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Research Article

Effects of Phytochemicals in Attenuating Melanoma: A Comprehensive Literature Review

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Abstract

Melanoma is an aggressive form of skin cancer associated with a low survival rate, high mortality, poor quality of life, and incidence that has risen significantly in the last few decades. While surgery, radiation, and chemotherapy drugs are available as treatment choices, melanoma still has an unfavorable clinical outcome. This can be related to the metastatic potential and heterogeneity of melanoma and to the multitude of adverse effects (AEs) that are caused by chemotherapy, the most common of which are alopecia, nausea, changes in taste and appetite, fatigue, vomiting, dry mouth, and constipation. The recent decade has seen a rise in the trend of studies using plant-derived phytochemicals in vivo and in vitro studies, which have demonstrated anti-tumor activity along with the added benefit of significantly lower AEs. These secondary metabolites of plants like chlorogenic acid, rosmarinic acid, palmatine, berberine, quercetin, myricadiol, and other phytochemicals found in natural sources like *Marrubium lutescens*, *Berberis pruinosa*, *Lannea coromandelica*, *Orbea variegata*, and *Galium verum*, among others, are now gaining considerable importance for use against melanoma. Related studies were collected through a literature review and are discussed in this article.

Keywords: Melanoma, phytochemicals, chlorogenic acid, rosmarinic acid, palmatine, berberine, quercetin, myricadiol

1. Introduction

Melanoma is the malignant neoplasm of melanocytes (Ali Khani et al. 2023). These are cells that secrete the pigment melanin, which gives the skin its color and protects it from the deteriorating effects of ultraviolet (UV) radiation, which is important as UV exposure is thought to be a major cause of skin cancer in many cases (Rashid, Shaughnessy, and Tsao 2023). Epidemiological data taken from published literature depict the global burden of melanoma, emphasizing its rising incidence and high mortality relative to other skin cancers. Melanoma has been responsible for roughly 57,000 deaths in 2020, accounting for 80% of all skin cancer deaths. In Europe, roughly 150000 patients get diagnosed with melanoma each year, and roughly 25000 of them die of it (Nurla and Forsea 2024). In the US alone, roughly 106,000 new cases were seen in 2021, making it the 5th leading cancer diagnosis of that year. The US has seen a 320% rise in melanoma since 1975. The 5-year survival seen from 2011 to 2017 in the US was 30% for stage 4, 68% for stage 3, and 99.4% for stage 1 or 2 melanoma (Saginala et al. 2021). This high mortality and limited treatment response can be attributed to factors like metastatic potential and heterogeneity of the tumor (Ng, Simmons, and Boyle 2022).

The current management of melanoma involves the surgical excision of the primary tumor, and in invasive cases, sentinel lymph node biopsy for proper staging of the disease (Garbe et al. 2022). If the disease is resected and classified as high risk

(stage IIB-IV), adjuvant systemic therapy will be offered, which includes anti-PD-1 immunotherapy (nivolumab or pembrolizumab) or targeted therapy (BRAF/MEK inhibitors dabrafenib plus trametinib) for BRAF V600 tumors (Marquez-Rodas et al. 2024; Eggermont et al. 2022). Recently, in resectable clinical stage IIIB-IV melanoma, neoadjuvant systemic therapy was recommended with immune therapy (pembrolizumab or nivolumab/ipilimumab) before surgical intervention (Swetter et al. 2021; Blank et al. 2024). In the case of unresectable or metastatic disease, the first line systemic therapy will incorporate strong immune therapies, either anti-PD-1 as a monotherapy, or anti-PD-1 plus anti-CTLA-4 or anti-LAG-3 combination therapy as the initial first line management (Garbe et al. 2025). Targeted therapy with BRAF/MEK inhibitors is pursued as either a primary first line option or a subsequent option for BRAF V600 mutant disease (Haist et al. 2022). In melanoma, multiple drugs such as ipilimumab (anti-CTLA-4), nivolumab (anti-PD-1), Tebentafusp (target gp100), Dabrafenib (target BRAF), Trametinib (target MEK1 and MEK2), Relatlimab (target LAG-3) are used which are mentioned in standard guidelines (Almoussalam and Zhu 2016; Faghfuri et al. 2015; Staeger et al. 2025; Hoffner and Benchich 2018). However, such options give low response rates and median overall survival especially in advanced stages of the disease as observed in published literature (Gaughan and Horton 2022; Galus et al. 2025; Goldinger et al. 2022). Many chemotherapeutic drugs such as Temozolomide and Dacarbazine are limited by their poor physicochemical and pharmacokinetic properties such as low stability, low water solubility and rapid metabolism (Lopes et al. 2022; Ahad et al. 2022; Almoussalam and Zhu 2016). These drugs in general cause a multitude of adverse effects (AEs) which in most cases are alopecia, constipation, changes in taste and appetite, fatigue, vomiting, and nausea but also include other AEs specific to the drug or combination used (Seth et al. 2020; Boutros et al. 2024; Altun and Sonkaya 2018).

