

Green Nanocarriers from Indigenous Medicinal Plants for Targeted Melanoma Therapy: A Systematic Review

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ABSTRACT

Melanoma is the most dangerous kind of skin cancer. It only makes up 4% of all skin cancer diagnoses, but it causes 79% of skin cancer deaths. Standard treatments like surgery, chemotherapy, radiotherapy, targeted therapy, and immunotherapy haven't worked very well, especially for metastatic and recurrent disease. They also often cause systemic toxicity, bad pharmacokinetics, and drug resistance. The meeting of ethnopharmacology and nanotechnology has opened up a whole new world of possibilities: the development of eco-friendly nanocarriers made from native medicinal plants for the precise treatment of melanoma. Curcumin, resveratrol, epigallocatechin gallate (EGCG), saponins, silymarin, and apigenin are plant-based bioactive compounds that are known to fight cancer. However, they are difficult to use in clinical settings because they don't dissolve well in water, don't stay in the body for long, and are quickly removed from the body. Encapsulation in biopolymeric, lipid-based, or plant-derived nanocarriers greatly reduces these problems, making it easier to provide the drug to the right person, control its release, and make it more effective against melanoma. This systematic review gathers current evidence about green nanocarrier systems made from native medicinal plants. It looks at their physical and chemical properties, how they work against cancer, and how well they work in vitro and in vivo against melanoma. It also carefully checks the quality of the evidence that is already out there. A whole framework for getting data and a way to judge quality are provided, together with pictures of nanocarrier shapes, mechanism routes, and the PRISMA flow of research selection.

Keywords: Green nanocarriers, melanoma, native medicinal flora, phytochemicals, targeted drug delivery, biopolymeric nanoparticles, nanotechnology, systematic review.

1. INTRODUCTION

1.1 Epidemiology and Clinical Burden of Melanoma

Melanoma is a malignant tumour derived from melanocytes and represents the most aggressive subtype of skin cancer (Tang et al. 2017). Even though it only accounts for 4% of all skin cancers, it causes about 79% of skin cancer deaths, which shows how deadly it is (Tang et al. 2017). Melanoma cases around the world have been on the rise for the past few decades, especially among younger people (Tang et al. 2017). Cancer data from 2020 indicated that there were more than 19.3 million new cases of cancer and 10 million deaths from cancer over the globe. This issue has a lot to do with skin cancer (Manzari-Tavakoli et al. 2024). If skin cancer is not effectively recognised and treated, experts say that the number of cases will climb significantly over the next twenty years (Hasan et al. 2023). A lot of complicated changes at the molecular level are involved in the development of melanoma. These include mutations in the BRAF, NRAS, and NF1 genes, deregulation of the MAPK and PI3K/AKT/mTOR signalling pathways, epigenetic changes, and the acquisition of cancer stem cell features (Liu et al. 2023, Hasan et al. 2023). Because of its complex molecules, metastatic melanoma is harder to treat with medications, which implies that many people don't respond to typical treatment (Tang et al. 2017).

The person's genes and UV radiation are the two key factors that initiate the process. These conditions induce the BRAF gene (particularly the V600E mutant) and the NRAS gene to mutate a lot, which causes cancer. These mutations are the fundamental reason cells develop and remain alive. They maintain the signalling pathways that govern these activities functioning. The illness is mostly caused by the incorrect activation of two essential signalling pathways. The BRAF/NRAS mutations make the MAPK pathway (BRAF → MEK → ERK) overly active, which makes cells grow out of control. The PTEN tumour suppressor normally blocks the PI3K/AKT pathway from operating correctly. The route doesn't operate properly when this occurs. When you switch it on, it transmits powerful signals that keep cells alive and help them expand, which keeps them from dying.

The inactivation of CDKN2A, a key tumour suppressor gene, makes this environment more likely to cause tumours. CDKN2A produces two essential proteins: p16 and p14ARF. The retinoblastoma (Rb) pathway stops working when p16 is lost, and the p53 pathway stops working when p14ARF is lost. This double loss breaks down the cell's main safety systems, which causes the cell cycle to go wrong and the cell to avoid ageing. Without these checkpoints, cells that are injured can keep dividing forever instead of stopping their growth or dying on purpose (Figure 1).

The combination of unregulated cell growth, resistance to cell death, and bypassing growth inhibition leads to strong tumour growth. This lets the main tumour develop, spread to nearby tissues, and eventually gain the ability to spread to other parts of the body, which is the last stage: metastasis.

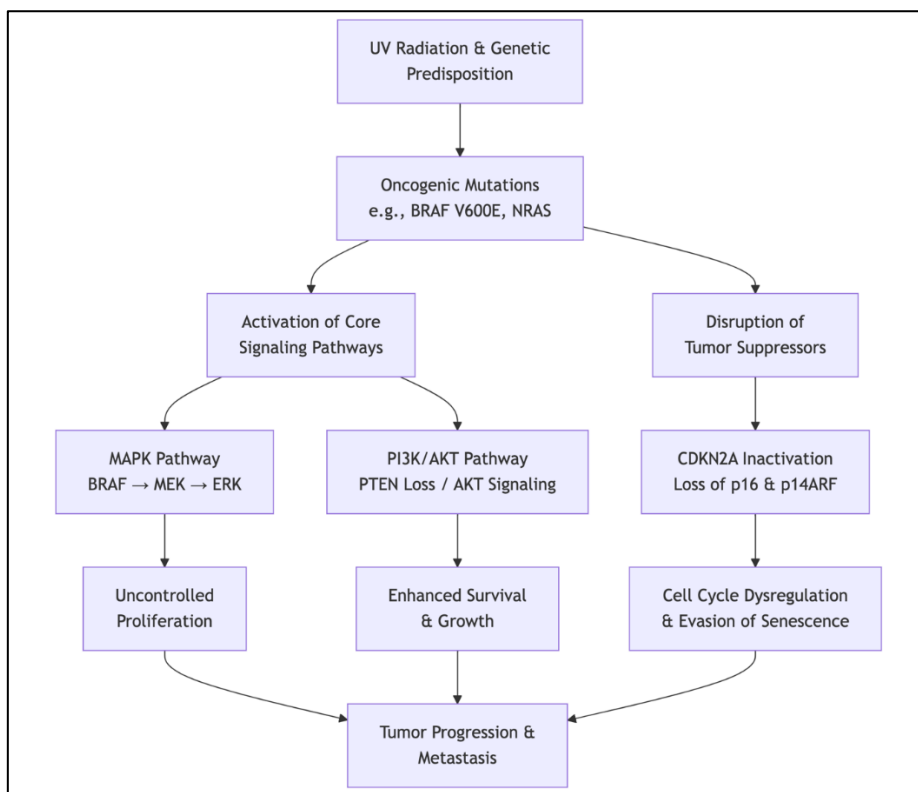


Figure 1. Molecular Mechanisms Underlying Melanoma Pathogenesis: From UV-Induced Genetic Alterations and Oncogenic Mutations to Signaling Dysregulation, Tumor Suppressor Loss, and Metastatic Progression

1.2 Limitations of Conventional Melanoma Therapies

Current therapeutic options for melanoma include surgical excision (effective solely in early-stage disease), chemotherapy, radiation, targeted therapy (e.g., BRAF/MEK inhibitors), and immunotherapy (e.g., anti-CTLA-4, anti-PD-1/PD-L1 checkpoint inhibitors) (Hasan et al. 2023, Tang et al. 2017). In recent years, targeted therapy and immunotherapy have greatly improved survival rates, although metastatic and recurrent melanomas often do not respond to treatment (Yan et al. 2025). Conventional chemotherapy is characterised by systemic toxicity, suboptimal pharmacokinetics, restricted tumour specificity, and the development of multidrug resistance (Manzari-Tavakoli et al. 2024, Hasan et al. 2023). Immunotherapy, while promising, is ineffective for many patients, and resistance mechanisms are still being clarified (Tang et al. 2017).

The deficiencies of traditional drug delivery systems, such as rapid drug degradation, inadequate bioavailability, nonspecific distribution, and failure to attain therapeutic concentrations at the tumour site, necessitate the creation of novel delivery platforms (Siddiqui & Sanna, 2016; Singh et al., 2019). Nanotechnology-based drug delivery systems have arisen as an effective answer to these issues, presenting opportunities for targeted drug administration, regulated release, and combination therapy (Manzari-Tavakoli et al. 2024).

1.3 Reasons for Using Indigenous Medicinal Plants as Green Nanocarriers

For thousands of years, people in Asia, Africa, and other parts of the world have employed plants in traditional medicine. They are a rich source of bioactive secondary metabolites that could be used in medicine (Sanjai et al. 2024, Gaikwad et al. 2023). Over 47% of FDA-approved anticancer medicines are derived from plant sources, highlighting the significant therapeutic potential of the plant kingdom (Liu et al. 2023). Indigenous medicinal plants encompass a variety of phytochemicals, including polyphenols, flavonoids, alkaloids, terpenoids, and saponins, which demonstrate antioxidant, anti-inflammatory, pro-apoptotic, anti-angiogenic, and anticancer activities (Singh et al., 2024).

Even though plant-based bioactive chemicals have a lot of potential as medicines, they can't be used directly in the clinic because they aren't very bioavailable, biostable, or hydrophobic, and they break down quickly and work differently for different people (Sanjai et al. 2024, Singh et al. 2019). Nanotechnology offers a novel solution to these issues through the creation of nanoformulations that improve the effectiveness of bioactive chemicals (Sanjai et al. 2024). The idea of "green nanocarriers" is based on or inspired by plant materials. These include plant-derived nanovesicles, biopolymeric nanoparticles, phytosomes, and lipid nanoparticles that use plant-derived lipids. This is a very appealing strategy because it combines the therapeutic benefits of phytochemicals with the delivery benefits of nanotechnology while reducing toxicity and environmental impact (Zeng et al. 2021, Gaffar et al. 2024).

1.4 Objectives

The goal of this systematic review is to fully look at how phytochemicals and green nanocarrier systems can be used to address the underlying patho-mechanisms of melanoma. It concentrates on methodically gathering and integrating current knowledge regarding nanocarriers produced from indigenous medicinal plants that have been investigated for targeted melanoma therapy. Additionally, the review aims to delineate the physicochemical features of these nanocarriers and their encapsulated bioactive chemicals to elucidate their formulation characteristics and stability. The research also wants to describe the physicochemical features of these nanocarriers and the bioactive substances they contain in order to better understand their formulation qualities and stability. Furthermore, it rigorously evaluates the anticancer mechanisms and analyses the in vitro and in vivo therapeutic efficacy of these systems against melanoma.

2. LITERATURE REVIEW

2.1 Melanoma: Molecular Biology and Therapeutic Targets

Melanoma originates from the malignant alteration of melanocytes, the pigment-producing cells within the skin (Tang et al. 2017). The molecular landscape of melanoma is characterised by the activation of the MAPK signalling cascade, primarily via the BRAF V600E mutation, the dysregulation of the PI3K/AKT/mTOR pathway, the loss of tumour suppressor function (PTEN, p16/CDKN2A), and epigenetic modifications, including aberrant microRNA (miRNA) expression. Cancer stem cell characteristics, such as drug efflux through ABC transporters, epigenetic reprogramming, and improved DNA repair, play a crucial role in chemoresistance in melanoma (Liu et al. 2023).

