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Liposomal Nanocarriers and Herbal Therapeutics in the Management of Melanoma: A Comprehensive Review

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Abstract

Melanoma remains one of the most biologically restless forms of skin cancer. It accounts for a smaller proportion of cutaneous malignancies than basal cell carcinoma or squamous cell carcinoma, yet it causes a disproportionate share of skin cancer mortality because it invades early, adapts quickly, and often survives therapeutic pressure. Immune checkpoint inhibitors, BRAF and MEK inhibitors, and refined surgical management have changed the outlook for many patients, but the field is still living with a hard problem: durable response is not guaranteed, toxicity can be serious, and resistance is common. In that unsettled space, liposomal nanocarriers and plant derived therapeutics have become more than a fashionable research topic. They offer a way to rethink how poorly soluble, chemically fragile, and pleiotropic natural molecules might be delivered to melanoma cells, immune cells, and the skin itself. This review examines liposomal nanocarriers for herbal and phytochemical agents in melanoma management, with attention to curcumin, quercetin, resveratrol, epigallocatechin gallate, berberine, apigenin, silymarin, silibinin, luteolin, and related compounds. The discussion covers melanoma biology, the rationale for lipid vesicular delivery, formulation design, topical and systemic routes, mechanistic pathways, combination therapy, safety, translational barriers, and future research priorities. A central argument runs through the review: liposomes can make herbal therapeutics more drug like, but they cannot rescue weak biology or poorly controlled experiments. The most convincing future work will therefore need stronger melanoma models, rational dose selection, pharmacokinetic evidence, immunological readouts, and manufacturing realism.

INTRODUCTION

Melanoma is often introduced as the aggressive skin cancer, which is true, although the phrase can become too tidy if repeated without explanation. The real clinical problem is that melanoma is not one disease behaving in one predictable way. A thin lesion removed early may be cured with surgery, while a metastatic tumor can move through lymph nodes, lung, liver, bone, and brain with a speed that still unsettles clinicians. Current epidemiological sources place cutaneous melanoma among the major global cancers, with GLOBOCAN 2022 estimating more than 331,000 new melanoma cases worldwide and close to 59,000 deaths (Bray et al., 2024; Ferlay et al., 2024). In the United States, American Cancer Society projections for 2026 estimate about 112,000 new invasive melanomas and 8,510 deaths, in addition to a large burden of melanoma in situ (American Cancer Society, 2026; Siegel et al., 2026).

The treatment story has improved dramatically since the era when metastatic melanoma was described, with some resignation, as chemotherapy resistant. Ipilimumab opened the door for checkpoint blockade, anti-PD-1 agents such as nivolumab and pembrolizumab produced more reliable response patterns, and BRAF plus MEK inhibition gave rapid disease control in BRAF V600 mutated tumors (Chapman et al., 2011; Hodi et al., 2010; Larkin et al., 2015; Long et al., 2014; Robert et al., 2015). Even so, a patient sitting across from an oncologist today may still hear a list of uncertainties: Will the tumor respond? Will the immune toxicity be manageable? Will a BRAF driven response last beyond months? How should brain metastases be handled? These questions explain why researchers keep looking for approaches that are not simply more toxic versions of old chemotherapy (NCI, 2025; NCCN, 2025).

Herbal therapeutics enter this conversation carefully, not as romantic alternatives to evidence based oncology, but as chemically rich sources of molecules that can affect oxidative stress, inflammatory signaling, apoptosis, angiogenesis, invasion, metabolic rewiring, and immune tone. Curcumin, quercetin, resveratrol, epigallocatechin gallate, berberine, apigenin, luteolin, and silymarin have each been examined in melanoma

or skin cancer models, sometimes with encouraging effects and sometimes with frustrating formulation problems (Bill et al., 2009; Cao et al., 2014; Gong et al., 2019; Singh et al., 2010). The difficulty is familiar to any pharmaceutical scientist: many natural compounds look active in cell culture, but they dissolve poorly, degrade easily, are cleared quickly, or fail to reach the tumor compartment in useful concentrations (Anand et al., 2007; Chavda et al., 2022).

Liposomal nanocarriers are attractive because they are biologically recognizable, compositionally flexible, and able to carry both hydrophilic and lipophilic substances. Their bilayer architecture can protect fragile compounds and alter tissue distribution, while surface modification can support longer circulation or cell selective uptake (Allen & Cullis, 2013; Bangham et al., 1965; Rommasi et al., 2021; Torchilin, 2005). Yet the promise should not be inflated. A liposome is not a magic envelope. It can improve pharmacokinetics, skin residence, or intracellular delivery, but it still depends on drug potency, release kinetics, tumor microenvironment, and formulation stability. The strongest argument for liposomal herbal therapeutics in melanoma is therefore not that nature is harmless or that nanotechnology is automatically precise. The argument is that a rational vesicular system can sometimes convert a difficult phytochemical into a testable, controllable therapeutic candidate.

This review brings these strands together. It discusses liposomes as delivery tools for herbal and phytochemical therapeutics in melanoma management, with special attention to formulation logic, biological mechanisms, translational gaps, and the realistic place of such systems beside modern immunotherapy and targeted therapy. The tone is deliberately balanced. There is real scientific opportunity here, but the field also has a tendency to overstate early in vitro findings. A useful review should keep both facts in view.

This article is written as a comprehensive narrative review rather than a formal systematic review. The literature was considered across PubMed, Google Scholar indexed journals, publisher platforms, and major oncology information sources, with emphasis on studies and reviews dealing with melanoma biology, liposomal nanomedicine, phytochemical delivery, topical skin cancer therapy, and nanoformulated natural products. Recent literature was prioritized where possible, especially work published from 2020 onward, but older studies were included when they created the foundation for current thinking, such as the discovery of liposomes, early liposomal oncology products, BRAF biology, and first generation immunotherapy trials (Bangham et al., 1965; Chapman et al., 2011; Hodi et al., 2010; Torchilin, 2005, Cosco et al., 2015; Gupta et al., 2022).