Phytochemicals, which are secondary metabolites obtained from plant material, have proven anti-cancer, anti-proliferative, and anti-inflammatory properties and have shown great potential in reducing the progression of skin cancer (Penta et al. 2018). Phytochemicals are gaining considerable importance for use against melanoma, which is evident from the rise in number of research articles in recent years (Tabolacci et al. 2023). The benefit of phytochemicals is that they have significantly lower AEs when compared with conventional chemotherapy. Herbal medicine, however, can also cause AEs especially when they are not prepared for the standards of allopathic medicine. Furthermore, phytochemicals, due to their varied lipophilic and hydrophilic properties, contribute to rapid degradation, low bioavailability, metabolic instability, and insufficient absorption, which ultimately lowers therapeutic efficacy. In addition, limited mechanistic understanding restricts patient stratification, and limited preclinical and clinical testing restricts the translation of phytochemicals into effective therapies for humans (Kim et al. 2025). The primary objective of this review is to explore the anti-neoplastic potential of such biological constituents for the purpose of managing skin cancer. In pursuit of this objective, a comprehensive review of the existing literature was conducted to evaluate the effects of phytochemicals on melanoma in vitro and in vivo. Furthermore, the review provides a discussion on the etiological and pathophysiological insights of melanoma, evaluates the limitations of current therapeutic options, and presents the selected studies in a tabulated format.

2. Classification, Etiology, and Pathophysiological Insights of Melanoma

2.1. Classification

WHO classifies melanoma on the basis of sun damage with emphasis on genetic hallmarks and divides melanoma into nine distinct groups,

which include low cumulative sun damage (CSD) melanoma, high-CSD melanoma, desmoplastic melanoma, melanoma arising in congenital nevus, malignant Spitz tumor, acral melanoma, nodular melanoma, mucosal melanoma, which develops in blue nevus, and uveal melanoma (Ferrara and Argenziano 2021). Genetic mutations identified in melanoma include those in *BRAF, NF1* and *NRAS* (Samlowski 2024), *NFKBIE* promoter mutations, activating mutations in the *MAPK* pathway like *MAP2K1* (Zob et al. 2022), kinase fusions in *NTRK3, NTRK1, RET, MET, ALK* and *ROS1* (Olmedo et al. 2022), *MAP3K8* truncating/fusions mutation (Sibira et al. 2024), *CDKN2A* homozygous deletion (Kreuger et al. 2023), *TERT* promoter mutation, *TERT, KIT and CCND1* amplification (Broit et al. 2022), *EIF1AX, SF3B1* and *BAP1* mutations (Skrehot, Alsoudi, and Schefler 2025), mutations initiating in the Gαq signaling pathway like *PLCB4*, *GNA11*, *CYSLTR2* and *GNAQ* (Akin-Bali 2021) and chromosome 8q gain (Delgado-Bellido et al. 2025).

Melanoma is usually seen on the skin but is found on mucosal surfaces like the uveal tract of the eye, oral cavity, upper gastrointestinal (GI) tract, leptomeninges, and genital mucosa. Melanoma that spreads to the skin, lymphatic vessels, or lymph nodes is referred to as regional metastasis. It includes satellite metastases that are seen within 2 cm of the original tumor, in-transit metastasis showing spread of tumor to lymphatic vessels or blood capillaries, and nodal metastasis showing the invasion of tumor to the lymph nodes (Zbytek et al. 2008). Cutaneous melanomas are grouped in accordance with their growth patterns. Superficial spreading melanoma, seen in 57% of patients, is the most prevalent. Within the epidermis, melanocytes with pagetoid spread are confined in an irregular pattern. This is seen on the skin as a network of brown dots having pseudopods with a blue/red coloration or depigmentation. Nodular melanoma is found in 21% of patients. It is seen as individual grey/blue colored globules containing asymmetric vessels and white streaks. Lentigo maligna melanoma is found in 9% of cases. It contains irregular follicular hyperpigmented openings outsized by asymmetric colored dots. Elastosis and epidermal atrophy are observed on the skin due to the growth of individual tumor cells within the adnexal structures of epithelium and epidermis. The least common acral lentiginous melanoma is observed in 4% of individuals. Multiple hypopigmented regions are seen in brown to grey colored asymmetric polygonal shapes. Melanocytes are seen alone or in groups spreading within the basal layer of hyperplastic dermis (Caraban et al. 2024). Non-cutaneous melanomas are less prevalent and can be present in areas harboring melanocytes. These include uveal melanoma, which is seen in the choroid, ciliary body, or iris of the eye's uvea, and mucosal melanoma seen in the mucosal surfaces of the nasal cavity, oral cavity, sinuses, and genitals (Vergara et al. 2022; Kibbi, Kluger, and Choi 2016). Mucosal melanoma is grouped into genomic subtypes such as *NF1*, *NRAS*, and *BRAF*, which arise from benign lesions after mutations such as loss of *CDKN2A*, *PTEN*, and *TP53*. In contrast, *BRAF*, *SPRED1*, *NF1*, *KIT*, *SF3B1*, and *NRAS* mutations are observed in uveal melanoma (Ma et al. 2021).

2.2. Etiology

Numerous risk factors contribute to the development of melanoma. Studies have revealed that excessive and prolonged exposure to sunlight or indoor tanning leads to inflammation, oxidative stress, and DNA damage in the skin. People with a family history of melanoma, those with lighter skin tones (which indicate lower levels of melanin), and those who frequently suntan are at much greater risk of UV skin damage and melanoma (Tang et al. 2024). Melanoma is prevalent in fair-skinned individuals due to the interplay of MC1R signaling and cysteine, which regulate the production of dark brown eumelanin and red to orange pheomelanin, two forms of melanin produced by melanocytes (Flanagan et al. 2000). Pheomelanin induces oxidative stress via the production of reactive oxygen species (ROS) and depletion of antioxidants (Morgan, Lo, and

Fisher 2013). The presence of an unusual number of dysplastic nevi has been associated with melanoma. In nevus-associated melanomas, a higher nevus count and thickness of sporadic dysplastic nevi are linked to age and intermittent exposure to UV radiation (Dessinioti et al. 2022).