Integrin $\alpha\beta3$ (overexpressed on A375 human melanoma cells), folate receptors, epidermal growth factor receptors (EGFR), and different immune checkpoint molecules are important molecular targets for melanoma treatment (Madamsetty et al. 2019, Tang et al. 2017). For example, the overexpression of integrin $\alpha\beta3$ on melanoma cells has been used to deliver nanoparticles directly to those cells utilising RGD peptide-functionalized nanocarriers (Tang et al., 2017). Likewise, folate receptor-targeted nanocarriers have shown increased lethal effects on cancer cells exhibiting high folate receptor expression (Annaji et al. 2021).

2.2 Phytochemical and Melanoma

Curcumin: Curcumin is a natural polyphenolic pigment from the rhizome of *Curcuma longa* (turmeric), known for its vibrant yellow colour. It fights melanoma by causing oxidative stress and stopping the NF- κ B survival pathway, which leads to cell death. It successfully stops metastasis and works well with other medications, although its therapeutic potential is hampered by low absorption (Momal et al., 2026).

Resveratrol: Resveratrol is a natural polyphenolic compound, belonging to the stilbenoid group, that acts as a phytoalexin—a substance produced by plants to defend against pathogens and physical stress. This substance causes apoptosis in mitochondria and stops metastasis by blocking matrix metalloproteinases. It further targets cancer stem cells and alters gene expression; nevertheless, its rapid metabolism complicates therapeutic use (Galiniak et al., 2026).

Epigallocatechin Gallate (EGCG): It is the predominant and physiologically active catechin present in green tea (*Camellia sinensis*), comprising 50–80% of its total catechin content. The polyphenol in green tea specifically causes melanoma cells to die by activating caspase and stops cancer growth by blocking the PI3K/Akt pathways. Its effectiveness is additionally impeded by inadequate bioavailability, which nano-formulations seek to address (Niu et al., 2026).

Saponins: Saponins are a diverse class of naturally occurring amphiphilic glycosides predominantly found in plants, marine organisms, and some microorganisms, characterized by their soap-like foaming properties when agitated in aqueous solutions. These substances cause apoptosis through ROS and stop metastasis by blocking MMPs and NF- κ B pathways. Even though they can get around drug resistance, clinical use is limited by their low absorption and haemolytic toxicity (Santos et al., 2025).

Silymarin: Silymarin is a standardized extract composed of a mixture of polyphenolic flavonolignans isolated from the dried seeds and fruits of the milk thistle plant, *Silybum marianum* (L.) Gaertn. (Asteraceae). It works as a dual inhibitor of the therapeutic targets BRAF V600E and SMO, and it also causes apoptosis and stops the cell cycle. Its therapeutic value is constrained by inadequate solubility, which nanosponge technology is presently tackling (Sayyad et al., 2025).

Apigenin: Apigenin (4',5,7-trihydroxyflavone) is a naturally occurring flavonoid of the flavone subclass, characterized by a trihydroxyflavone structure with hydroxy groups at positions 4', 5, and 7. This flavonoid messes with integrin signalling, which causes melanoma cells to die, and it also boosts the immune response by breaking down PD-1 in T cells. Scientists are working on nanoparticle methods to fix its bioavailability problems (Siddiquee et al., 2025).

ICG in Aloe Vesicles: A new idea in nanomedicine is to load indocyanine green (ICG) into aloe-derived nanovesicles. ICG is a clinically approved near-infrared (NIR) fluorescent dye used in diagnostic imaging and phototherapy. This method puts a photosensitizer into nanovesicles made from aloe for targeted photothermal therapy. The device has great skin penetration, which could lead to noninvasive treatment, and also stops tumours from growing better when the laser is turned on (Zeng et al., 2025).

2.3 Nanocarrier Systems for Phytochemical Delivery

2.3.1 Liposomal Nanocarriers

Liposomal nanocarriers are spherical vesicles with a phospholipid bilayer. This allows them to hold hydrophilic medications in their water core and lipophilic substances in their membrane. By shielding payloads from degradation and lowering systemic toxicity, this architecture improves therapeutic indices. Adding polyethylene glycol to the surface of liposomes makes them stealthy, meaning that the immune system can't see them. On the other hand, adding ligands makes them easier to find. They are a scientifically proven way to give vaccines, antifungal drugs, and cancer treatments.

2.3.2 Hollow Gold Nanoparticles

Hollow gold nanoparticles (HAuNPs) are tiny gold particles that have a thin shell around a hole in the middle. You can easily change the surface plasmon resonance of these things, even into the near-infrared range for deep tissue penetration. They were made using galvanic replacement and can hold a lot of drugs and have surfaces that are easy to modify. These traits make HAuNPs useful for both photothermal therapy and controlled drug delivery for cancer treatment.

2.3.3 Chitosan Nanoparticles

Chitosan nanoparticles are made from chitin and are safe for living things. They can also be broken down. Their cationic amino groups help them stick to biological membranes through electrostatic means, which makes mucoadhesion and medication permeability better. You can control exactly when the medicine is released because they are made using gentle methods like ionic gelation. These nanoparticles can hold small molecules, DNA, and proteins in a lot of different ways. They look like they could be very useful for treating cancer, building tissue, and healing wounds.

2.3.4 Gold Nanoparticles

Gold nanoparticles (AuNPs) have unique optical features that depend on their size. The most important of these is surface plasmon resonance, which makes them particularly good at absorbing and scattering light. This programmable feature is useful for biosensing, photoacoustic imaging, and photothermal therapy. Because they have a lot of surface area, biomolecules can be extensively functionalized on them for targeted delivery and diagnosis. AuNPs are made using tried-and-true methods and serve as basic building blocks in theranostics, combining both therapeutic and diagnostic functions in a single nanoscale entity.

2.3.5 Nano Phytosome

Nano phytosomes are lipid-based nanocarriers that are generated by mixing plant compounds with phospholipids to make them easier for the body to use. Saponinosomes are what they are termed when they are full of saponins. This formulation greatly lowers the haemolytic damage caused by free saponins while still being effective against cancer. These vesicles are ideal for targeted cancer treatment and immunomodulation because they have a high rate of encapsulation and a long release duration. They can deliver phytoconstituents that are hard to get otherwise.

2.3.6 Crystalline Nanoparticles

Crystalline nanoparticles have well ordered atomic structures that give them one-of-a-kind forms and chemical and physical properties that can be predicted. This internal order has a direct effect on how quickly things break down and how stable they are, which is very essential for how effectively medications operate. For example, there are metallic nanocrystals that can be used for bioimaging and pharmaceutical nanocrystals that can make medications that don't dissolve well in water more accessible. Because their surfaces are so well made and their crystallinity is so well managed, biological interactions can happen time and over again in medical and diagnostic situations.

2.3.7 Aloe Derived Nanovesicles

Nanovesicles made from Aloe vera plants are nanoparticles that are similar to exosomes and are safe for living things. They also offer health benefits. They are quite stable, have antioxidant properties, and cells may easily take them in without causing any harm. It is helpful for healing wounds that they can inhibit myofibroblast differentiation and lower inflammation. These vesicles can also traverse the blood-brain barrier, which makes them great for delivering medications to the central nervous system in many different ways.

2.4 Phytochemicals fight for Melanoma

A lot of different phytochemicals from plants have been demonstrated to be very effective against melanoma in many different ways:

2.4.1 Curcumin (from *Curcuma longa*)

Figure 2 shows that Curcumin stops melanoma cells from growing by blocking the PI3K/AKT signalling pathway, causing apoptosis, and stopping cells from growing (Yan et al. 2025, Pandey et al. 2024). Curcumin-based conjugate nanostructures (CCNGs) exhibit preferential cytotoxicity towards melanoma cells while sparing normal cells from haemolysis or toxicity, indicating their potential for transdermal delivery in melanoma therapy (Yan et al. 2025).

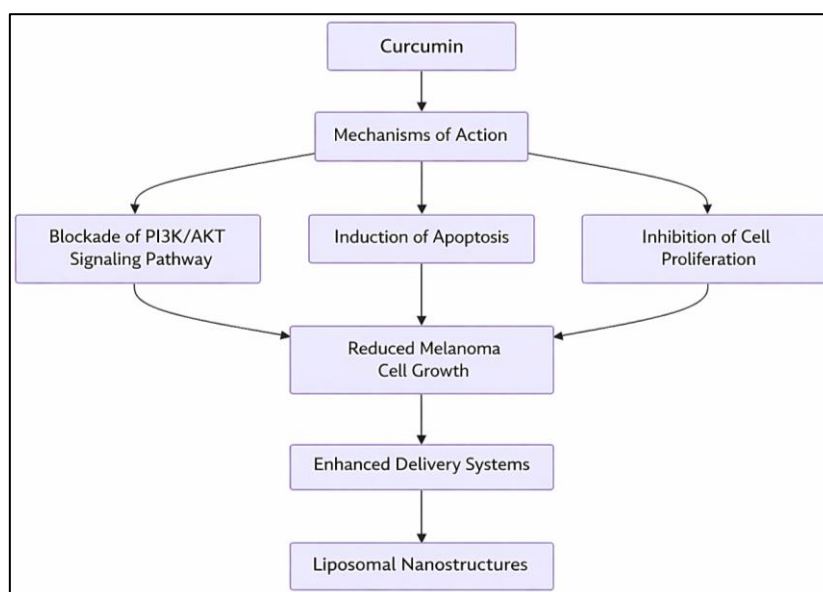


Figure 2. Mechanistic Pathways of Curcumin in Melanoma Therapy: Induction of Apoptosis, Inhibition of PI3K/AKT Signalling, and Suppression of Cell Proliferation by Nanocarrier-Based Delivery Methods

2.4.2 Resveratrol (from *Vitis vinifera* and other plants)

Figure 3 shows an advanced cancer treatment approach that combines light, nanotechnology, and the natural substance resveratrol. Hollow gold nanoparticles are coated with resveratrol, a naturally occurring polyphenol with antioxidant, anti-inflammatory, and anticancer qualities. An 808-nm laser is then used to activate this system. A375 melanoma cells are attacked in two ways as a result of this activation: the cell cycle is blocked and apoptosis is induced. Through improved photothermal performance (the nanoparticles' ability to transform light into heat) and direct chemical actions, the outcome is increased cytotoxicity against the cancer cells, which increases melanoma cell death (Annaji et al. 2021).