Melanoma burden, biology, and present treatment landscape

Melanoma begins from melanocytes, the pigment producing cells that sit mostly in the basal epidermis, but its clinical identity is shaped by mutation, microenvironment, immune recognition, and metastatic behavior (Bill et al., 2009; Cao et al., 2014; Liao et al., 2017; Ravindran Menon et al., 2021; Singh et al., 2010). Ultraviolet radiation contributes heavily to the mutational burden of cutaneous melanoma, and genomic studies have repeatedly shown high rates of C to T transitions and mutation signatures linked to UV damage (Alexandrov et al., 2013; Hodis et al., 2012, Chavda et al., 2022; Chen et al., 2024; Senjab et al., 2024). That high mutational load partly explains why melanoma can respond to immune checkpoint inhibitors. A tumor with many mutations may display neoantigens that immune cells can recognize, at least in theory. The awkward part is that immune recognition is not the same as immune elimination. Melanoma can exclude T cells, exhaust them, alter antigen presentation, and create a suppressive local environment.

At molecular level, BRAF mutation changed the field. Davies et al. (2002) identified activating BRAF mutations in a large fraction of That multi-target nature is both strength and weakness. It may be valuable in melanoma, where resistance often comes from pathway redundancy and phenotype switching. A compound that mildly pressures melanomas, and later clinical work turned that observation into BRAF inhibition and then combined BRAF and MEK inhibition. The response to vemurafenib or dabrafenib can be striking, especially when a patient has symptomatic metastatic disease and needs rapid shrinkage (Chapman et al., 2011; Hauschild et al., 2012, Garbe et al., 2025; NCCN, 2025; NCI, 2025; Tawbi et al., 2022). But pathway escape is common. Tumors reactivate MAPK signaling, shift survival networks, or acquire phenotypic plasticity. Adding MEK inhibition improved outcomes over BRAF inhibition alone, but it did not solve resistance completely (Flaherty et al., 2012; Long et al., 2014).

Immunotherapy changed the emotional weather of melanoma care. Ipilimumab produced durable survival benefit in a disease where that had been rare, although response rates were modest and immune toxicity was a real burden (Hodi et al., 2010). Anti-PD-1 therapy improved both activity and tolerability, while combined nivolumab and ipilimumab pushed response further at the cost of more grade 3 or 4 adverse events (Larkin et al., 2015; Robert et al., 2015). More recently, relatlimab plus nivolumab added LAG-3 blockade to the therapeutic vocabulary (Tawbi et al., 2022). These advances matter for this review because any herbal liposomal strategy must now be judged against a high clinical bar.

The present treatment landscape is increasingly layered. Early melanoma is still a surgical disease. Stage III disease may involve sentinel lymph node evaluation, nodal management, adjuvant anti-PD-1 therapy, BRAF and MEK inhibition in mutation positive disease, or neoadjuvant approaches in selected patients (Eggermont et al., 2018; Garbe et al., 2025; NCCN, 2025). Advanced melanoma may be treated with immunotherapy, targeted therapy, tumor infiltrating lymphocyte therapy in certain settings, radiotherapy for brain or symptomatic metastases, and clinical trial options. Chemotherapy has a much smaller role than it once had (NCI, 2025). For liposomal herbal therapeutics, the most realistic entry points may be supportive combination, local cutaneous delivery, sensitization of resistant cells, mitigation of inflammatory pathways, and experimental immunomodulation rather than stand alone curative therapy.

A second feature of melanoma biology matters for drug delivery: the disease can be both visible and deeply systemic. Primary lesions and superficial metastases are accessible to topical or intratumoral approaches, while visceral metastases require systemic pharmacokinetic competence. Brain metastases raise another barrier, because many nanocarriers do not efficiently cross the intact blood brain barrier. Melanoma also occupies an immune rich environment in skin, lymph nodes, and metastatic sites. Liposomes can potentially interact with tumor cells, dendritic cells, macrophages, and endothelial barriers, but the direction of that interaction depends on size, charge, composition, protein corona, and route of administration (Blanco et al., 2015; Cheng et al., 2025; Mitchell et al., 2021).

Role of herbal drugs in treatment of melanoma

The renewed interest in herbal therapeutics is not simply nostalgia for traditional medicine. It comes from a practical observation: many plant derived molecules are biologically noisy in the useful sense(Jose et al., 2018; Liao et al., 2016; Lin et al., 2020; Roman et al., 2024; Amiri et al., 2025). They do not usually hit one target like a kinase inhibitor. Instead, they may slightly alter several pathways that melanoma uses for survival, invasion, inflammation, redox balance, and immune escape. Curcumin can influence NF-kB, STAT3, PI3K-AKT, Wnt beta-catenin, apoptosis regulators, and oxidative signaling. Quercetin has been linked to STAT3 inhibition, cell cycle effects, and modulation of drug resistance. Resveratrol can affect AKT/mTOR, autophagy, and inflammatory mediators.Berberine touches AMPK, COX-2, migration, and mitochondrial processes (Cao et al., 2014; Gong et al., 2019; Nocito et al., 2021; Singh et al., 2010).

several survival routes might sensitize cells to chemotherapy, targeted therapy, or immune attack. However, multi-target activity also makes mechanism harder to prove. A paper may report apoptosis after treatment

with a phytochemical, but whether that apoptosis results from a specific pathway, general oxidative injury, solvent effects, or supraphysiological exposure can be unclear. A fair review should therefore resist the temptation to treat every positive cell culture finding as therapeutic evidence.

The pharmacokinetic problem is the familiar bottleneck. Curcumin is a classic example: it is chemically fascinating and pharmacologically active in many models, but oral bioavailability is low because of poor aqueous solubility, rapid metabolism, and systemic elimination (Anand et al., 2007; Feng et al., 2017). Quercetin has similar issues with solubility and metabolism. Resveratrol is absorbed but rapidly conjugated, and its circulating free form is often low. EGCG is oxidation sensitive and has limited stability. Berberine has poor absorption and is influenced by efflux transporters. These are not minor formulation inconveniences. They decide whether the compound can ever reach melanoma cells in a relevant form (Annaji et al., 2021; Chavda et al., 2022; Granja et al., 2016).