2.3. Pathophysiology

Our current understanding of genetic predisposition and molecular basis has helped us identify relevant genes responsible for melanoma, such as RB1, CDK4/6, and CDKN2A encoding for two proteins, p14/ARF and p16/INK4a (Nelson and Tsao 2009). Histologic changes in melanoma progression and their link to specific genetic mutations, showing their impact on molecular signalling, can be seen using the Clark model (Scolyer, Long, and Thompson 2011). This model offers a structure for understanding the multi-stage development of non-chronic sun-damaged melanomas primarily found in Caucasian populations, from a benign lesion to invasive cancer. Using this model, specific histopathological stages are correlated to the described sequential genetic and molecular changes, focusing on pathways of importance that could become therapeutic targets, including phytochemical approaches.

2.3.1. Formation of Benign Nevus

Normal melanocytes in the skin proliferate, forming benign nevi. These are dark brownish, elevated or flat lesions in which the color is either uniformly distributed or present in the form of pigmented dots. Histological examination shows multiple nested melanocytes in the basal layer of these lesions (Miller and Mihm Jr 2006). This phase generally starts with the acquisition of an oncogenic driver mutation, typically a BRAF V600E, which is an important first step to melanocytic neoplasia. However, continued BRAF V600E expression in normal melanocytes induces oncogene-induced senescence, a cell-cycle arrest mechanism. This is associated with the induction of $p16^{INK4a}$ and acidic β-galactosidase activity that helps to maintain tumor size and its benign behavior (Yu et al. 2009; Mackiewicz-Wysocka et al. 2017). Most melanocytic nevi resulting from BRAF V600 mutations do not progress to melanoma. This is attributed to tumor-suppressive mechanisms, most notably, oncogene-induced senescence, which in melanocytic nevi leads to growth arrest and suppression of tumor (Damsky and Bosenberg 2017).

2.3.2. Development of Dysplastic Nevi

Next begins the abnormal development, plus a benign nevus at a prior or new area. These nevi develop into thicker, multicolored lesions with irregular or asymmetric borders. Irregular, sporadic cytologic atypia are seen in histological studies. At this phase, the melanocyte must move out of senescence (Goldstein and Tucker 2013). The main molecular abnormality that allows the cell to escape senescence is a change or inactivation of the $p16^{INK4a}$-retinoblastoma (Rb) pathway. This change frequently includes the inactivation of the *CDKN2A* gene, which encodes $p16^{INK4a}$ and $p19^{ARF}$. Evidence for the mutation includes frequent loss of heterozygosity at the *CDKN2A* locus or rare mutations in the *CDKN2A* gene in sporadic dysplastic nevus (Gray-Schopfer et al. 2006; Shain et al. 2015).

2.3.3. Radial-Growth Phase

Following intraepidermal proliferation of cells, the lesions in the radial-growth phase (RGP) become raised, and continuous atypia is presented as cytomorphologic cancer. Tumor cells can further proliferate either alone or in a group into the papillary dermis (Paluncic et al. 2016). To transition into this stage, the progressively proliferating melanocytes must become immortalized to escape replicative senescence, which is conferred by telomerase reverse transcriptase (TERT) activation. It is presumed that external factors (likely keratinocyte products) are required for RGP cells to survive, and thus their growth is limited to the upper layers of skin, adjacent to the epidermis (Takata, Murata, and Saida 2010). Aberrant TERT activation can often be attributed to TERT promoter mutations that generate binding motifs for transcription factors

Table 1: Comparison of efficacy outcomes, toxicity profiles, and specific biomarker requirements across targeted therapies, immune checkpoint inhibitors, and bispecific molecules used to treat different subtypes of advanced melanoma.