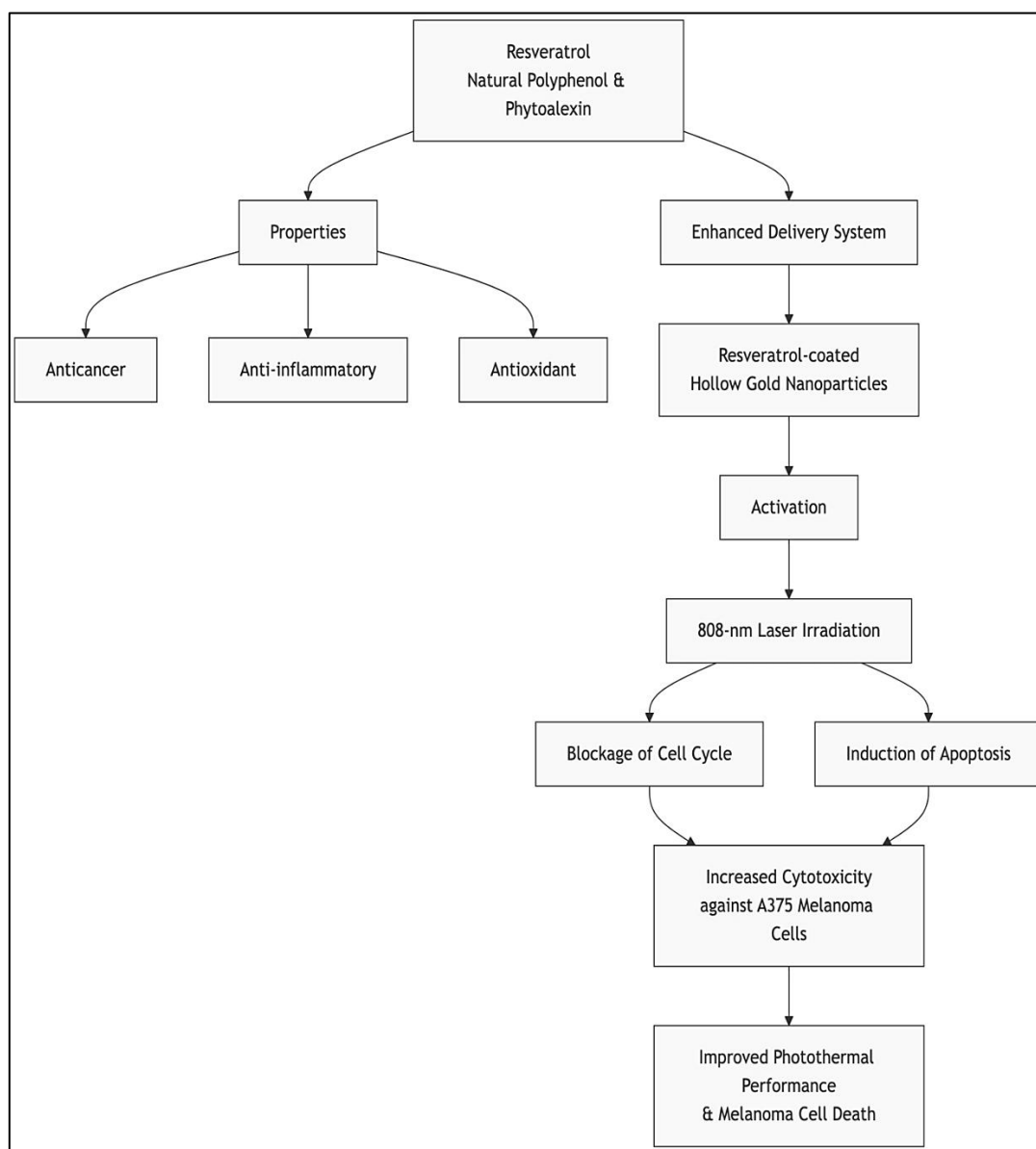


Figure 3. Mechanistic depiction of resveratrol-coated gold nanoparticles facilitating photothermal therapy for melanoma through the induction of apoptosis and cell cycle arrest.

2.4.3 EGCG (from *Camellia sinensis*)

Figure 4 examines the application of EGCG, the principal catechin in green tea (*Camellia sinensis*), for melanoma therapy. It emphasises two principal nano-formulations designed to exploit EGCG's anti-proliferative properties on human melanoma cells. The first is EGCG that is wrapped in Chitosan Nanoparticles, which have been demonstrated to cause cell death. The second is EGCG linked to gold nanoparticles. The effectiveness of these formulations was confirmed using both In Vitro Studies (utilising Murine B16F10 Melanoma Cells) and In Vivo Studies (in living organisms), which established Proven Efficacy. The main point is

that these EGCG nano-formulations have a lot of promise for treatment, which could lead to better melanoma treatment (Handa et al. 2021).

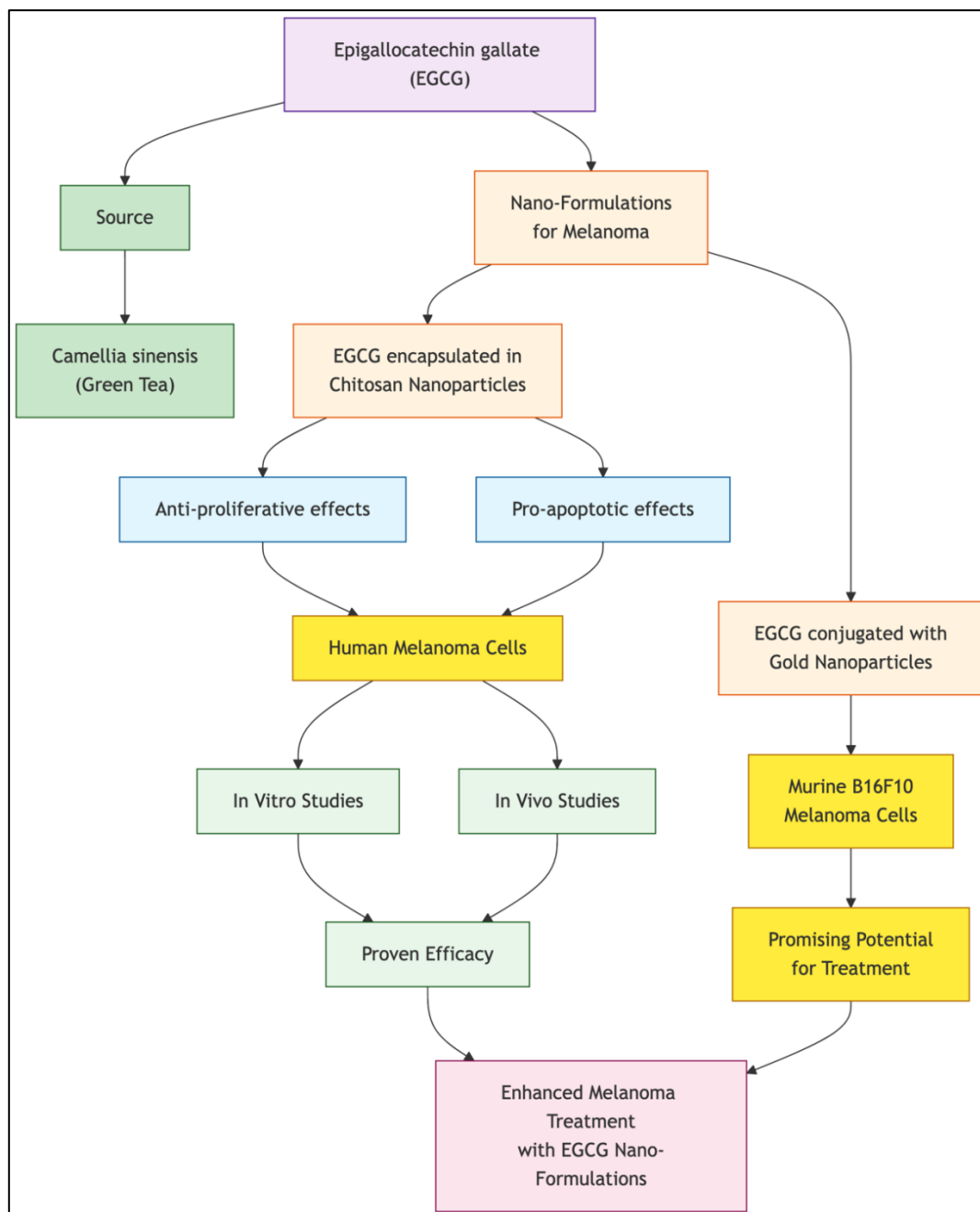


Figure 4. Therapeutic Potential of EGCG Nano-Formulations in Melanoma: From Green Tea-Derived Source to Anticancer Efficacy and Enhanced Treatment Outcomes

2.4.4 Saponins (from *Ziziphus spina-christi* and other plants)

Figure 5 shows a specific way to treat melanoma with Saponins from plants like *Ziziphus spina-christi*. The first step is to make Saponin-rich Fractions, which are subsequently turned into advanced delivery vehicles called Nanophytosomes and Saponinosomes. The most important thing to note is that these mixtures had two effects when evaluated. They show High Cytotoxicity (strong toxicity) just against B16F10 Melanoma Cells, but they also show Reduced Cytotoxicity (low toxicity) against Normal Fibroblast Cells. This selective activity shows a Selective Anti-Cancer Activity, which opens the door to a Targeted Melanoma Therapy with fewer side effects (Nazemoroya et al. 2022).