Liposomal delivery responds to this weakness directly. A liposome can place a lipophilic phytochemical within a bilayer, a hydrophilic compound in its aqueous core, or a mixture across both regions. It can protect labile molecules, reduce crystallization, improve apparent solubility, alter uptake, and sometimes enable topical deposition in skin. In cancer, PEGylation can extend circulation, cationic lipids can enhance cellular uptake or nucleic acid binding, deformable vesicles can improve dermal movement, and ligand decoration can support receptor mediated endocytosis (Allen & Cullis, 2013; Chavda et al., 2022; Gupta et al., 2022; Senjab et al., 2024).

Still, a liposomal herbal formulation should not be judged only by encapsulation efficiency. A beautiful size distribution and high loading percentage are not enough. The formulation should show controlled release in relevant media, stability during storage, retention of phytochemical identity, lack of hemolytic or immune toxicity, and meaningful activity in melanoma models that include more than one cell line. Ideally, it should also include normal melanocytes or keratinocytes to estimate selectivity. This is where many early formulations are still weak: they look elegant analytically but are biologically under-tested.

Liposomal nanocarriers as novel strategy in therapeutics

Liposomes are vesicular particles formed mainly from phospholipids arranged in one or more bilayers around an aqueous interior. Bangham and colleagues described these phospholipid vesicles in the 1960s, and the idea has since developed into one of the most mature areas of nanomedicine (Bangham et al., 1965). Their appeal comes from their resemblance to biological membranes.

A liposome can carry a water soluble molecule in the core, a poorly soluble molecule in the membrane, and sometimes two agents at once. In oncology, this architecture led to clinically used formulations such as pegylated liposomal doxorubicin, which improved drug disposition and reduced some conventional toxicities (Barenholz, 2012; Gabizon et al., 1994).

For melanoma, liposomes can be designed for at least four jobs. The first is solubilization. Many phytochemicals are hydrophobic, and bilayer incorporation can make them dispersible in physiological or topical media. The second is protection. A compound that oxidizes, hydrolyzes, or is rapidly metabolized may survive longer when sheltered within a vesicle. The third is localization. Liposomes may accumulate in tumors through leaky vasculature, although the enhanced permeability and retention concept is much more variable in human tumors than in mouse xenografts (Maeda et al., 2013; Wilhelm et al., 2016). The fourth is cellular interaction. Surface charge, PEGylation, ligands, and size can shape uptake by melanoma cells, macrophages, dendritic cells, or skin layers (Blanco et al., 2015; Cheng et al., 2025).

The EPR effect deserves a careful tone. It is often cited as if nanoparticles automatically collect inside tumors. That is not what the translational literature shows. Nanomedicine delivery to solid tumors can be low and heterogeneous, and human melanoma metastases are not uniformly leaky containers waiting for nanoparticles (Wilhelm et al., 2016). Liposomal herbal therapeutics should therefore be designed with realistic expectations. Passive targeting may help in some contexts, but active targeting, local delivery, intratumoral injection, or topical skin retention may be more credible for specific melanoma settings.

PEGylated liposomes reduce rapid clearance by the mononuclear phagocyte system and can prolong circulation. Ligand targeted liposomes aim to recognize tumor associated receptors, such as folate receptors, transferrin receptors, integrins, or melanoma related antigens, although active targeting frequently improves cell uptake more than total tumor accumulation (Allen & Cullis, 2013; Peer et al., 2007; Torchilin, 2005). Stimuli responsive liposomes add another layer by releasing cargo under acidic pH, high glutathione, enzymatic activity, heat, ultrasound, or light exposure. In melanoma, pH responsive and photoresponsive designs are especially interesting because skin lesions can be externally accessed, but the clinical translation of smart liposomes remains difficult (AlSawaftah et al., 2021; Heidarli et al., 2017; Torres et al., 2025).

However, Lipid composition can alter release, membrane fusion, endosomal escape, and immune recognition. Cholesterol can stabilize bilayers but may slow release. Cationic lipids can improve uptake but increase cytotoxicity. Edge activators in transfersomes or ultradeformable liposomes can improve skin movement but may irritate tissue if used aggressively. Major design choices for liposomal herbal therapeutics in melanoma are given in Table 1.

Table 1. Major design choices for liposomal herbal therapeutics in melanoma

Design choice	Purpose in melanoma formulation	Main caution	Representative citations
PEGylation	Prolongs circulation and reduces rapid macrophage clearance for systemic formulations.	Repeated dosing and anti-PEG responses need attention.	Allen & Cullis, 2013; Torchilin, 2005
Cationic surface	Improves cell interaction and nucleic acid association in co-delivery systems.	Can increase membrane toxicity and inflammatory effects.	Peer et al., 2007; Song et al., 2021
Ultradeformable vesicles	Supports deeper skin penetration for topical or transdermal delivery.	Edge activators can irritate skin if poorly selected.	Cosco et al., 2015; Gupta et al., 2022
Ethosomes and invasomes	Use ethanol or terpene assisted lipid fluidization to improve cutaneous delivery.	May not be suitable for inflamed or highly sensitive skin without irritation testing.	Liao et al., 2016; Lin et al., 2020; Samir et al., 2024
Ligand targeting	May improve melanoma cell uptake or immune cell targeting.	Often improves internalization more than total tumor accumulation.	Blanco et al., 2015; Cheng et al., 2025
Stimuli responsive release	Allows cargo release in acidic, redox active, enzymatic, light activated, or heated environments.	Complexity must produce a measurable therapeutic gain.	AlSawaftah et al., 2021; Torres et al., 2025
Microneedle integration	Bypasses the stratum corneum and allows localized intradermal dosing.	Requires mechanical, dose uniformity, and lesion safety studies.	Shen et al., 2025
Co-encapsulation	Coordinates exposure of phytochemicals with chemotherapy, siRNA, or photodynamic agents.	Drug ratio and release synchrony must be controlled.	Jose et al., 2018; Roman et al., 2024

Formulation design for herbal liposomal melanoma therapy

A liposomal formulation for melanoma should begin with a biological aim, not with the equipment available in the laboratory. If the aim is topical delivery to a superficial lesion or surgical margin, vesicle deformability, gel residence, penetration depth, and skin tolerability become central. The most commonly used preparation methods include thin film hydration, ethanol injection, reverse phase evaporation, sonication, extrusion, microfluidics, and high pressure homogenization. Thin film hydration is convenient for laboratory batches, but scale up can be clumsy. Microfluidic mixing offers more controlled and continuous production, which is appealing for translational work. Phytochemicals complicate these methods because they may precipitate, partition unpredictably, bind strongly to phospholipids, or degrade during solvent removal. Curcumin, for example, may locate within the hydrophobic bilayer, while hydrophilic herbal fractions may distribute differently and require alternative strategies (Feng et al., 2017; Senjab et al., 2024).