Drug	Target/ Class	Specific Biomarker	Efficacy	Major Toxicities	Key Limitations	Ref.
Ipilimumab Monotherapy	Fully human mAb blocking CTLA-4	None required for enrollment; studies ongoing to identify predictive biomarkers.	Phase II study (CA184-008). ORR: 5.8%. Median OS: 10.2 months. 2-year survival rate: 32.8%.	AEs were largely immune related, primarily in the skin and GI tract. 19% grade 3 and 3.2% grade AEs.	Response kinetics differ from chemotherapy, requiring specific response criteria. No pre-treatment marker exists to predict response.	(O'Day et al. 2010)
Ribociclib + Binimetinib	Ribociclib (selective CDK4/6 inhibitor) + Binimetinib (selective MEK inhibitor)	NRAS-mutant melanoma. Enhanced efficacy noted with concurrent alterations in CDKN2A, CDK4, or CCND1.	Phase I-b/II study. ORR: 19.5%. ORR with cell-cycle alterations: 32.5%. Median PFS: 3.7 months. Median OS: 11.3 months.	Common treatment-related toxicities included creatine phosphokinase elevation, rash, edema, anemia, nausea, diarrhea, and fatigue. Increased CPK, AST, and ALT elevations were the most common Grade 3/4 AEs.	Genomic analyses were descriptive and exploratory. The recommended Phase II dose; Ribociclib exposure was much lower than the label monotherapy dose.	(Schuler et al. 2022)
Tebentafusp	First-in-class T-cell receptor–bispecific molecule. Targets glycoprotein 100 (gp100) and CD3.	HLA-A*02:01–positive. Patients must have previously untreated unresectable or metastatic uveal melanoma	Phase 3 trial. Median OS: 21.6 months (vs. 16.9 months for control). 3-year survival Rate: 27% (vs. 18% for control). ORR: 11% (vs. 5% for control). Median PFS: 3.4 months (vs. 2.9 months for control).	Overall incidence of any grade AEs: 99%. Grade 3–4 AEs incidence: 50%. High incidence of Cytokine Release Syndrome (CRS) (80% any grade). Low discontinuation rate due to AEs (1%).	Most common AEs (any grade): rash (83%), pyrexia (76%), pruritus (70%), and hypotension (38%). Cytokine Release Syndrome (CRS) occurred in 89% (mostly Grade 1/2). Grade 3/4 AEs occurred in 47% of patients, commonly rash (19%) and elevated AST (6%). Low discontinuation rate due to AEs (2%).	(Hassel et al. 2023)
Pembrolizumab Monotherapy	Anti-PD-1 agent (Immune Checkpoint Inhibitor).	Non-uveal, unresectable stage III/IV melanoma.	Cohort study. Median OS (1st line): 32.6 months. ORR (1st line): 49%. Median real-world PFS (1st line): 4.7 months.	Toxicities were not examined in this specific real-world study.	Effectiveness appears lower in later lines (median OS 14.4 months for 2nd line, 9.3 months for 3rd line).	(Casarotto et al. 2021)
Nivolumab Monotherapy	Anti-PD-1 immune checkpoint inhibitor.	High Neutrophil-to-Lymphocyte Ratio and presence of liver metastases predicted poor OS outcome in this study.	Real-World Retrospective study in first line metastatic melanoma. Median PFS: 26 months. Median OS: 31 months. 2-year OS: 62.5%.	Most common AEs were dermatological (23.5%) and endocrinological (15.6%). Grade 3 AEs occurred in 6.8% of patients.	Retrospective design, small patient cohort (N=51), and selection bias. Potential for incomplete data or underreporting of adverse events.	(Afrăsânie et al. 2023)
Dabrafenib + Trametinib	Dabrafenib (BRAF inhibitor) + Trametinib (MEK inhibitor).	BRAF V600-mutant metastatic malignant melanoma (specifically BRAF V600E).	Case reported achieved long-term Complete Metabolic Remission (CR) after 7 months. Contextual trial data: 5-year OS: 28%; ORR: 76%.	Combination therapy is generally well tolerated. Common AEs reported include diarrhea, anorexia, nausea, and vomiting. Case reported modest Grade 1–2 cutaneous	Acquired resistance is common, evidenced by a strong decline in mean survival curves after about 6 months of	(Brugnara et al. 2018)

				and mucosal side effects.	treatment. Lack of clear guidelines on safely discontinuing treatment after CR.	
Dabrafenib Monotherapy	BRAF inhibitor targeting the MAPK pathway.	BRAF V600E mutation.	Case achieved maintenance of radiological response (stable disease/partial reduction of lesions) for 7.1 months. Patients survived for 15 months.	Minimal toxicity, including beard alopecia and milium cysts.	Patients with the BRAF V600 mutation have been systematically excluded from most pivotal trials. Clinical evidence is primarily limited to case reports and small series.	(Casadevall et al. 2016)

Abbreviations: OS (Overall Survival), ORR (Objective Response Rate), PFS (Progression-free Survival).

that enhance TERT transcriptional activity (Heidenreich et al. 2014). Invasion into the deeper layers is primarily restricted due to the regulatory mechanisms involving cell-to-cell adhesion molecules and integrity of the basement membrane (Ciarletta, Foret, and Ben Amar 2011).

2.3.4. Vertical-Growth Phase

Moving to the vertical-growth phase, these lesions proliferate into the papillary dermis, forming an expanded nodule. Tumor cells may extend lower into the reticular dermis and fat region. Further tumor progression requires additional genetic or epigenetic hits that suppress apoptosis, allowing the cells to survive independently of keratinocytes. The primary genetic events seen at this stage include the loss of *PTEN* (which inhibits apoptosis via AKT activation) and RAS activation (Parkman et al. 2025). Phenotypically, progression is marked by the loss of E-cadherin and the aberrant expression of αVβ3 integrin and N-cadherin (Arias-Mejias et al. 2020). The diminished expression of microphthalmia-associated transcription factor (MITF) causes the cells to switch from the differentiated, melanocytic phenotype to a less differentiated, motile state (Huang et al. 2021). Increased activity of matrix metalloproteinases (MMPs) leads to the degradation of the extracellular matrix, allowing deeper penetration into the dermal tissue (Napoli et al. 2020). Tumor cells at this stage can be used for tumor studies in nude mouse models. The reduction of TRPM1, increased expression of MMP-2, αVβ3 integrin, and N-cadherin, and loss of E-cadherin can be seen during both the vertical-growth phase and metastatic melanoma phase (Wagstaff et al. 2022).