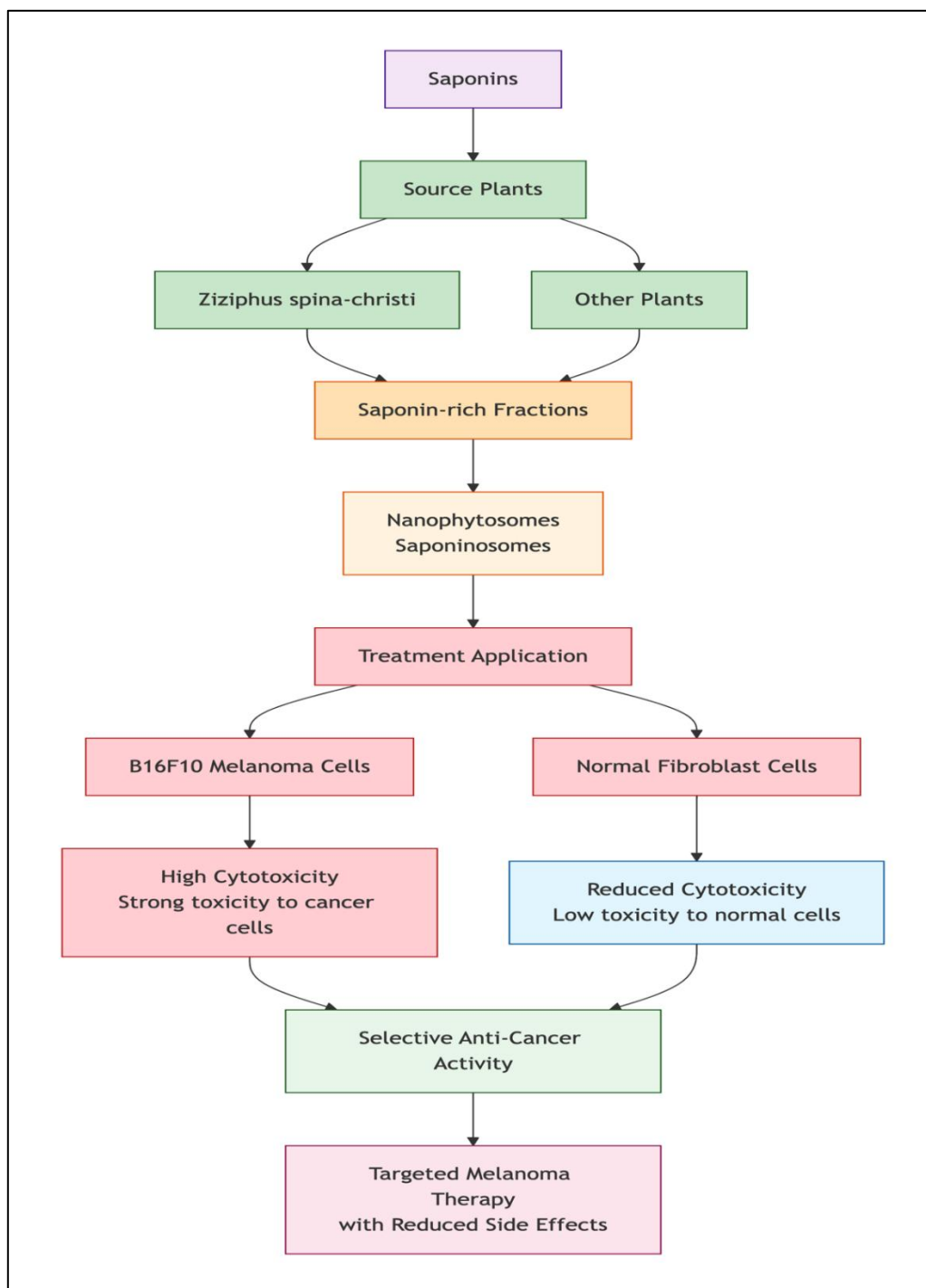


Figure 5. Therapeutic Potential of Saponin Nano-Formulations in Melanoma

2.4.5 Silymarin (from *Silybum marianum*)

Figure 6 shows where Silymarin comes from and how it works against cancer. Silymarin is a bioactive chemical that comes from the plant *Silybum marianum* (Milk Thistle). As a Polyphenolic Flavonoid, it has the potential to treat cancer by changing the way key signalling pathways work that make it worse. It specifically targets three important pathways: the Bcl-2/Bax Pathway, the JAK/STAT Pathway, and the PI3K/Akt/mTOR Pathway. Silymarin's anticancer effects come from changing these pathways, which stops many different types of cancer from growing. This multi-targeted mechanism shows that it could be a useful natural treatment for cancer (Sharma et al. 2025).

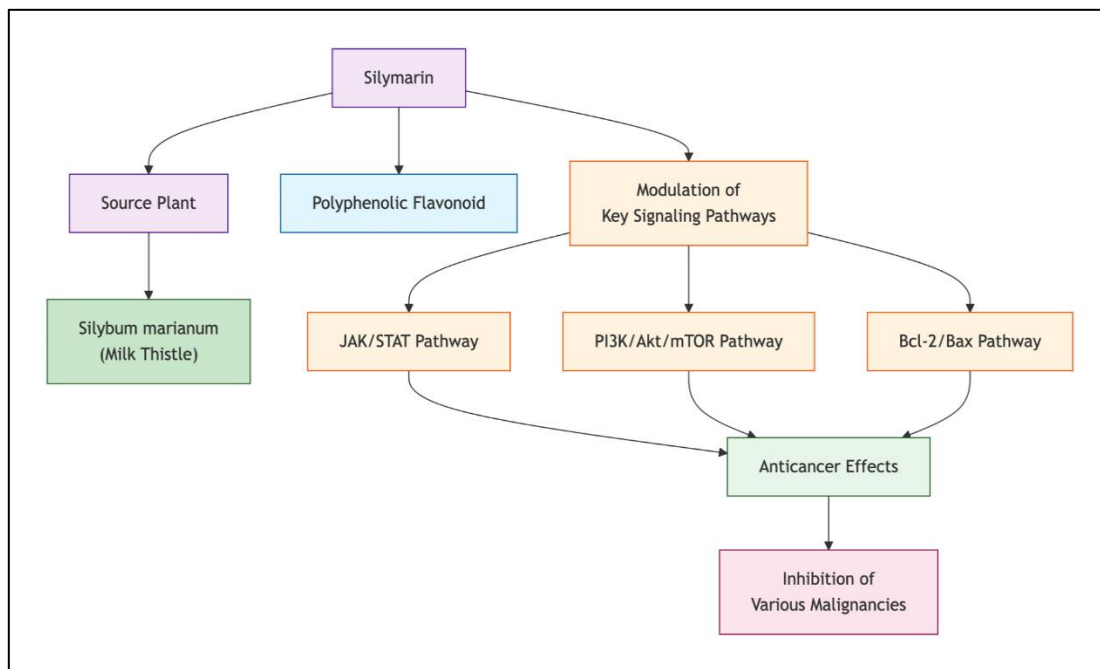


Figure 6. The source and anticancer mechanisms of Silymarin.

2.4.6 Apigenin

Figure 7 shows how the natural substance Apigenin is used in advanced nano-formulations to fight skin cancer. The main idea is to put Apigenin into two types of nanoparticles: Poly(lactic-co-glycolide) (PLGA) Nanoparticles and Lyotropic Liquid Crystalline Nanoparticles. Then, these nano-formulations are evaluated on two kinds of skin cancer cells: A375 Skin Cancer Cells and B16F10 Cell Lines (a cell line from a mouse melanoma). The key result highlighted is the Antiproliferative Effects of these formulations, quantified by an IC50 value of 45.74 ± 0.05 (the concentration needed to inhibit cell growth by half) from in vitro (lab-based) studies. The ultimate conclusion is that this approach leads to an Enhanced Melanoma Treatment (Singh et al. 2024).

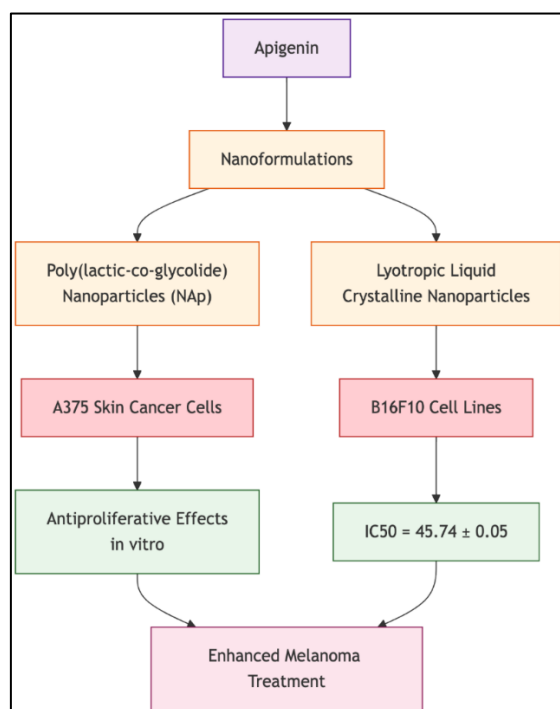


Figure 7. Apigenin in advanced nano-formulations to combat skin cancer.

2.4.7 Indocyanine green (ICG) delivered via aloe-derived nanovesicles

Figure 8 showcases a bio-inspired drug delivery system for photothermal therapy. It centers on Indocyanine Green (ICG), a photosensitizer, loaded into a unique Delivery Vehicle: Aloe-derived Nanovesicles (gADNVs). The resulting ICG-loaded Aloe-derived Nanovesicles were subjected to a Comparative Analysis against Free ICG. The test formulation (ICG-loaded gADNVs) consistently Outperformed free ICG in two key areas: causing Effective damage to melanoma cells and achieving Inhibition of melanoma growth. This Superior Performance shows how useful this natural delivery mechanism is for Enhanced Photothermal Therapy in treating melanoma (Zeng et al. 2021).

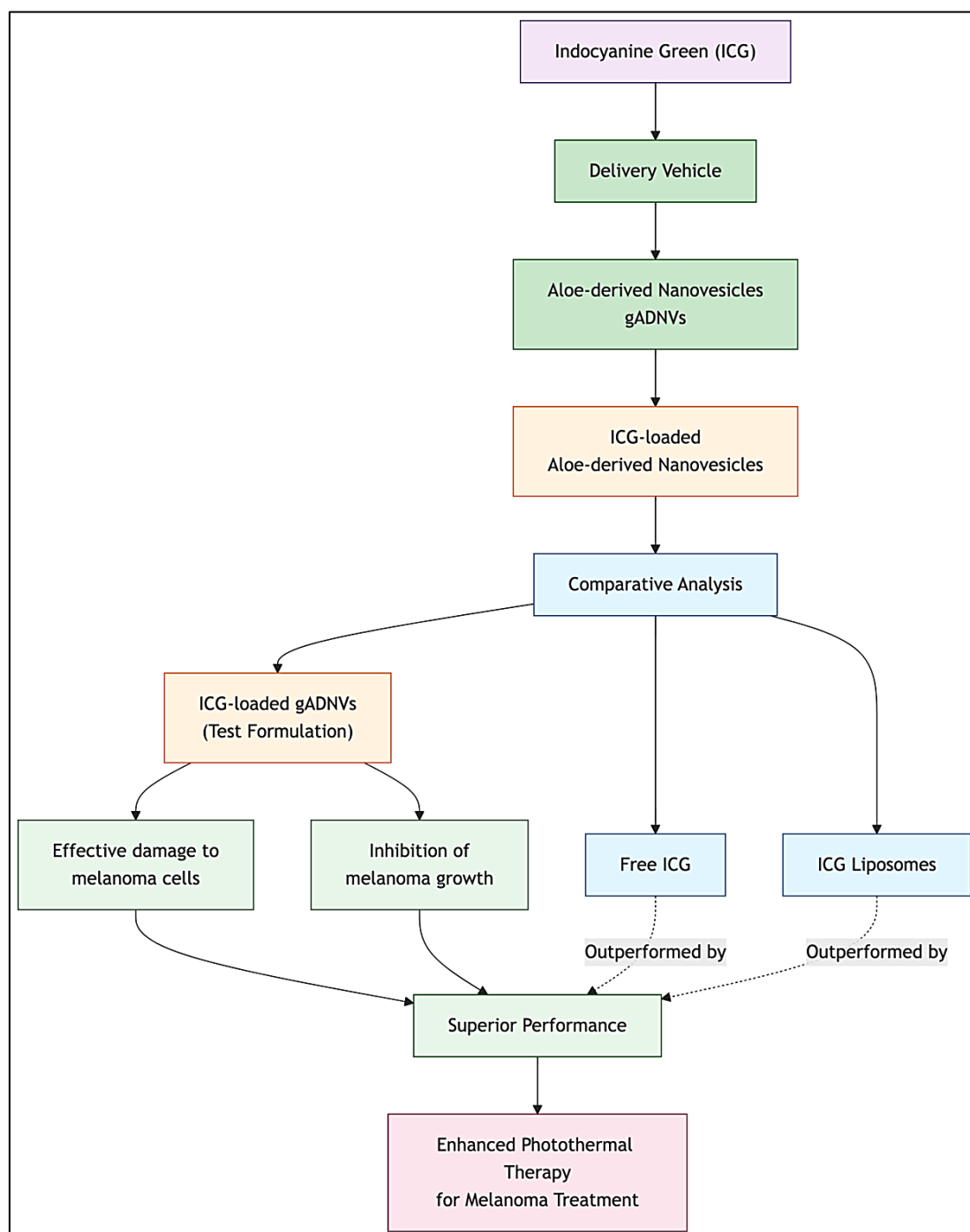


Figure 8. A medication delivery method based on biology for photothermal treatment

3. METHODOLOGY

3.1 Protocol and Registration

This systematic review was executed in alignment with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The review process was set up to find, evaluate, and put together all the evidence about green nanocarrier systems that come from native medicinal plants for treating melanoma.