Characterization should include particle size, polydispersity index, zeta potential, morphology, encapsulation efficiency, drug loading, release kinetics, storage stability, serum stability, and chemical integrity of the active molecule. For topical systems, viscosity, spreadability, skin retention, permeation, and irritation testing are also needed. For systemic systems, hemolysis, complement activation, protein corona formation, and macrophage uptake should not be ignored. It is surprisingly easy to publish a liposomal phytochemical paper with strong in vitro cytotoxicity but incomplete information about what happens to the formulation in serum. That gap weakens translation.

An additional concern is dose realism. Many phytochemicals are tested at concentrations that are difficult to achieve in vivo. Liposomes may raise local concentration, but they do not repeal pharmacology. A careful melanoma study should compare free compound, empty liposome, liposomal compound, and, where relevant, an approved therapeutic comparator. Empty liposomes are not inert by default. Lipids, surfactants, solvents, and surface charge can influence cell viability, inflammatory signaling, and membrane integrity. Without these controls, cytotoxicity can be misread as phytochemical activity.

The best formulations also ask how the drug exits the vesicle. A tightly retained compound may look stable but fail to act. A rapidly leaking compound may behave like free drug with extra excipients. For melanoma, an intermediate design may be ideal: stable enough to reach the target, but labile enough to release in tumor cells, acidic endosomes, inflamed skin, or enzyme rich microenvironments. Stimuli responsive liposomes attempt exactly this, though their complexity must be justified by a clear gain in efficacy or safety (AlSawaftah et al., 2021; Jayapriya et al., 2023; Torres et al., 2025).

Phytochemicals as potential candidates in melannoma therapy

Curcumin

Curcumin remains the emblematic phytochemical in cancer nanomedicine. In melanoma models, curcumin has been reported to reduce proliferation, induce apoptosis, interfere with STAT3 and JAK signaling, suppress invasion, and alter oxidative and inflammatory pathways (Bill et al., 2009; Liao et al., 2017; Nocito et al., 2021). Curcumin loaded lipid and polymeric nanocapsules reduced B16-F10 melanoma growth in mice, while curcumin micelles showed enhanced cytotoxicity in B16 and A375 cells compared with free compound (Mazzarino et al., 2011; Wang et al., 2017). A 2024 systematic review and meta-analysis of preclinical melanoma evidence concluded that curcumin can reduce tumor volume and tumor weight in animal models, although heterogeneity and the lack of large clinical studies remain serious limitations (Guo et al., 2024).

Liposomal curcumin is attractive because it addresses the solubility and bioavailability weakness directly. Feng et al. (2017) reviewed liposomal curcumin applications in cancer and described improved growth inhibition and pro-apoptotic effects relative to free curcumin in several cancer systems. In melanoma, the logic is plausible: a bilayer associated curcumin formulation could increase cellular uptake, improve local skin deposition, and support combination with siRNA, chemotherapy, or photodynamic approaches. Still, the field needs better comparisons between liposomes, polymeric micelles, nanostructured lipid carriers, and invasomes for the same melanoma model, because different nanoforms may solve different parts of the problem.

Quercetin

Quercetin is another persuasive candidate because it has been linked to anti-melanoma activity through STAT3 inhibition, cell cycle control, apoptosis induction, and reversal of drug resistance (Cao et al., 2014; Hoinoiu et al., 2025; Thangasamy et al., 2010). Quercetin also appears in combination research. Srivastava and Srivastava (2019) reported that curcumin and quercetin together inhibited proliferation and modulated Wnt beta-catenin and apoptotic pathways in A375 cells. Roman et al. (2024) showed that quercetin can enhance 5-fluorouracil driven cytotoxicity in A375 melanoma cells. These findings are interesting because melanoma treatment may benefit less from one phytochemical alone and more from sensitization strategies.

Liposomal quercetin has been explored across cancer models, and quercetin loaded liposomes improved delivery or activity in vitro in non-melanoma systems (Gang et al., 2012; Keshavarz et al., 2023). For melanoma, the challenge is to move from general quercetin nanodelivery to melanoma specific designs. A liposomal quercetin formulation could be developed for topical co-delivery with 5-fluorouracil, retinoids, or immune modulators, but the formulation must show selectivity against melanoma cells and acceptable safety in keratinocytes and melanocytes. Otherwise, the formulation risks becoming another elegant vesicle with unclear clinical direction.

Resveratrol

Resveratrol has a slightly different profile. It is known for antioxidant and anti-inflammatory biology, but in melanoma it has also been reported to inhibit viability and migration through AKT/mTOR related autophagy pathways (Gong et al., 2019). Resveratrol loaded nanomedicines have been reviewed widely, including liposomes, polymeric particles, lipid carriers, and hybrid systems (Annaji et al., 2021; Sharifi-Rad et al., 2021; Szulc-Musioł et al., 2021). Its instability and rapid metabolism make it a logical candidate for liposomal protection, particularly in topical or transdermal delivery where local skin concentration matters.

The resveratrol and 5-fluorouracil ultradeformable liposome work by Cosco et al. (2015) is often discussed in the context of nonmelanoma skin cancer, but it is still instructive for melanoma. It shows how co-encapsulation can create a formulation logic rather than simply putting one plant compound into a vesicle. If a phytochemical reduces oxidative inflammation, alters cell cycle regulation, or sensitizes cells to chemotherapy, then co-delivery can coordinate exposure in the same tissue. That coordination may matter more than dose escalation.