2.3.5. Metastatic Melanoma

Melanoma spreads to regional in-transit lesions, lymph nodes, and distant organs. Chemotaxis and lymph flow guide the movement of melanoma cells away from their initial location. After settling, melanoma cells develop a variety of methods to defend themselves against destruction by the immune defense through strategies such as by retaining MHC class 1 polypeptide-related sequence A (MICA) intracellularly to prevent attack by natural killer (NK) cells, and by modifying oncostatin M receptor (OSMR) to resist the antiproliferative effects of cytokines (Zbytek et al. 2008; Miller and Mihm Jr 2006). Molecular markers typically observed in metastases, but not in primary tumors, are loss-of-function *CDKN2A* mutations, increased TERT promoter mutations, and genetic or epigenetic alterations targeting the *PTEN* tumor suppressor or copy number gains/overexpression of AKT3 that activate the PI3K/AKT pathway in a constitutive manner (Guo et al. 2022; Wagstaff et al. 2022). *PTEN* silencing is recognized as a molecular marker of metastatic melanoma (Vidotto et al. 2020). *KISS1* (a metastasis suppressor gene) knockout results in neoplastic proliferation after the tumor cells seed in the metastatic niche. Increased *MITF* amplification was observed in metastases as compared to primary melanomas. Increased expression of anti-apoptotic proteins (MCL1, BCL-

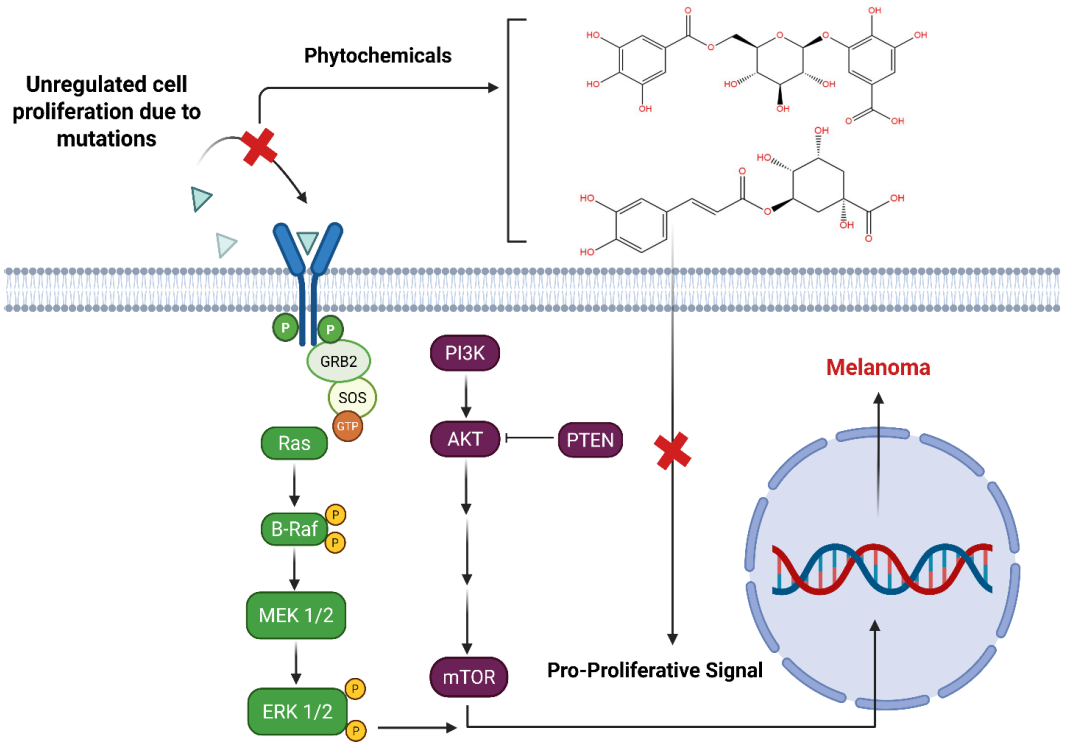

Figure 1: Schematic representation of the attenuation of the molecular pathways of melanoma through phytochemicals derived from various plant sources.

XL, survivin (*BIRC5*), XIAP) and decreased expression of BCL-2 are seen when moving from the radial to vertical growth phase. Overall, the process requires tumor cells first to dissociate from the primary tumor mass, survive the trip, and begin to proliferate within a distant niche, therefore requiring the coordinated expression of many genes. Tumor cells of this stage can grow in soft agar and are used for murine model studies (Frischhut et al. 2022).

3. Chemotherapeutic Drugs Used in Melanoma Treatment and Their Limitations

Treatment options for melanoma are provided in ASCO guidelines. HLA-A*02:01-positive uveal melanoma can be treated using tebentafusp. For cutaneous melanoma that can be surgically resected, pembrolizumab as neoadjuvant and adjuvant is recommended for stage IIB or IIC cutaneous melanoma. Adjuvant nivolumab, pembrolizumab, or a combination of dabrafenib and trametinib is used for resectable melanoma stage IIIA to IIID (the combination of dabrafenib and trametinib is used in BRAF mutant (V600E/K*) patients and not in *BRAF* wild type ones). Metastatic or non-resectable cutaneous melanoma can be dealt with options including pembrolizumab, nivolumab, a combination of relatlimab and nivolumab, and nivolumab given after combination of ipilimumab and nivolumab for BRAF wild-type, while those having BRAF-mutant (V600), nivolumab alone or combinations of cobimetinib plus vemurafenib, binimetinib plus encorafenib, trametinib plus dabrafenib, pembrolizumab plus nivolumab, relatlimab plus nivolumab, and ipilimumab after nivolumab are recommended for use (Seth et al. 2023). An overview of the safety, toxicity, and efficacy status of chemotherapeutic drugs used in melanoma treatment, as provided in guidelines, is summarized in **Table 1**.

In the management of melanoma, limitations are seen, such as unwanted AEs which can result in GI and dermatologic toxicities, and reduced drug

effectiveness as a result of drug resistance (Domingues et al. 2018). This resistance, developed either during administration of chemotherapy (acquired resistance) or present at onset (primary or intrinsic resistance) is a major issue limiting the efficacy of such drugs (Kalal, Upadhya, and Pai 2017). Molecular mechanisms such as defective drug transport through ABC efflux pumps, altered apoptotic pathway regulation (like Bcl-2 overexpression), enhanced enzymatic detoxification, and increased DNA repair activity are observed in chemoresistance (Nigam et al. 2025). This resistance and the invasive and metastatic potential of melanoma are a major reason behind treatment failure and extremely poor prognosis (Krasowska, Kurzepa, and Błaszczak 2024).