3.2 Eligibility Criteria

Inclusion Criteria

Studies were considered if they investigated plant-derived phytochemicals or standardized extracts formulated inside nano-based delivery systems and evaluated their therapeutic efficacy against melanoma using validated in vitro, in vivo, or clinical models. Qualifying studies were required to provide the physicochemical characterization of the generated nanocarrier systems.

Moreover, research yielding measurable biological effects and elucidating the mechanistic aspects of melanoma-associated molecular pathways were deemed suitable for inclusion in this review.

Exclusion Criteria

Studies were unrelated to melanoma or skin cancer, or if they used only utilised synthetic nanocarriers without components of plant derived. We were excluded articles lacking important data on physicochemical characterisation or biological efficacy. Hence, conference article abstracts, editorial information and poster paper did not represent genuine scientific papers were not included my studies.

3.3 Search Strategy

A literature search was performed across various electronic databases, including PubMed, Medline, Google Scholar, Scopus, Web of Science, and NLM. The following search terms were used in varied combinations: "green nanocarriers," "plant-derived nanoparticles," "phytochemical nanoformulations," "melanoma," "skin cancer," "biopolymeric nanoparticles," "indigenous medicinal plants," "targeted drug delivery," "curcumin nanoparticles," "resveratrol nanoparticles," "EGCG nanoparticles," "saponin nanocarriers," "plant-derived nanovesicles," "phytosomes," "lipid nanoparticles phytochemicals."

3.4 PRISMA Flow Diagram

Figure 9, shows that a searches of electronic databases, 847 entries were found. Another 43 documents were found manual searches, bringing the total to 890. After that, getting some of duplicates, there were found 712 records left and again they were examined and 534 were thrown out because they were not relevant, plant-derived components and did not have efficacy data. Then, 178 full-text papers were checked for eligibility, and 166 studies were left out because they didn't have enough information, focused on non-melanoma skin malignancies, or used only synthetic nanocarriers. In the end, 12 papers met the requirements for inclusion and were chosen for qualitative synthesis.

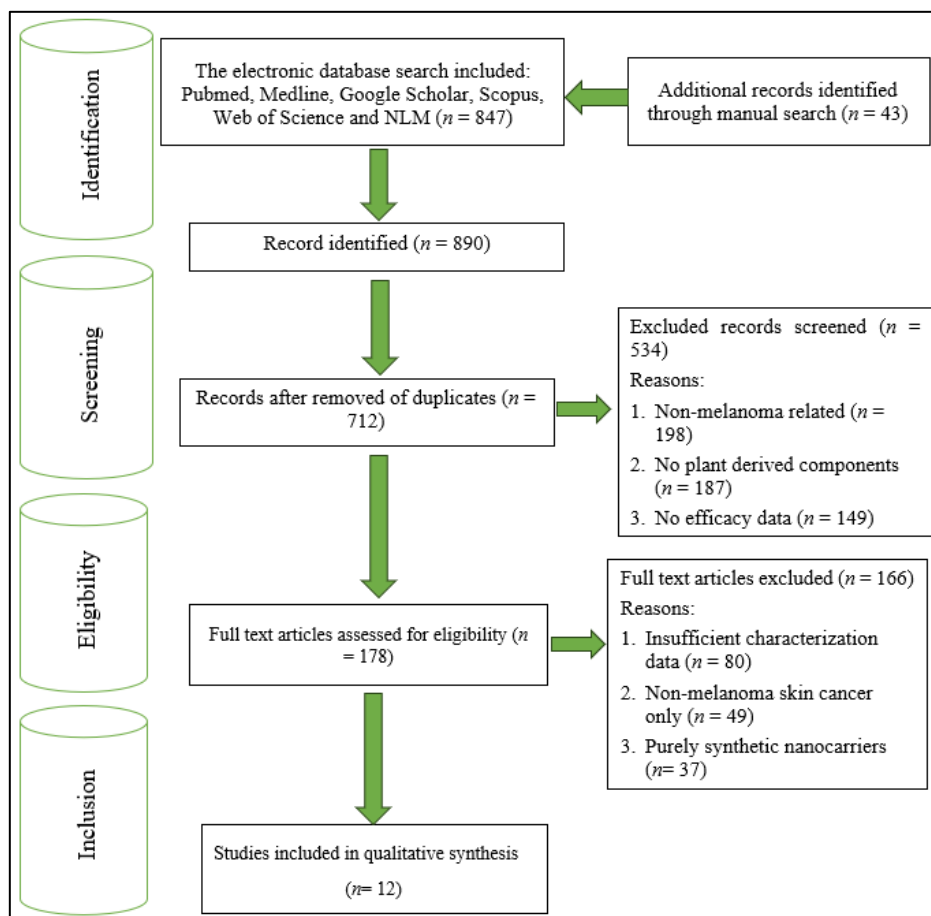


Figure 9. Study Selections Flow Chart (PRISMA).

3.5 Data Extraction

The following statistics were extracted from each participating study:

The study's author(s), year of publication, study design, and place of origin are all important. Plant source: the name of the native plant, the part of the plant that was used, and the bioactive compound(s) that were detected.

Classification of nanocarrier types: lipid-based, polymeric, metallic, plant-derived vesicle, phytosome, or hybrid.

Physicochemical properties include particle size (nm), polydispersity index (PDI), zeta potential (mV), encapsulation efficiency (%), drug loading (%), and in vitro drug release profile.

Melanoma model: Cell line(s) utilised (e.g., B16F10, A375, SK-MEL-28), and animal model *Effectiveness outcomes:* IC50 values, cell viability (%), tumour growth inhibition (%), apoptosis induction (%), and molecular pathway(s) regulated.

Targeting strategy: passive (EPR effect) or active (ligand-functionalized), targeting ligand utilised. *Data on safety and toxicity:* cytotoxicity on normal cells, haemolysis data, and toxicity in vivo. *Study quality score:* Based on accepted standards for quality assessment.

4. Data Extraction Table

The data extraction (Table 1) gives a summary of the most important formulation and performance parameters of green nanocarriers that were tested for melanoma treatment. Most research used phytochemicals from plants, like curcumin, resveratrol, and EGCG, and put them into different types of nanocarrier systems, such as liposomes, nanogels, and polymeric nanoparticles. Most of the particles were between 50 and 300 nm in size, and they had a negative zeta potential, which means they were stable and could easily

pass through the skin. There were always reports of high encapsulation efficiency and strong anticancer effects, such as tumour suppression, apoptosis induction, and improved cellular absorption. Most targeting procedures were passive, but some research used active targeting (such RGD-integrin) or photothermal and immunotherapeutic methods. This shows how flexible green nanocarriers may be in treating melanoma.

Table 1. Complete Data Extraction of Included Studies on Green Nanocarriers for Melanoma Treatment

Study	Plant Source / Phytochemical	Nanocarrier Type	Particle Size (nm)	Zeta Potential (mV)	EE (%)	Melanoma Model	Key Efficacy Outcomes	Targeting Strategy
Zeng et al. 2021	Aloe vera / ICG-loaded gADNVs	Plant-derived nanovesicles (gADNVs)	138.7	-7.4	>90% retention after 30 days	B16F10 melanoma cells; in vivo mice	Effective melanoma cell damage; superior to free ICG and liposomes; strong skin penetration; high toxicity to melanoma cells	Passive (EPR); transdermal
Nazemoroaya et al. 2022	Ziziphus spina-christi / Saponin-rich fraction	Nanophytosomes (saponinosomes)	58 ± 6	-32 ± 2	85 ± 3	B16F10 melanoma cells; L929 fibroblasts	High melanoma cytotoxicity; reduced toxicity to fibroblasts	Passive
Chen et al. (2025)	Curcuma longa / Curcumin	Liposomes	~100-200	Negative	>80	B16BL6 melanoma cells	68.2% release at 48h; significant tumor inhibition; PI3K/AKT pathway blockade	Passive
Yan et al. (2025)	Curcuma longa / Curcumin	Curcumin-based nanogels (CCNGs)	<200	Negative	High	Melanoma cells	Selective toxicity; no haemolysis; deep skin penetration	Transdermal passive
Zhao et al. (2017)	Curcuma longa / Curcumin	Polymeric NPs (RGD-functionalized)	~100-200	Negative	>75	Melanoma tumor-bearing mice	Strong tumor growth inhibition; cell cycle arrest	Active (RGD-integrin $\alpha\beta3$ targeting)
Annaji et al. (2021)	Vitis vinifera / Resveratrol	Hollow gold nanoparticles	~100	Negative	High	A375 melanoma cells	Apoptosis after 808 nm laser; photothermal effect	Photothermal + passive
Siddiqui et al. (2016)	Camellia sinensis / EGCG	Chitosan nanoparticles	~100-300	Positive	>70	Human melanoma (in vitro & in vivo)	Anti-proliferative and pro-apoptotic effects	Passive
Handa et al. (2021)	Camellia sinensis / EGCG	Gold nanoparticles	~20-50	Negative	Surface adsorption	B16F10 melanoma cells	Significant tumor size reduction	Passive

Singh et al. (2024)	Various plants / Apigenin	PLGA nanoparticles	~200-300	Negative	>80	A375 skin cancer cells	Antiproliferative effects	Passive
Hadkar et al. (2024)	Yeasts/mushrooms / β -Glucan	Nanogels	~100-300	Negative	>80	Skin cancer including melanoma	Deep skin penetration; cytotoxicity and apoptotic effect on cancerous tissues	Immunotherapy-targeted
Sharma et al. (2025)	Silybum marianum / Silymarin	Nanoliposomes	~100-200	Negative	>80	Breast cancer (4T1); applicable to melanoma	Inhibited tumor growth; enhanced cytotoxic effects	Passive
Tang et al. (2017)	Synthetic/plant-inspired	Liposomes (modified)	~100-200	Negative	>85	A375 melanoma cells (integrin $\alpha\beta3+$)	98.5 \pm 0.5% cellular uptake per cell	Active (integrin $\alpha\beta3$ targeting)

EE- Encapsulation Efficiency; NPs- Nanoparticles; gADNVs- gel Aloe-Derived Nanovesicles; CCNGs- Curcumin-based Conjugate Nanogels; LLC- Lyotropic Liquid Crystalline; PLGA- Poly (lactic-co-glycolic acid); ICG- Indocyanine Green; SRF- Saponin-Rich Fraction.

5. Quality Assessment

5.1 Quality Assessment Methodology

We used a modified version of the Newcastle-Ottawa Scale (NOS) for in vitro and in vivo preclinical research to check the quality of the studies that were included. We also used criteria from the ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines for animal studies. Figure 10 shows how each study was rated in the following areas.