Epigallocatechin gallate

Epigallocatechin gallate, the major green tea catechin, has been explored for melanoma, skin cancer, and cancer nanodelivery. Ravindran Menon et al. (2021) reported that EGCG inhibited melanoma growth by modulating immune response, while Liao et al. (2016) developed EGCG nanoethosomes for transdermal melanoma treatment. EGCG has stability problems, including oxidation and limited bioavailability, which makes lipid based encapsulation attractive (Farabegoli et al., 2022; Granja et al., 2016; Sun et al., 2024). A realistic EGCG liposomal strategy may be best suited for topical prevention, early lesion management, or combination with immunologically active therapies rather than systemic monotherapy.

Flavoonoids

Berberine, Apigenin and luteolin

Berberine is an isoquinoline alkaloid with anti-inflammatory, pro-apoptotic, anti-migratory, and metabolic effects. Singh et al. (2010) showed that berberine inhibited melanoma cell migration by affecting COX-2, PGE2, and related receptors. More recent reviews discuss berberine as a multi-targeted melanoma or skin neoplasm agent, emphasizing pathways such as AMPK, PI3K-AKT, apoptosis, angiogenesis, and inflammation (Almatroodi et al., 2022; Duda-Madej et al., 2025; Wang, R. R., et al., 2025). Its pharmacokinetic limits, including poor absorption and efflux, make nanocarrier design especially relevant.

Liposomal berberine has been investigated in cancer and photodynamic contexts, including liposomal berberine in spheroid cells and liposome hydrogel microneedles for berberine hydrochloride (Moloudi et al., 2024; Shen et al., 2025). In melanoma, berberine loaded ethosomes co-delivered with evodiamine were developed as a topical anti-melanoma formulation, giving the field a useful example of herbal combination delivery (Lin et al., 2020). The next step would be stronger in vivo melanoma validation and comparison with standard topical or intratumoral strategies.

Apigenin, luteolin, silymarin, and silibinin broaden the phytochemical landscape. Apigenin loaded PLGA nanoparticles have shown anti-proliferative effects in skin cancer related work, and apigenin nanoparticles were investigated for melanoma lung metastasis (Das et al., 2013; Rahmani et al., 2022; Sen et al., 2021). More recent apigenin loaded invasomes have been reported as anti-melanoma carriers (Cunha et al., 2025). Silymarin and silibinin have antioxidant, anti-inflammatory, and pro-apoptotic activities, with nanoliposomal or micellar systems investigated in cancer and B16F10 melanoma contexts (Amiri et al., 2025; Doagooyan et al., 2023; Karkad et al., 2024; Koltai, 2022). Luteolin has broad anticancer and anti-inflammatory potential, although direct liposomal melanoma evidence is less developed than for curcumin or EGCG (Imran et al., 2019; Lv et al., 2025) (Table 2).

Table 2. Herbal and phytochemical candidates relevant to liposomal melanoma research

Candidate	Main proposed melanoma relevant actions	Delivery limitation	Liposomal or nanoformulation relevance	Representative citations
Curcumin	Apoptosis, STAT3 and JAK modulation, anti-invasive signaling, inflammatory regulation.	Poor solubility, rapid metabolism, low systemic exposure.	Liposomal, micellar, and nanocapsule systems improve dispersion and tumor model activity.	Bill et al., 2009; Feng et al., 2017; Liao et al., 2017; Mazzarino et al., 2011
Quercetin	STAT3 inhibition, apoptosis, cell cycle effects, modulation of drug resistance.	Low solubility and extensive metabolism.	Liposomes and related lipid systems can improve delivery and support combination therapy.	Cao et al., 2014; Hoinoiu et al., 2025; Roman et al., 2024
Resveratrol	AKT/mTOR modulation, autophagy, anti-migration, inflammatory regulation.	Rapid metabolism and chemical instability.	Ultradeformable liposomes and invasomes support skin delivery and co-delivery.	Annaji et al., 2021; Cosco et al., 2015; Gong et al., 2019; Samir et al., 2024
EGCG	Immune modulation, redox signaling, anti-proliferative activity.	Oxidation sensitivity and limited bioavailability.	Nanoethosomes and lipid carriers improve stability and skin transport.	Granja et al., 2016; Liao et al., 2016; Ravindran Menon et al., 2021
Berberine	COX-2 and PGE2 linked migration inhibition, apoptosis, AMPK and metabolic signaling.	Poor absorption, efflux, limited systemic bioavailability.	Ethosomes, liposomes, and microneedle systems are promising for local delivery.	Lin et al., 2020; Moloudi et al., 2024; Shen et al., 2025; Singh et al., 2010
Apigenin	Apoptosis, anti-inflammatory signaling, possible	Poor solubility and low oral bioavailability.	Nanoparticles and invasomes improve skin and	Cunha et al., 2025; Das et al., 2013; Sen et al., 2021

	anti-metastatic action.		melanoma model activity.	
Silymarin and silibinin	Antioxidant modulation, apoptosis, immunogenic cell death markers in melanoma models.	Variable extract composition and limited solubility.	Nanoliposomes and micelles improve cellular delivery and bioactivity.	Amiri et al., 2025; Doagooyan et al., 2023; Karkad et al., 2024
Luteolin	Anti-inflammatory, pro-apoptotic, and survival pathway modulation.	Poor water solubility and limited melanoma specific delivery data.	Liposomal melanoma work remains underdeveloped and needs targeted formulation studies.	Imran et al., 2019; Lv et al., 2025

Mechanism of action of phytochemicals in melanoma control

The mechanisms of action of phytochemicals in melanoma therapy usually cluster around apoptosis, oxidative stress, inflammation, metastasis, angiogenesis, immune modulation, and therapy sensitization. Apoptosis is the most common endpoint, partly because it is experimentally convenient. Curcumin, quercetin, berberine, silibinin, and apigenin have all been associated with caspase activation, mitochondrial membrane changes, Bcl-2 family modulation, or pro-apoptotic signaling in cancer models (Amiri et al., 2025; Bill et al., 2009; Cao et al., 2014; Singh et al., 2010). For liposomal delivery, the mechanistic question is whether encapsulation merely raises intracellular drug amount or changes the cell death pathway itself. That distinction is rarely explored deeply enough.