4. Phytochemicals with Anti-proliferative Effect on Melanoma Cells

The WHO reports that a significant number of the world's population uses traditional medicine to treat various ailments. These medicinal plants contain phytochemicals in their stem, leaves, roots, flowers, and grains. that exhibit significant therapeutic potential in a multitude of diseases (Sood, Choi, and Lee 2024). Furthermore, due to their minimal cost and toxicity, and use as supplements, they are worth considering for disease treatment. Multiple studies have identified phytochemicals that can be used in the treatment and prevention of metastatic melanoma, such as silymarin, capsaicin, genistein, curcumin, resveratrol, proanthocyanidins, luteolin, apigenin, fisetin, indole-3-carbinol, and epigallocatechin-3-gallate (Chandra Pal et al. 2016).

4.1. Insights from Published *in vitro* and *in vivo* Studies

Compounds that are derived from plants have demonstrated significant anti-melanoma effects in in vitro and in vivo studies. A summary of 24 studies demonstrating the anti-neoplastic effects of plant- derived phytochemicals is given in Table 2. Many phytochemicals, especially polyphenols (such as chlorogenic acid, rosmarinic acid, quercetin, catechin derivatives, and rutin), broadly impact oxidative stress, inflammation, and the activity of multiple melanoma-related proteins (such as TYRP1, MITF, and certain kinases) to consistently reduce melanoma cell viability (Nargatti and Wadkar 2024; Sarikurkcu, Erdoğmuş, and Yazar 2024; Ko et al. 2020). This is illustrated in **Figures 1** and **2**. The limited pre-clinical and clinical data regarding the safety and efficacy of these extracts highlight the need for a broader understanding of the mechanisms of multi-target effects of these phytochemicals. Extracts rich in alkaloids and terpenoids from *Berberis* species, *Cedrus atlantica*, *Corallocarpus epigaeus*, and plants that produce isoquinoline alkaloids disrupt mitochondrial function, inhibit protein synthesis, and interfere with cell-cycle regulation (Aiswarya et al. 2022; Tuzimski et al. 2024; Moyo, Mhlongo, and Sitole 2024). Multiple studies also report that these compounds amplify the effects of standard chemotherapeutic agents. For instance, extract from *Cedrus atlantica* increases the sensitivity of melanoma cells to 5-fluorouracil (5-FU) and diminishes markers of drug resistance. This is significant as the development of resistance to 5-fluorouracil, dacarbazine, and even BRAF and MEK inhibitors is a major hurdle in the treatment of melanoma. There are many phytochemicals that directly target the signaling pathways that are involved in cell survival and apoptosis, and these may also help reverse or delay resistance to treatment (Moyo, Mhlongo, and Sitole 2024).

Animal studies further support this. Extracts from plants that include *Melilotus indicus*, *Aloysia citrodora*, *Allium subhirsutum,* and *Ramalina terebrata* have all been shown to reduce tumor burden, inflammation, angiogenesis, or metastasis in mouse models (Choi et al. 2023; Badraoui et al. 2020; Rashid et al. 2022; Bashir et al. 2022). Such studies are relevant as most approved therapies, whether immune checkpoint inhibitors or targeted therapies, have efficacy but are often associated with AEs. Many reports on these phytochemicals cite far lower toxicity, although pharmacokinetic

Table 2: Summary of phytochemical constituents in plant extracts in in vivo, in vitro, and *in silico* studies demonstrating anti-melanoma activity.