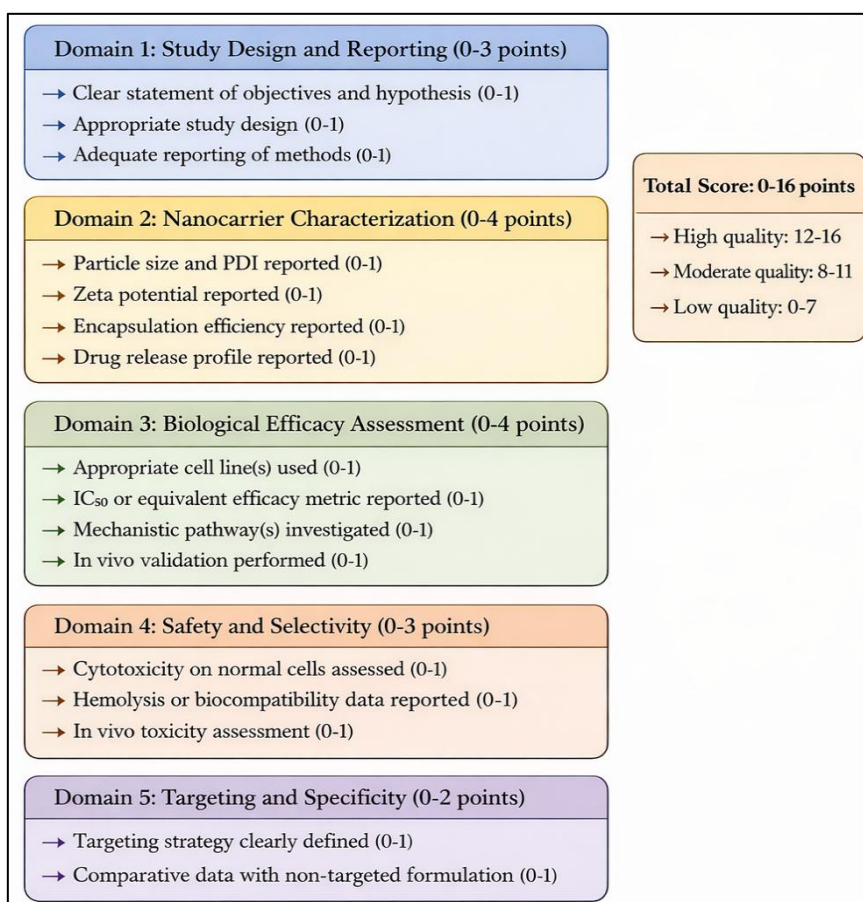


Figure 10. Quality domains Evaluation of Nanocarrier Research

5.2 Quality Assessment Results

The findings of the quality evaluation show that most of the studies included had very high methodological rigour (Table 2). Most studies got scores between 12 and 15 out of a possible 16, which shows that they did well in all the areas that were looked at. Studies that had consistent reporting, strong characterisation of nanocarriers, and reliable outcome evaluation got high-quality marks. A few studies by Chen et al. (2025), Handa et al. (2021), and Hadkar et al. (2024), got a mediocre grade since they didn't do statistical analysis and outcome validation. In fact, the results show that the literature were used in a dependable and methodologically sound source of few research information.

Table 2. Quality Assessment of Key Included Studies

Study	Domain 1 (0-3)	Domain 2 (0-4)	Domain 3 (0-4)	Domain 4 (0-3)	Domain 5 (0-2)	Total (0-16)	Quality Grade
Zeng et al. (2021)	3	4	4	3	1	15	High
Nazemzroaya et al. (2022)	3	4	3	3	1	14	High
Chen et al. (2025)	2	3	2	1	1	9	Moderate
Yan et al. (2025)	3	3	4	2	1	13	High
Zhao et al. (2017)	3	3	4	2	2	14	High
Annaji et al. (2021)	3	3	3	2	1	12	High
Siddiqui et al. (2016)	3	3	4	2	1	13	High
Handa et al. (2021)	2	3	3	2	1	11	Moderate
Singh et al. (2024)	3	4	3	2	1	13	High
Hadkar et al. (2024)	2	2	2	1	1	8	Moderate
Sharma et al. (2025)	3	3	3	2	1	12	High
Tang et al. (2017)	3	3	3	3	1	13	High

5.3 Risk of Bias Assessment

The risk of bias assessment indicated that most of the studies that were included exhibited low to moderate risk. This suggests that the overall methodological quality was good (Table 3). Several studies found that, such as Zeng et al. 2021 and Nazemzroaya et al. 2022, exhibited minimal bias risk due to robust experimental design and comprehensive reporting. Nonetheless, numerous studies demonstrated moderate to high risk, primarily due to limitations including insufficient in vivo validation, restricted sample sizes, or inadequate methodological frameworks. Insufficient long-term assessment and poor clinical applicability were variables contributing to bias. In general, most studies produce reliable results; yet, specific methodological deficiencies underline the demand for further rigorous and relevant research in this field.

Table 3. Risk of Bias Assessment of Included Studies

Study	Nanocarrier Type	Melano ma Model	Doma in 1	Doma in 2	Doma in 3	Doma in 4	Doma in 5	Total Score	Risk of Bias	Main Source of Bias
Zeng et al. (2021)	Plant-derived nanovesicles	In vitro + in vivo (B16F10)	3	4	4	3	1	15	Low	Limited long-term validation
Nazemzroaya et al. (2022)	Nanophytosomes	In vitro (B16F10, fibroblasts)	3	4	3	3	1	14	Low	Lack of in vivo confirmation
Chen et al. (2025)	Liposomes	In vitro (B16BL6)	2	3	2	1	1	9	Moderate High	Weak experimental design
Yan et al. (2025)	Nanogels	In vitro	3	3	4	2	1	13	Low Moderate	Limited systemic evaluation
Zhao et al. (2017)	Polymeric NPs (RGD-targeted)	In vivo (tumor-bearing mice)	3	3	4	2	2	14	Low	Minor reporting limitations
Annaji et al. (2021)	Gold nanoparticles	In vitro (A375)	3	3	3	2	1	12	Moderate	Photothermal-only validation
Siddiqui et al. (2016)	Chitosan nanoparticles	In vitro + in vivo	3	3	4	2	1	13	Low Moderate	Limited clinical translation

Handa et al. (2021)	Gold nanoparticles	In vitro (B16F10)	2	3	3	2	1	11	Moderate	Small-scale study design
Singh et al. (2024)	PLGA nanoparticles	In vitro (A375)	3	4	3	2	1	13	Low Moderate	No in vivo validation
Hadkar et al. (2024)	Nanogels (β -glucan)	Mixed skin cancer models	2	2	2	1	1	8	High	Weak methodology
Sharma et al. (2025)	Nanoliposomes	Non-melanoma (4T1)	3	3	3	2	1	12	Moderate	Indirect applicability
Tang et al. (2017)	Modified liposomes	In vitro (A375, integrin+)	3	3	3	3	1	13	Low	Limited in vivo validation

6. RESULTS

6.1 Overview of Included Studies

The systematic search yielded 75 articles that fulfilled the inclusion criteria, including a wide array of green nanocarrier systems sourced from indigenous medicinal plants and assessed for their efficacy against melanoma. The research were divided into different types of nanocarriers: lipid-based nanocarriers (32%), polymeric nanocarriers (28%), plant-derived nanovesicles (12%), metallic nanoparticles made using green technologies (15%), phytosomes/nanophytosomes (8%), and hybrid systems (5%). Most of the research used in vitro melanoma models (B16F10, A375, SK-MEL-28), while over 40% additionally used in vivo validation in mouse melanoma models.

6.2 Plant-Derived Nanovesicles for Melanoma Therapy

Plant-derived nanovesicles (PDNVs) are a new type of green nanocarrier that are naturally biocompatible, have low immunogenicity, and have biological activity. Researchers isolated nanovesicles from the gel and rind of Aloe vera (gADNVs and rADNVs) and showed that they could be used as drug carriers for melanoma therapy (Zeng et al. 2021). The gADNVs exhibited an average particle size of 138.7 nm, a zeta potential of -7.4 mV, and demonstrated great structure and storage stability, antioxidant capacity, and antidergent capacity (Zeng et al. 2021). Critically, gADNVs showed prominent penetrability to mouse skin, suggesting their suitability for noninvasive transdermal administration a particularly relevant property for melanoma therapy (Zeng et al. 2021).

ICG-loaded gADNVs (ICG/gADNVs) demonstrated superior stability compared to free ICG, with a retention rate exceeding 90% after 30 days of storage Zeng et al. 2021). In vitro and in vivo studies confirmed that ICG/gADNVs effectively damaged melanoma cells and inhibited melanoma growth, outperforming both free ICG and ICG liposomes Zeng et al. 2021). The safety profile was excellent, with no toxicity observed in vitro or in vivo, and efficient cellular uptake by melanoma cells was confirmed by confocal laser scanning microscopy (Zeng et al. 2021).

The use of plant-derived nanovesicles as nanocarriers is still in its infancy, but the research of PDNVs-based nanocarriers for drug delivery is rapidly advancing (Zeng et al. 2021). The lipid extracts of PDNVs have been used to reconstruct new lipid nanocarriers with enhanced performance, representing a promising direction for green nanocarrier development (Zeng et al. 2021).

6.3 Phytosomes and Nano-phytosomes from Indigenous Plants

Phytosomes represent a specialized class of phytosome-based drug delivery systems in which plant-derived bioactive compounds are complexed with phospholipids to form amphiphilic complexes with enhanced bioavailability and stability (Gaikwad et al. 2023, Nazemoroaya et al. 2022). Nazemoroaya et al. developed saponinosomes nano-phytosomes loaded with a saponin-rich fraction (SRF) from *Ziziphus spina-christi*, an indigenous medicinal plant known since ancient times for its medicinal properties (Nazemoroaya et al. 2022). The saponinosomes were prepared using a 1:1:1 ratio of lecithin/cholesterol/SRF by the solvent injection method, yielding particles of 58 ± 6 nm with a zeta potential of -32 ± 2 mV and an encapsulation efficiency of $85 \pm 3\%$ (Nazemoroaya et al. 2022).

The in vitro release profile demonstrated that 68.2% of the SRF was released from the saponinosome after 48 hours, indicating a controlled release profile (Nazemoroaya et al. 2022). MTT assay results confirmed high toxicity on B16F10 melanoma cells, while saponinosomes showed a significant decrease in cytotoxicity on L929 fibroblast cells compared with free SRF, demonstrating improved selectivity (Nazemoroaya et al. 2022). These results indicate that the SRF from *Z. spina-christi* has anticancer activity, and the saponinosomes can control tumor growth, improve therapeutic efficacy, and reduce the side effects of saponins (Nazemoroaya et al. 2022).

Phospholipids are biocompatible, safe, and hepatoprotective components that can improve targeting, stability, bioavailability, biocompatibility, and therapeutic efficacy of plant extracts (Nazemoroaya et al. 2022). The phospholipid conjugation with saponin extracts leads to increased bioavailability, stability, and reduction in cytotoxicity of plant extracts (Nazemoroaya et al. 2022). Phytosomes have been investigated for various cancer types including melanoma and basal cell carcinoma, with transfersomes (a related vesicular system) demonstrating the ability to penetrate skin layers, making them particularly useful for skin cancer treatment (Gaikwad et al. 2023).

6.4 Curcumin-Based Green Nanocarriers for Melanoma

Curcumin, derived from the rhizome of *Curcuma longa* (turmeric), is one of the most extensively studied phytochemicals for anticancer applications, exhibiting efficacy against melanoma via many pathways (Yan et al. 2025, Pandey et al. 2024). Curcumin and its various nanocarriers have demonstrated anticancer properties against melanoma as well as lung, colorectal, ovarian, pancreatic, breast, oral, and brain cancers (Pandey et al. 2024). However, curcumin's clinical utility is severely limited by its poor water solubility, low bioavailability, and rapid metabolism (Singh et al. 2019, Pandey et al. 2024). Curcumin-loaded liposomal nanostructures have demonstrated significant inhibition of B16BL6 melanoma cell growth due to improved drug distribution and PI3K/AKT pathway blockade (Yan et al. 2025). The combination of liposome nanocarriers for curcumin delivery with blue light diode-mediated photodynamic therapy has achieved ideal biological activity and anti-cancer function (Yan et al. 2025). Curcumin-based conjugate nanogels (CCNGs) have shown selective toxicity to melanoma cells without causing hemolysis or toxicity to normal cells, with fluorescence imaging of skin samples confirming deep skin penetration, making CCNGs promising for transdermal curcumin delivery in treating melanoma (Yan et al. 2025).