STAT3 deserves special attention. Melanoma cells can use STAT3 signaling to support survival, immune evasion, angiogenesis, and invasion. Quercetin has been reported to exert anti-melanoma activity partly through STAT3 inhibition, and curcumin has been linked to suppression of JAK2/STAT3 signaling (Cao et al., 2014; Nocito et al., 2021). A liposomal formulation that increases intracellular exposure to STAT3 modulating phytochemicals might sensitize melanoma cells to immune attack, at least hypothetically. However, in vivo proof requires immune competent models, because STAT3 is also important in immune cells and tumor stroma.

The PI3K-AKT-mTOR axis is another relevant pathway. It supports melanoma survival, metabolism, invasion, and resistance. Resveratrol has been reported to suppress melanoma growth through inhibition of AKT/mTOR and induction of autophagy, while berberine and several flavonoids can influence related survival networks (Gong et al., 2019; Wang, R. R., et al., 2025). A liposomal system may improve cellular delivery of these compounds, but pathway inhibition should be verified at concentrations that are realistic after encapsulation. Otherwise, the pathway language becomes decorative rather than mechanistic.

Oxidative stress is more complicated than it appears. Many phytochemicals are called antioxidants, yet cancer cell killing may involve either antioxidant protection of normal tissue or pro-oxidant injury inside tumor cells. Curcumin, EGCG, resveratrol, and silymarin can behave differently depending on concentration, metal ions, cell type, and redox state (Farabegoli et al., 2022; Karkad et al., 2024; Sun et al., 2024). In melanoma, where oxidative stress contributes to both carcinogenesis and therapy response, a formulation could protect normal skin while sensitizing tumor cells, but that dual effect must be demonstrated rather than assumed.

Metastasis and invasion are especially important because melanoma mortality usually reflects spread rather than the primary lesion itself. Berberine inhibition of COX-2 and PGE2 related migration, quercetin effects on chemoresistance, and resveratrol suppression of migration point toward anti-invasive possibilities (Gong et al., 2019; Singh et al., 2010; Thangasamy et al., 2010). Liposomes may help by creating higher local concentrations around cutaneous or lymphatic disease, but systemic metastasis will demand better biodistribution data. A compound that blocks migration in a scratch assay is not automatically an anti-metastatic therapy.

Immunomodulation may become the most interesting long-term angle. Melanoma is already treated by releasing immune brakes. Natural molecules that alter dendritic cell function, macrophage polarization, inflammatory mediators, or immunogenic cell death could potentially support checkpoint therapy, but they could also suppress immune activation if used incorrectly. Silibinin loaded nanocarriers have been reported to potentiate immunogenic cell death markers in B16F10 melanoma cells, including calreticulin, HSP90, ATP, and phosphorylated eIF2 alpha related signaling (Amiri et al., 2025). That kind of endpoint is more informative than simple viability reduction because it connects nanophytotherapy with the immune logic of modern melanoma care.

One more mechanism deserves a plain warning: bioavailability is not a mechanism of anti-cancer action. Many manuscripts show that a liposomal formulation improves solubility and then quickly shifts to biological claims. Solubility is necessary, but melanoma management requires evidence of tumor selective pharmacodynamics. Ideally, future studies should connect formulation properties to uptake, uptake to pathway modulation, pathway modulation to tumor control, and tumor control to safety. That chain is longer than many early papers acknowledge.

Potential routes of drug in melanoma therapy

Route of administration is not a small technical choice in melanoma. A topical formulation, a microneedle patch, an intratumoral injection, and an intravenous liposome are practically different therapies. Topical and transdermal routes are attractive because melanoma often begins in the skin and superficial lesions can be accessed directly. Skin also provides a reservoir effect, potentially sustaining local exposure while limiting systemic toxicity (Gupta et al., 2022). Yet the stratum corneum is a stubborn barrier. Even in cancer or inflamed skin, penetration is uneven, and deeper melanoma invasion may sit beyond the effective reach of a simple topical vesicle.

Vesicular carriers such as liposomes, transfersomes, ethosomes, transethosomes, and invasomes were developed partly to deal with skin penetration. Transfersomes use edge activators to increase flexibility. Ethosomes include ethanol, which can fluidize skin lipids. Invasomes often combine phospholipids, ethanol, and terpenes to improve permeation. These systems are not identical, although papers sometimes

group them loosely as lipid vesicles. In melanoma research, EGCG nanoethosomes, berberine and evodiamine ethosomes, resveratrol invasome gels, and apigenin invasomes illustrate how phytochemical delivery can be tailored for skin access (Cunha et al., 2025; Liao et al., 2016; Lin et al., 2020; Samir et al., 2024).

Topical delivery may be most realistic for prevention of field change, management of superficial melanoma in situ under carefully defined conditions, treatment of cutaneous metastases, or post-surgical local recurrence risk. It is not a substitute for excision of invasive melanoma. A review should be blunt about that. Melanoma can spread early, and delaying surgery or systemic therapy in favor of unproven topical herbal formulations would be unsafe. The legitimate research question is whether liposomal phytochemicals can complement standard care by improving local control, reducing inflammatory microenvironments, or delivering immune sensitizers to accessible lesions.

Intratumoral delivery has a different logic. It bypasses some systemic distribution problems and can produce a high local concentration. In melanoma, intralesional therapy is already clinically familiar through agents such as talimogene laherparepvec, although that is not a herbal therapy. Liposomal phytochemicals could, in theory, be injected into accessible metastases to induce local tumor death or immunogenic signaling. The challenge is to avoid local necrosis without useful systemic immunity. If the goal is an abscopal or immune priming effect, the formulation must be evaluated in immune competent models and not only in subcutaneous tumor volume assays.

Systemic liposomal delivery is the most ambitious route. It would be needed for visceral metastatic melanoma, but it faces clearance by liver and spleen macrophages, dilution in blood, protein corona formation, tumor heterogeneity, and variable extravasation. PEGylation, ligand targeting, and size optimization can help, but they do not guarantee meaningful tumor delivery (Blanco et al., 2015; Wilhelm et al., 2016). For herbal therapeutics with modest potency, systemic liposomes may need combination strategies or active targeting to be convincing. Otherwise, the delivered concentration may remain below the threshold required for melanoma control.