Plant Source	Phytochemicals Identified	Cell Line / Model Used	Findings	References
Marrubium lutescens	Chlorogenic acid, Rosmarinic acid	G361 cells	Significant anti-tumor activity, inhibited TYRP1 and MARK4 in docking results	(Sarikurkcu, Erdoğmuş, and Yazar 2024)
Berberis pruinosa	Palmatine, Berberine	Danio rerio larvae, A375 melanoma cells	Strong cytotoxic activity (IC_{50}= 32.54 µg/mL)	(Tuzimski et al. 2024)
Lannea coromandelica	Quercetin, Myricadiol, Catechin	B16F10 melanoma cells	Potential anti-cancer activity (IC_{50} = 9.69 µg/mL), highest binding affinity for TYRP1	(Nargatti and Wadkar 2024)
Orbea variegata	Flavonoids, Tannins, Phenolic compounds	Swiss mouse model	Reduced oxidative stress, inflammation, and skin hyperplasia	(Chgari et al. 2024)
Galium verum	Isoquercitrin, Rutin, Chlorogenic acid	A375 melanoma cells	Reduced cell viability even at low concentrations (55 µg/mL)	(Semenescu et al. 2024)
Alchemilla vulgaris	Not mentioned	Fem-X, 518A2, B16F10, B16F1 melanoma cells	Suppressed tumor growth and reduced viability	(Jelača et al. 2024)
Campomanesia xanthocarpa	Epigallocatechin gallate, Ellagic acid, Rutin, Chlorogenic acid, Isoquercitrin, Kaempferol-3-O-rutinoside	SK-MEL-28 melanoma cells	Fruit infusion had stronger antineoplastic activity than leaf infusion	(da Silva et al. 2024)
Luisia tenuifolia Blume	Tannins, Flavonoids, Phenolic compounds	A431 human skin squamous carcinoma cells	Significant anti-melanoma activity (IC_{50} = 24.29 µg/mL)	(Sethuraman and Ramachandran 2024)
Kalanchoe fedtschenkoi	Gallic acid 3-O-(6′-O-galloyl)-glucopyranoside, Gallic acid 4-O-(6′-O-galloyl)-glucopyranoside, Gallic acid	MV3, B16F10 melanoma cells	Cytotoxic activity: IC_{50} = 56.6 µg/mL, 43.0 µg/mL (MV3), 66.1 µg/mL, 93.6 µg/mL (B16F10)	(Casanova et al. 2024)
Cedrus atlantica	α-cedrene, Cedrol, Cuparene, γ-muurolene, Thujopsene	B16F10 murine cells	Synergistic suppression of tumor growth and reduction in 5-FU resistance	(Gao et al. 2024)
Ocimum tenuiflorum	Methyl palmitate, Linolenic acid, Stearic acid, Palmitic acid, Myristic acid	A375 melanoma cells	IC_{50} values < 50 µg/mL, ethyl acetate extract had greater cytotoxicity	(Moyo, Mhlongo, and Sitole 2024)
Betula pendula	Lupeol, Botulin, Betulinic acid, Erythrodiol	Walker 256 carcinoma cells, B16F10 murine cells	Nanolipid complexes and Pegylated liposomes showed in vitro antitumor activity	(Rugină et al. 2024)
Melilotus indicus	Quercetin, Coumarin	DMBA-induced cancer mouse model	Significant anti-tumor activity plus multiple tumor reduction parameters	(Bashir et al. 2022)
Pseudofumaria lutea, Fumaria officinalis, Thalictrum foetidum, Macleaya cordata, Lamprocapnos spectabilis, Meconopsis cambrica	Isoquinoline alkaloids	SK-MEL-3, G-361, A375 melanoma cells	Cytotoxic activity dependent on isoquinoline alkaloid levels	(Misiurek et al. 2023)
Ramalina terebrata	1,3,7,9-tetrahydroxy-2,8-dimethyl-4,6-di[ethanoyl]dibenzofuran	B16F10 melanoma cells	Dose and time-dependent reduction of cell viability, reduced tumor growth	(Choi et al. 2023)
Aloysia citrodora	Eupatilin, 5,6,4′-Trihydroxy-7,3′-Dimethoxyflavone, 5,7-Dihydroxy-2′-Methoxyflavone, Baicalein, Hispidulin, Naringenin	MDA-MB231, Vero, EMT-6, T47D, MCF7 cell lines	Significant reduction in tumor size and undetected tumors in Balb/C mice	(Rashid et al. 2022)
Corallocarpus epigaeus	Cucurbitacin B	A375 melanoma cells, Swiss albino mice, NOD-SCID murine model	Tumor reduction and safety assessment confirmed antineoplastic activity	(Aiswarya et al. 2022)
Piper capense	Saponins, Polyphenols, Sterols, Tannins, Alkaloids	B16F10 cells, C57BL/6J mice	Cytotoxic effects in vitro and tumor size mitigation in vivo	(Wamba et al. 2021)
Allium subhirsutum	p-coumaric acid	Murine model and Walker 256/B cells	Reduced osteolytic metastases and tumor angiogenesis. IC_{50} value is roughly 150 µg/mL.	(Badraoui et al. 2020)
Dracocephalum kotschyi Boiss	Xanthomicrol (a trimethoxylated hydroxyflavone)	C57BL/6 mice + B16F10 melanoma cells	Reduced cell viability. IC_{50} = 3.433 µg/mL. Significant potential for	(Ghazizadeh et al. 2020)

			melanoma treatment is shown by the MTT assay.	
Annona squamosa	β-sitosterol, 18-oxokauran-17-yl acetate, ent-kaur-16-en-19-ol	B16F10 melanoma cell line	Anti-proliferative activity via activation of p38 and inhibition of MITF	(Ko et al. 2020)
Oenothera biennis	Rosmarinic acid, ferulic acid, epicatechin, gallic acid, coumaric acid, rutin, caffeic acid	A375 melanoma cell line	Cytotoxic effects observed at 60 µg/m;	(Fecker et al. 2020)
Moringa oleifera	Flavonoids	B16-F10 – Mouse melanoma cell lines	Significant cytotoxicity (IC_{50} of 127.12 ug/ml); Showed high apoptosis potential (67.89%);	(Umaima et al. 2025)
Sphagneticola trilobata	Terpenoids, Trilobolide-6-O-isobutyrate, and a mixture of kaurenoic acid/grandiflorenic acid.	A-431 cell line (human epidermoid skin carcinoma).	Kaurenoic acid/grandiflorenic acid exhibited stronger cytotoxicity.	(Ali et al. 2025)

studies to date are still sparse (Guven et al. 2022).

The pharmacokinetic profile is one of the limitations of current melanoma therapies. For instance, dacarbazine is poorly bioavailable, and targeted therapies require carefully planned dosing due to narrow safety margins. Immunotherapies can produce long-lasting toxicities that affect quality of life. While phytochemicals offer lower toxicity, they can suffer from issues such as poor circulation time, compromised stability, modest bioavailability, and rapid clearance (Mohapatra et al. 2022). New formulations, such as nanolipid carriers, can help address these issues and improve delivery to tumor tissue through *Betula pendula* extracts, providing therapeutic strategies.

