses. Anticancer Res. 2014;34(6):2735–2743.
[92] Frampton RJ, Omond SA, Eisman JA. Inhibition of human cancer cell growth by 1,25-dihydroxyvitamin D3 metabolites. Cancer Res. 1983;43(9):4443–4447.

[93] Yudoh K, Matsuno H, Kimura T. 1alpha,25-dihydroxyvitamin D3 inhibits in vitro invasiveness through the extracellular matrix and in vivo pulmonary metastasis of B16 mouse melanoma. J Lab Clin Med. 1999;133(2):120–128. doi: 10.1016/s0022-2143(99)90004-5

[94] Shariev A, Painter N, Reeve VE, et al. PTEN: A novel target for vitamin D in melanoma. J Steroid Biochem Mol Biol. 2022;218:106059. doi: 10.1016/j.jsbmb.2022.106059

[95] Danielsson C, Fehsel K, Polly P, et al. Differential apoptotic response of human melanoma cells to 1 alpha,25-dihydroxyvitamin D3 and its analogues. Cell Death Differ. 1998;5(11):946–952. doi: 10.1038/sj.cdd.4400437

[96] Essa S, Denzer N, Mahlknecht U, et al. VDR microRNA expression and epigenetic silencing of vitamin D signaling in melanoma cells. J Steroid Biochem Mol Biol. 2010;121(1–2):110–113. doi: 10.1016/j.jsbmb.2010.02.003

[97] Reichrath J, Rech M, Moeini M, et al. In vitro comparison of the vitamin D endocrine system in 1,25(OH)2D3-responsive and -resistant melanoma cells. Cancer Biol Ther. 2007;6(1):48–55. doi: 10.4161/cbt.6.1.3493

[98] Seifert M, Rech M, Meineke V, et al. Differential biological effects of 1,25-dihydroxyVitamin D3 on melanoma cell lines in vitro. J Steroid Biochem Mol Biol. 2004;89–90(1–5):375–379. doi: 10.1016/j.jsbmb.2004.03.002

[99] Cotter MA, Thomas J, Cassidy P, et al. *N*-acetylcysteine protects melanocytes against oxidative stress/damage and delays onset of ultraviolet-induced melanoma in mice. Clin Cancer Res. 2007;13(19):5952–5958. doi: 10.1158/1078-0432.CCR-07-1187

[100] Le Gal K, Ibrahim MX, Wiel C, et al. Antioxidants can increase melanoma metastasis in mice. Sci Transl Med. 2015;7(308):308re8. doi: 10.1126/scitranslmed.aad3740

[101] Piskounova E, Agathocleous M, Murphy MM, et al. Oxidative stress inhibits distant metastasis by human melanoma cells. Nature. 2015;527(7577):186–191. doi: 10.1038/nature15726

[102] Elmets CA, Slominski A, Athar M. The challenge of melanoma chemoprevention. Cancer Prev Res (Phila). 2022;15(2):71–74. doi: 10.1158/1940-6207.CAPR-21-0595