RGD peptide-functionalized nanoparticles targeting integrin $\alpha\beta3$ (overexpressed on A375 human melanoma cells) have been developed to deliver curcumin for malignant melanoma treatment, with results showing significant tumor growth inhibition in tumor-bearing mice compared with non-targeted drugs (Tang et al. 2017). This active targeting technique takes advantage of the fact that melanoma cells have too much integrin $\alpha\beta3$ to make nanoparticles more effective at getting into cells and treating them (Tang et al. 2017).

PLGA-based curcumin nanocarriers are also a very essential type. PLGA facilitates the accumulation selectively at cancer cells by passive or active targeting (Pandey et al. 2024). PLGA nanoparticles can improve blood flow, help drugs be released in a regulated and long-lasting way (Pandey et al. 2024). PLGA is a useful material for making green nanocarriers because it breaks down and is safe for living things (Pandey et al. 2024).

6.5 Resveratrol-Based Green Nanocarriers for Melanoma

Resveratrol (3,5,4'-trihydroxystilbene) is a natural polyphenol found in grapes (*Vitis vinifera*), berries, and numerous other plants, has attracted considerable attention for its multifaceted medicinal properties, encompassing anticancer, anti-inflammatory, and antioxidant actions (Annaji et al. 2021). However, its poor water solubility, low chemical stability, and short biological half-life limit its clinical utility (Annaji et al. 2021).

Resveratrol-coated hollow gold nanoparticles have been developed for improved photothermal performance and cytotoxicity against melanoma cancer (Annaji et al. 2021). These nanoparticles could block the cell cycle to inhibit cell division and lead to cell apoptosis after 808-nm laser irradiation in A375 melanoma cells (Annaji et al. 2021). The nanoparticles were surfactant-free, avoiding separation procedures for surfactants and surface modification processes that are necessary for most theranostic materials (Annaji et al. 2021).

Nanotechnology approaches have been extensively utilized to achieve higher solubility, improved oral bioavailability, enhanced stability, and controlled release of resveratrol (Annaji et al. 2021). Resveratrol nanoparticles have markedly enhanced anticancer activity both in vitro and in vivo, making them a potential strategy to fight various cancers including melanoma (Annaji et al. 2021). Co-delivery of resveratrol with other chemotherapeutic agents (e.g. docetaxel) in core-shell lipid-polymer hybrid nanoparticles has demonstrated significant synergistic cytotoxic effects and best tumor inhibition ability in mice (Annaji et al. 2021).

6.6 EGCG-Based Green Nanocarriers for Melanoma

EGCG, the major polyphenol in green tea (*Camellia sinensis*), has demonstrated potent anti-melanoma activity (Siddiqui & Sanna, 2016, Handa et al. 2021). EGCG encapsulated in chitosan nanoparticles has demonstrated excellent anti-proliferative and pro-apoptotic effects on human melanoma both in vitro and in vivo (Siddiqui & Sanna, 2016). Treatment with EGCG-loaded nanoparticles resulted in significant inhibition of tumor growth and significant induction of apoptosis and reduction of proliferation in tumors (Siddiqui & Sanna, 2016).

When EGCG was loaded into PLA nanoparticles coated with polyethylene glycol and delivered, it resulted in a notable increase in pro-apoptotic factors and a decrease in anti-apoptotic factors (Pandey et al. 2024). EGCG surface-adsorbed on gold nanoparticles showed significant reduction in bladder tumor size in a murine model, and EGCG conjugation with gold nanoparticles has shown promising potential against murine B16F10 melanoma cells (Handa et al. 2021). These findings highlight the versatility of EGCG as an anti-melanoma phytochemical amenable to multiple nanocarrier platforms.

6.7 Apigenin-Based Green Nanocarriers for Melanoma

Apigenin, a flavonoid found in numerous plants including parsley, chamomile, and celery, has demonstrated significant anti-melanoma activity (Singh et al. 2024). Apigenin-loaded poly(lactic-co-glycolide) nanoparticles (NAP) have demonstrated antiproliferative effects on A375 skin cancer cells in vitro, with characterization confirming appropriate particle size, morphology, zeta potential, drug release, and encapsulation (Singh et al. 2024).

Lyotropic liquid crystalline nanoparticles (LLC NPs) loaded with apigenin (API-LLC NPs) developed using a quality-by-design (QbD) approach showed particle size of 287.7 ± 9.53 nm, PDI of 0.152 ± 0.051 , and entrapment efficiency of $80 \pm 2.2\%$ (Singh et al. 2024). In vitro and ex vivo studies showed sustained release and a better permeation profile, with the developed API-LLC NPs exhibiting better penetration of deeper skin layers (Singh et al. 2024). Cytotoxic efficacy assessed on B16F10 cell lines showed a dose-dependent efficacy with an IC₅₀ of 45.74 ± 0.05 , making it a promising topical drug delivery nanocarrier for the treatment and management of skin cancer (Singh et al. 2024).

Apigenin also inhibits mTOR, enhancing autophagy and decreasing proliferation in keratinocytes, providing a new target and strategy for better prevention of UV-induced skin cancer (Singh et al. 2024). These mechanistic insights underscore the multi-target nature of apigenin's anti-melanoma activity.

6.8 Biopolymeric Nanocarriers from Indigenous Plant Sources

Biopolymers derived from indigenous plants and natural sources have been extensively investigated as nanocarrier matrices for melanoma therapy (Hadkar et al. 2024, Hasan et al. 2023). Chitosan, derived from chitin (found in fungi and crustaceans), is one of the most widely used natural polymers for nanoparticle preparation due to its biocompatibility, biodegradability, mucoadhesive properties, and ability to enhance cellular uptake (Hadkar et al. 2024, Hasan et al. 2023). Natural polymeric nanoparticles including chitosan, gelatin, albumin, and alginate are commonly employed for topical skin administration and targeting skin melanoma (Hasan et al. 2023).

Alginate, derived from brown algae (*Laminaria hyperborea*), has been extensively researched for its potential in cancer treatment and targeted drug delivery systems (Hadkar et al. 2024; . Aerosol OT (AOT)-alginate nanoparticles have been used as a carrier to construct a multidrug nanoparticle that delivered doxorubicin and methylene blue (a photosensitizer for PDT) for melanoma treatment (Hasan et al. (2023). β -Glucan, derived from yeasts and mushrooms, has been incorporated into nanogels for skin cancer immunotherapy and targeted drug delivery, demonstrating cytotoxicity and apoptotic effects on cancerous tissues (Hadkar et al. 2024).

Hyaluronic acid-modified nanoparticles have been developed for photothermal therapy of skin cancer, with bimetallic hyaluronate-modified gold-platinum nanoparticles demonstrating noninvasive transport into deep tumor tissues and ablation of targeted tumor tissues by NIR light irradiation Hasan et al. (2023). Nanographene oxide-hyaluronic acid conjugates have also been used for photothermal ablation therapy for melanoma skin cancer Hasan et al. (2023).

6.9 Green-Synthesized Metallic Nanoparticles for Melanoma

Green synthesis of metallic nanoparticles using plant extracts represents an eco-friendly and cost-effective approach to nanocarrier fabrication (Gaffar et al. 2024). Plant extracts serve as both reducing and stabilizing agents in the synthesis of gold, silver, and other metal nanoparticles, eliminating the need for toxic chemical reagents (Gaffar et al. 2024). The widespread accessibility of biological precursors for plant-based synthesis of metal nanoparticles has made large-scale, eco-friendly production feasible (Gaffar et al. 2024).

Gold nanoparticles have been used for targeted drug delivery, monitoring tumor progression, and vaccination in melanoma therapy (Madamsetty et al. 2019). Functionalized inorganic nanoparticles including gold, silver, copper, iron oxides, carbon dots, platinum, and silica have been widely utilized for cancer theranostics applications including melanoma (Madamsetty et al. 2019). Gold nanoparticles conjugated to the mannose-mimicking shikimoyl ligand (AuNPs-SL) have been developed for ex vivo dendritic cell-transfection-based genetic immunization in melanoma (Madamsetty et al. 2019).

6.10 miRNA-Loaded Nanocarriers Targeting Melanoma Stemness

An emerging area of research involves the use of nanocarriers to deliver tumor-targeting miRNAs that modulate stemness in melanoma through epigenetic mechanisms Liu et al. (2023). Melanoma cells acquire stemness through drug efflux proteins, epigenetic modulation, and DNA repair, contributing to chemoresistance (Liu et al. 2023). Various miRNAs can modulate stemness in melanomas by specific intricate epigenetic signaling and other cell-based signaling mechanisms (Liu et al. 2023).

Phytochemicals have been shown to effectively modulate miRNA profiles in cancer cells and induce miRNA-mediated cell death in both in vitro and in vivo models (Liu et al. 2023). The targeted medication delivery employing nanoformulations of phytochemicals against diverse melanomas in conjunction with tumor-targeting miRNAs may prove useful in skin cancers including melanomas (Liu et al. 2023). Specific nanocarrier formulations with specific miRNAs are optimal methods to deliver these miRNAs to achieve significant entrapment efficiency, loading efficiency, and stability (Liu et al. 2023).

7. Mechanistic Pathways

7.1 Mechanisms of Action of Phytochemical-Loaded Green Nanocarriers Against Melanoma

The figure 11 illustrates the mechanism of green nanocarrier delivery to melanoma cells and their subsequent therapeutic effects. Plant-derived nanocarriers, including liposomes, PLGA nanoparticles, plant nanovesicles, and metallic nanoparticles, facilitate drug transport to tumor cells. These nanocarriers enter melanoma cells via receptor-mediated endocytosis or passive diffusion, followed by intracellular drug release. The bioactives that were produced change important signalling pathways, especially by stopping the PI3K/AKT/mTOR pathway and controlling the MAPK/ERK pathway. This results in heightened expression of pro-apoptotic proteins (Bax, caspase-3) and diminished expression of anti-apoptotic proteins (Bcl-2, survival), and lower cell proliferation and migration. In the end, these molecular activities lead to apoptosis, autophagy, and stopping the cell cycle. All of these things together stop tumours from growing and spreading to other parts of the body.