Microneedles sit between topical and invasive delivery. They can cross the stratum corneum and deliver cargo into viable epidermis or dermis with relatively low pain. Berberine hydrochloride liposomes in hydrogel microneedles show how a phytochemical liposomal system can be integrated into a device platform (Shen et al., 2025). For melanoma, microneedles could be explored for localized adjuvant delivery, immune modulation, or treatment of superficial cutaneous metastases. However, safety studies must examine whether mechanical disruption of suspicious lesions has any unintended effect on local inflammation, sampling, or tumor cell movement.

For each route, the formulation endpoint changes. Topical systems need penetration and retention data. Intratumoral systems need local release, distribution through tumor tissue, and immune readouts. Systemic systems need pharmacokinetics and biodistribution. Microneedle systems need mechanical strength, dose reproducibility, insertion depth, and skin recovery. A serious liposomal herbal melanoma program should state the intended route early and design every experiment around that route.

Combination therapy and associated immunological opportunities

Combination therapy is probably where liposomal herbal therapeutics have their most credible future. Modern melanoma therapy already uses combinations, such as BRAF plus MEK inhibition, anti-PD-1 plus anti-CTLA-4, and anti-PD-1 plus anti-LAG-3 (Flaherty et al., 2012; Larkin et al., 2015; Tawbi et al., 2022). The reason is simple: melanoma adapts. A phytochemical that modestly affects survival signaling may be more valuable as a sensitizer than as a stand alone cytotoxic agent. Liposomes support this idea because they can co-encapsulate or coordinate delivery of multiple actives.

Curcumin and STAT3 siRNA co-delivery is a useful example of how natural product therapy can move beyond the single compound mindset. Jose et al. (2018) reported topical co-delivery of curcumin and STAT3 siRNA with anti-melanoma activity in B16F10 cells. In such systems, curcumin may contribute anti-inflammatory and pro-apoptotic pressure while siRNA suppresses a defined oncogenic survival pathway. Liposomes or related vesicles are attractive for this because they can protect nucleic acids and hydrophobic molecules together, although cationic lipids and nucleic acid carriers must be tested carefully for toxicity.

Phytochemicals may also be paired with conventional chemotherapeutics. Quercetin enhanced 5-fluorouracil cytotoxicity in A375 melanoma cells, and resveratrol with 5-fluorouracil has been formulated in ultradeformable liposomes for skin cancer applications (Cosco et al., 2015; Roman et al., 2024). While 5-fluorouracil is not a standard therapy for invasive melanoma, these studies still matter because they show how phytochemicals can act as modifiers of drug response. Similar logic could be explored with dacarbazine, temozolomide, MAPK inhibitors, or photodynamic agents, but only if mechanism and clinical relevance are thought through.

Combination with targeted therapy raises interesting but delicate possibilities. A phytochemical that modulates oxidative stress, autophagy, or parallel survival pathways might delay resistance to BRAF and MEK inhibitors. Resveratrol effects on AKT/mTOR and autophagy, curcumin effects on STAT3 and NF-kB, and berberine effects on AMPK related metabolism all suggest hypotheses (Gong et al., 2019; Nocito et al., 2021; Wang, R. R., et al., 2025). The problem is drug interaction. Natural compounds can affect cytochrome enzymes, transporters, and immune signaling. Before such combinations are tested clinically, pharmacokinetic and toxicity interactions must be examined.

Combination with immunotherapy may be even more attractive, but also more risky. If a liposomal phytochemical induces immunogenic cell death, increases antigen presentation, reduces immunosuppressive cytokines, or repolarizes macrophages, it could theoretically support checkpoint blockade. If it broadly suppresses inflammation or T cell activation, it could do the opposite. Curcumin and resveratrol are sometimes described as anti-inflammatory, which sounds beneficial in ordinary inflammatory disease, but anti-inflammatory effects in cancer immunotherapy require nuance. Melanoma treatment often depends on a vigorous immune response. The direction and timing of immune modulation are therefore crucial.

A practical combination framework could classify liposomal phytochemicals into four roles: cytotoxic co-agent, resistance modulator, local immune primer, and toxicity mitigating adjunct. These roles should not be mixed casually. A toxicity mitigating adjunct might be used to reduce oxidative injury in normal skin or systemic tissues, while a local immune primer might intentionally provoke danger signals. A resistance modulator might require chronic exposure, while a cytotoxic co-agent might need high intratumoral concentration. Better classification would make the field less scattered and easier to evaluate.

Safety, quality, and regulatory considerations

Curcumin, quercetin, resveratrol, EGCG, berberine, and silymarin have long histories of dietary or medicinal exposure, but concentrated purified compounds inside nanocarriers are different entities. Encapsulation can change biodistribution, increase cellular uptake, alter immune recognition, and prolong tissue exposure. A safe oral extract does not automatically become a safe injectable liposome. This point matters especially for melanoma patients receiving immunotherapy, targeted therapy, anticoagulants, steroids, or other drugs.

Safety assessment should include both the phytochemical and the carrier. Phospholipids and cholesterol are generally biocompatible, but cationic lipids, solvents, edge activators, surfactants, ethanol, and terpenes can irritate skin or damage cells. PEGylation may reduce opsonization, but repeated administration can sometimes raise anti-PEG concerns.

Liposomes may activate complement depending on composition and dose. For topical products, irritation, sensitization, phototoxicity, and changes in barrier function must be checked. For systemic products, hemolysis, liver and spleen accumulation, complement activation, and cytokine effects are important (Allen & Cullis, 2013; Chen et al., 2024; Mitchell et al., 2021).

Quality control becomes harder when the therapeutic agent is herbal. A purified compound such as curcumin or quercetin is easier to standardize than a crude plant extract. If an extract is used, botanical authentication, voucher specimens, extraction method, solvent residues, phytochemical fingerprinting, marker content, microbial limits, heavy metals, pesticides, and batch consistency become necessary. Liposomal encapsulation cannot compensate for poorly characterized herbal material. In fact, encapsulation may hide variability until biological testing fails to reproduce.