In summary, published literature indicates multiple strengths of phytochemicals, such as their ability to act on multiple pathways at once. They have demonstrated evidence of providing a synergistic response with chemotherapeutic agents. In general, pre-clinical and clinical evidence suggest phytochemicals have lower toxicity than systemic therapy. Phytochemicals have also been shown to alter pathways against which chemotherapies are not consistently effective, such as metastasis, inflammation, and angiogenesis. This provides a strong scientific basis for the investigation of melanoma treatment and the exploration of phytochemicals as part of combination approaches, to decrease the potential for resistance with toxic agents, decrease toxicity, and broaden therapeutic options.

4.2. Limitation of Phytochemicals

Despite being considered safe to consume, herbal products can also produce AEs, urging their careful administration. The emergence of AEs can be related to factors like contamination by microbes, pollutants, or adulterants, and the use of certain plant metabolites or parts that have a toxic potential. Unlike allopathic medicine, the limited availability of clinical and toxicity data and loose regulations on manufacture reduce the safety of herbal medicine. When they are taken concomitantly with certain medicines, they may manipulate their plasma levels by inhibiting or inducing certain enzymes that play a role in the metabolism of that drug, thus decreasing their efficacy or causing AEs, especially for drugs with a low therapeutic index. The absorption of phytochemicals is compromised because of their diverse hydrophilicity and lipophilicity. They also have reduced pharmacologic activity, a high risk of degradation, and low stability. As a result, the bioavailability of phytochemicals is relatively low, thus limiting the therapeutic potential of these compounds. In addition, it is difficult to convince patients of their usage due to the limited understanding of the biological pathways of phytochemicals, which restricts translation of phytochemical models from preclinical models to practice (Kim et al. 2025). Furthermore, for approval of their use as anticancer agents in patients, phytochemicals require substantial data of efficacy, safety, and quality derived from appropriate clinical trials (Garcia-Oliveira et al. 2021).

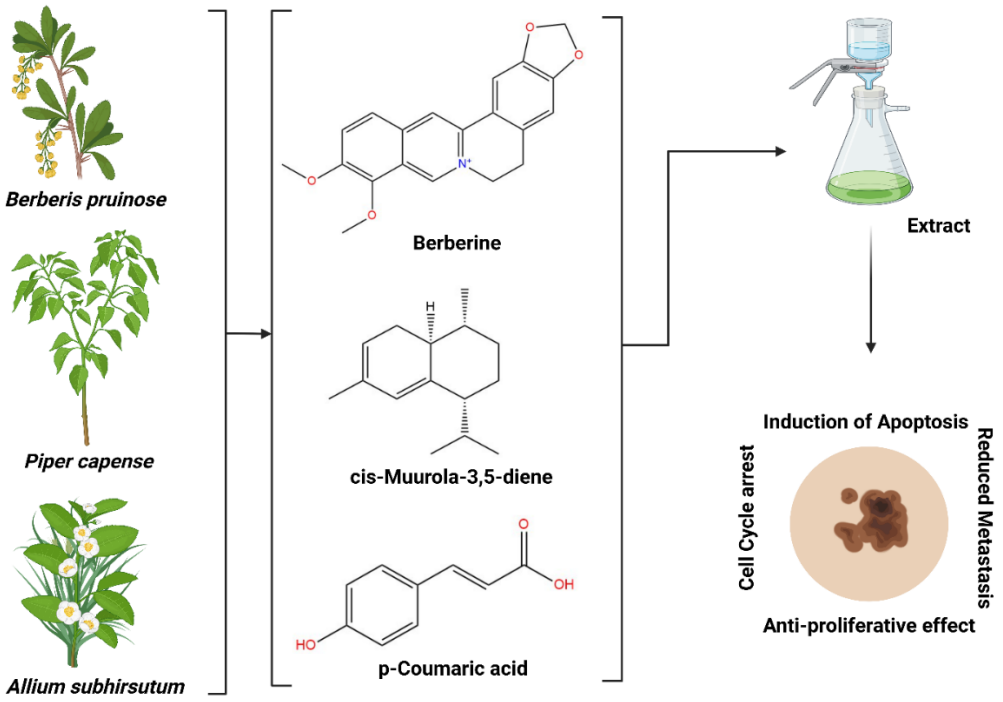

Figure 2: Schematic representation of the anti-proliferative activity of the major phytochemicals obtained from various plant extracts.

5. Conclusion

The undesirable therapeutic outcome, low survival rate, high mortality, and increasing incidence of melanoma exist despite the presence of clinical choices like radiation therapy, surgery, and chemotherapy. This is linked to the metastatic potential and heterogeneity of melanoma and the many AEs caused by chemotherapy drugs. This is the reason why phytochemicals have received focus by researchers, as evident from the increase in the quantity of scholarly articles in the last decade. This review compiled such in vivo, in vitro, and *in silico* studies to showcase the anti-proliferative potential of such plant-derived secondary metabolites against melanoma while having the benefit of being significantly safer to use in comparison to chemotherapy. However, herbal medicine should be taken following careful consideration, as it can also cause certain AEs. If we are considering the use of phytochemicals in melanoma, they must be prepared to the level of quality and regulation as allopathic medicine and must undergo clinical trials to assess their safety and clinical efficacy, find optimal dosage, investigate possible interactions between herbs and medications, and see if the preclinical benefits can be translated to patients with melanoma.

Conflict of Interest

The authors declare no competing interests.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article. Data can be available on demand.

Ethics approval and consent to participate.

Not applicable

Authors' contributions

AI designed the study and carried out most of the data-acquiring parts. MMJ and MHH performed data acquisition and search. All authors read and approved the final manuscript.

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