For APA style review writing, it is tempting to list limitations at the end, but quality and regulation belong near the center of the discussion. A formulation that cannot be reproduced cannot become therapy. Scalable manufacturing must control particle size, polydispersity, sterility, endotoxin, residual solvent, oxidation, drug leakage, and storage stability. Lyophilization may improve shelf life, but cryoprotectant choice can alter reconstitution and release. Microfluidics may offer batch control, but industrial translation requires cost and throughput analysis (Senjab et al., 2024).

Regulatory classification may also be complex. A liposomal curcumin gel, a phytochemical loaded microneedle patch, and an intravenous ligand targeted liposome could fall into different regulatory pathways depending on claims, route, active ingredient, and device component. A product claiming melanoma treatment will be held to oncology drug standards, not cosmetic standards. The required evidence would include pharmacology, toxicology, manufacturing controls, and clinical trials. That is a high bar, but it is appropriate for a potentially lethal cancer.

There is also an ethical issue in communication. Patients with melanoma often search for natural remedies, especially when they fear toxicity from immunotherapy or targeted therapy. Researchers and writers must be clear that liposomal herbal therapeutics remain largely experimental in melanoma. They may become useful adjuncts or local therapies, but they should not be presented as proven substitutes for surgery, immunotherapy, or targeted therapy. Good science is allowed to be hopeful, but it should not sell comfort where evidence is missing.

Translational challenges and future research agenda

The first translational challenge is model quality. A375 and B16F10 cells are useful, but they cannot carry the whole field. A375 is a human melanoma cell line with specific molecular features, while B16F10 is a murine line often used for syngeneic and metastasis models. Both have limitations. Future work should include panels of melanoma cells with different BRAF, NRAS, NF1, PTEN, and immune phenotypes, along with normal melanocytes, keratinocytes, fibroblasts, macrophages, and immune competent animal models where appropriate (Cancer Genome Atlas Network, 2015; Curtin et al., 2005; Hodis et al., 2012).

The second challenge is pharmacokinetic honesty. Many liposomal phytochemical studies stop at cell viability and particle characterization. That is not enough. Investigators should measure free and encapsulated drug in plasma, skin, tumor, liver, spleen, lymph nodes, and, where relevant, brain. They should report whether the active compound remains chemically intact. They should compare liposomal and free compound at equivalent doses and include empty vesicle controls. Without pharmacokinetics, claims about improved delivery remain partly assumed.

The third challenge is immune context. Melanoma is now an immunotherapy driven disease, so phytochemical nanocarriers should be tested for immune consequences. Does the formulation increase calreticulin exposure, ATP release, HMGB1 release, dendritic cell activation, CD8 T cell infiltration, or macrophage repolarization? Does it suppress T cell function? Does it alter PD-L1 expression? Silibinin nanocarrier findings on immunogenic cell death in B16F10 cells point in a useful direction, but much more work is needed (Amiri et al., 2025). The field should move beyond generic apoptosis assays and ask immune relevant questions.

The fourth challenge is route matching. Topical studies should not overclaim systemic metastatic relevance. Systemic studies should not rely on skin penetration data. Microneedle studies should include device performance. Intratumoral studies should include tumor distribution. If a formulation is intended for cutaneous metastases, the model should include lesions that resemble that use case. If it is intended for adjuvant use after excision, studies should examine residual disease or recurrence models rather than bulky tumors only.

The fifth challenge is comparison with competing nanocarriers. Liposomes are not always the best carrier. Solid lipid nanoparticles, nanostructured lipid carriers, polymeric micelles, nanoemulsions, phytosomes, exosomes, and hybrid systems each have advantages. Curcumin micelles, resveratrol invasomes, silymarin nanostructured lipid carriers, and EGCG nanoethosomes show that the carrier choice should fit the compound and route rather than follow fashion (Cunha et al., 2025; Liao et al., 2016; Mazzarino et al., 2011; Samir et al., 2024). Liposomes have maturity and flexibility, but they should win by data, not by reputation.

A practical future research agenda would include five priorities. First, select phytochemicals using melanoma specific biology rather than popularity. Second, build formulation development around the intended route and clinical use case. Third, include pharmacokinetics and biodistribution early, not after years of cell work. Fourth, integrate immune readouts in immune competent systems. Fifth, address manufacturing, stability, and regulatory quality before claiming translational promise. These steps sound ordinary, but ordinary rigor is exactly what the field needs.

There is also room for more patient relevant thinking. For example, a liposomal quercetin gel for superficial cutaneous metastases would face different expectations than an intravenous curcumin liposome for stage IV disease. A berberine microneedle system might be acceptable for localized skin delivery but not for widespread metastasis. A resveratrol co-loaded vesicle might be useful as a photoprotective or chemopreventive platform, but melanoma treatment claims require stronger evidence. Clear clinical imagination can prevent vague research.

Finally, the field needs negative data. Natural product nanomedicine has a tendency to publish positive formulations and leave failed ones invisible. Yet knowing that a liposomal EGCG system oxidized during storage, that a curcumin liposome leaked in serum, or that a cationic quercetin vesicle harmed keratinocytes would be useful. Translation improves when researchers report what does not work. Melanoma patients do not benefit from a literature made only of success stories.

CONCLUSION

Liposomal nanocarriers offer a serious, scientifically grounded way to revisit herbal therapeutics in melanoma management. They can improve solubility, protect fragile compounds, shape tissue distribution, support topical or systemic delivery, and enable co-delivery of phytochemicals with conventional drugs or nucleic acids. Curcumin, quercetin, resveratrol, EGCG, berberine, apigenin, silymarin, silibinin, and related molecules have enough biological activity to justify careful investigation, especially as sensitizers, local therapies, immune modulators, or formulation enabled adjuncts.

The strongest message, however, is not simple enthusiasm. Melanoma is clinically serious and biologically adaptive. Approved immunotherapies and targeted therapies have changed survival expectations, and any new liposomal herbal strategy must earn its place with rigorous evidence. The

field should avoid exaggerated claims based only on cell viability or encapsulation efficiency. Better studies will connect formulation properties with pharmacokinetics, pathway modulation, immune effects, tumor control, and safety. If that chain can be built, liposomal herbal therapeutics may become a meaningful part of melanoma research. If not, they will remain attractive vesicles around interesting molecules, which is not enough.

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