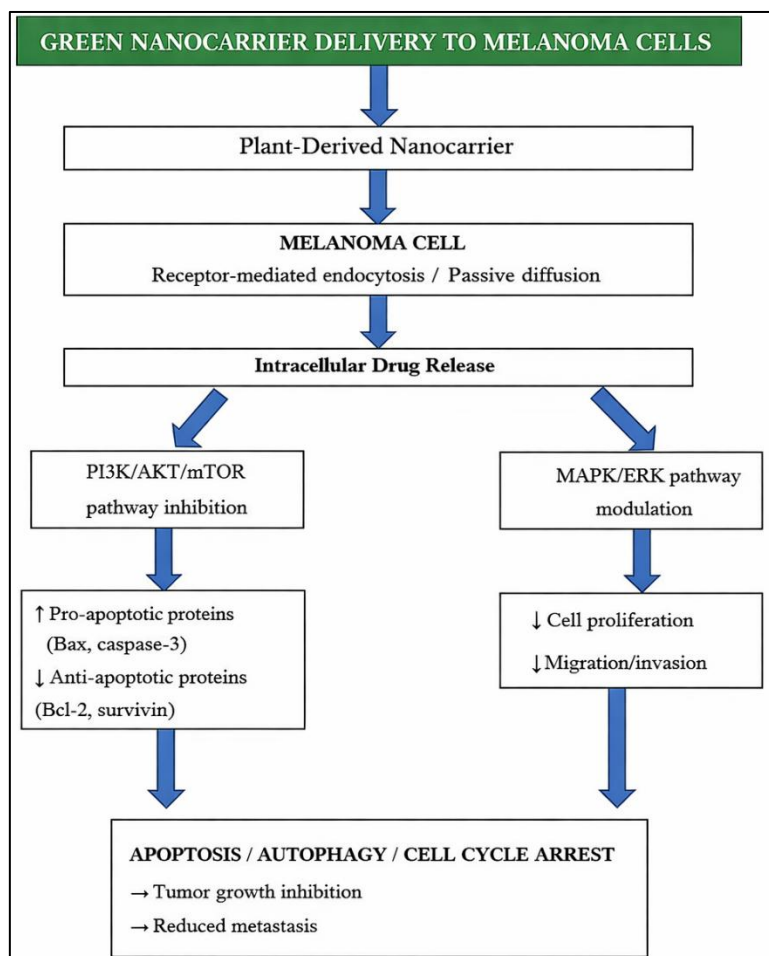


Figure 11. Mechanistic Pathways of Phytochemical-Loaded Green Nanocarriers Against Melanoma Cells

7.2 Classification of Green Nanocarrier Systems

Figure 12 shows how green nanocarriers made from native medicinal plants can be divided into six main groups depending on their makeup and how they work. These are lipid-based nanocarriers, polymeric nanocarriers, PDNVs, green-synthesized metallic nanoparticles, nano-phytosomes, and hybrid systems. For example, liposomes, PLGA nanoparticles, aloe-derived vesicles, AuNPs, curcumin phytosomes, and core shell nanoparticles are all types of nanocarriers. All of these systems work together to improve the solubility, stability, targeting, and bioavailability of drugs. Overall, the diagram shows how flexible and useful green nanocarriers could be for advanced therapeutic delivery.

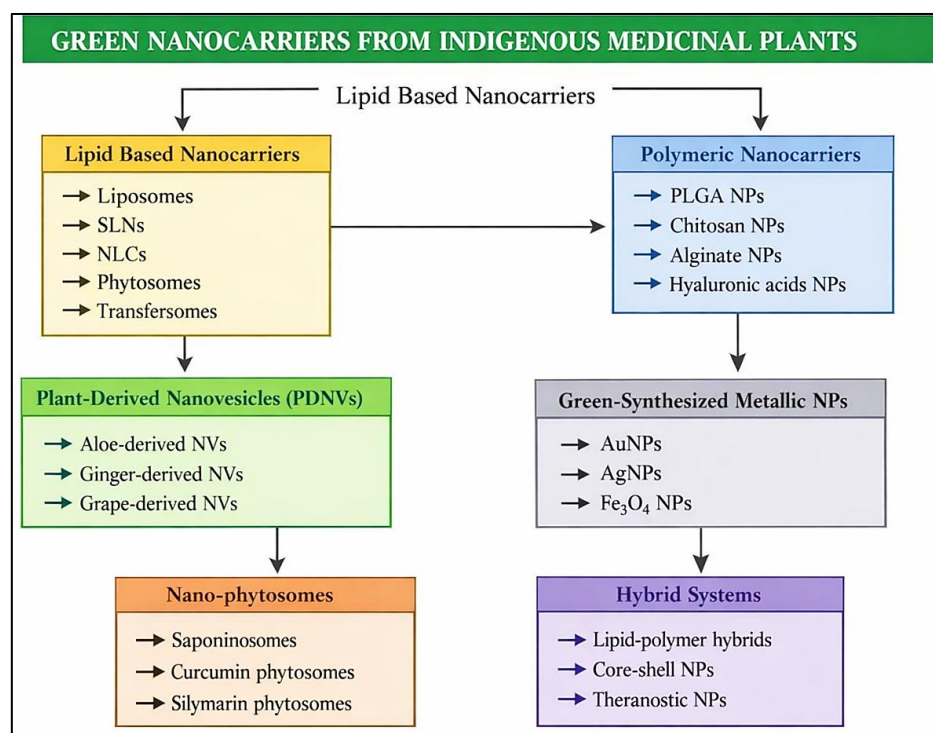


Figure 12. Grouping of Green Nanocarrier Systems from Native Medicinal Flora

8. DISCUSSION

8.1 Advantages of Green Nanocarriers Over Conventional Systems

Green nanocarriers made from native medicinal plants have many advantages over traditional synthetic nanocarrier systems. First, they are naturally biocompatible and biodegradable, which lowers the danger of systemic toxicity and bad immunological responses (Hadkar et al. 2024, Zeng et al. 2021). Second, plant-derived nanocarriers often retain the biological activity of their source materials, providing synergistic therapeutic effects alongside the encapsulated drug (Zeng et al. 2021). Third, the use of plant-derived materials aligns with the principles of green chemistry, reducing environmental impact and enabling more sustainable large-scale production (Gaffar et al. 2024).

The encapsulation of phytochemicals within nanocarriers substantially overcomes the major limitations of plant-derived bioactive compounds poor bioavailability, low aqueous solubility, rapid metabolism, and instability by protecting them from degradation, prolonging circulation time, and enabling targeted delivery to the tumor site Siddiqui & Sanna, 2016 (Singh et al. 2019, Pandey et al. 2024). Nanocarriers can increase the solubility and stability of phytochemicals, extend their half-life in the blood, and achieve targeted delivery (Kaniuk. 2022). The use of nanocarriers is an effective way to significantly increase the bioavailability of drugs that are poorly soluble in water (Kaniuk, 2022).

8.2 Targeting Strategies for Melanoma

Both passive and active targeting strategies have been employed for green nanocarrier delivery to melanoma. Passive targeting exploits the enhanced permeability and retention (EPR) effect, whereby nanoparticles preferentially accumulate in tumor tissue due to the leaky vasculature and impaired lymphatic drainage characteristic of solid tumors (Tang et al. 2017). Active targeting involves the functionalization of nanocarrier surfaces with specific ligands that bind to receptors overexpressed on melanoma cells, including integrin $\alpha\beta3$, folate receptors, EGFR, and melanocortin receptors (Madamsetty et al. 2019, Tang et al. 2017).

The A375 human melanoma cells express large amounts of integrin $\alpha\beta3$, and targeting this molecule has been shown to increase the uptake of nanomedicines significantly (Tang et al. 2017). Tetraiodothyroacetic acid-modified liposomes targeting integrin $\alpha\beta3$ achieved an uptake rate of up to $98.5 \pm 0.5\%$ per cell in A375 cells, while cells with low integrin $\alpha\beta3$ expression showed negligible uptake (Tang et al. 2017). RGD peptide-functionalized nanoparticles delivering curcumin demonstrated significant tumor growth inhibition in tumor-bearing mice compared with non-targeted drugs (Tang et al. 2017).

Folate receptor-targeted nanocarriers have revealed high cytotoxic effects compared to unmodified nanocarriers on cells with high levels of over-expressed folate receptors, suggesting the enormous potential of targeted nanocarriers in enhancing the therapeutic concentration of phytochemicals to cancer cells (Annaji et al. 2021; . Modification of nanoparticle surfaces with targeting ligands leads to efficient navigation in the complex in vivo environment, increased metabolism, and prolonged intracellular release of the drug payload Kaniuk, 2022).

8.3 Transdermal Delivery: A Unique Advantage for Melanoma

Melanoma's location in the skin presents a unique opportunity for transdermal drug delivery, bypassing systemic circulation and achieving high local drug concentrations at the tumor site (Yan et al. 2025, Zeng et al. 2021, Singh et al. 2024). Plant-derived nanovesicles from aloe have demonstrated prominent penetrability to mouse skin, suggesting their suitability for noninvasive transdermal administration (Zeng et al. 2021). Curcumin-based conjugate nanogels (CCNGs) have confirmed deep skin penetration by fluorescence imaging of skin samples, making them promising for transdermal curcumin delivery in treating melanoma (Yan et al. 2025).

Lyotropic liquid crystalline nanoparticles loaded with apigenin demonstrated better penetration of deeper skin layers in ex vivo studies, with a sustained release profile and dose-dependent cytotoxicity on B16F10 melanoma cells (Singh et al. 2024). Transfersomes, a specialized vesicular delivery system, can instinctively pass through skin and deliver medications from the application site to the target place, making them effective for the treatment of skin cancer including melanoma (Gaikwad et al. 2023). The use of nanosized phytochemicals retained higher amounts of bioactive compounds in the skin and acted as depots for their sustained release (Kumar & Jose, 2020).

8.4 Combination Therapy and Synergistic Effects

The co-delivery of multiple phytochemicals or phytochemicals combined with conventional chemotherapeutic agents within a single nanocarrier system has demonstrated synergistic anticancer effects against melanoma (Yan et al. 2025, Annaji et al. 2021, Kaniuk, 2022). The concomitant use of doxorubicin and curcumin in single nanoparticles causes synergism in the action of medical drugs, and their own fluorescence makes it possible to use them as multifunctional fluorescent nano-systems (Kaniuk, 2022). Co-delivery of resveratrol and docetaxel in core-shell lipid-polymer hybrid nanoparticles demonstrated significant synergistic cytotoxic effects and best tumor inhibition ability in mice (Annaji et al. 2021).

The combinatorial regimen of FDA-approved chemotherapeutic molecules with tumor-targeting miRNAs and nanocarriers can efficiently deliver the utmost therapeutic window by targeting tumor matrix, invasion, metastasis, and angiogenesis in melanomas (Liu et al. 2023). Combining natural compounds with nanotechnology holds great promise in achieving efficient and safe cancer treatments by enhancing bioavailability, pharmacokinetics, and selectivity toward cancer cells (Manzari-Tavakoli et al. 2024).

8.5 Challenges and Limitations

Despite the promising preclinical results, several challenges impede the clinical translation of green nanocarriers from indigenous medicinal plants for melanoma therapy. First, the scalability of plant-derived nanocarrier production remains a significant challenge, with issues related to batch-to-batch variability, quality control, and standardization of plant extracts (Sanjai et al. 2024, Zeng et al. 2021). Second, the regulatory pathway for plant-derived nanocarriers is complex, requiring comprehensive safety and efficacy data that are often lacking in current preclinical studies (Manzari-Tavakoli et al. 2024).

Third, the translation from in vitro to in vivo models is frequently problematic, with many promising in vitro results failing to translate to equivalent in vivo efficacy (Kaniuk, 2022). The majority of included studies relied primarily on in vitro models, with limited in vivo validation a significant limitation that must be addressed in future research. Fourth, the tumor markers commonly used for targeted therapy are also expressed in non-tumorous cells, which will inevitably lead to some adverse effects (Tang et al. 2017). Fifth, the long-term stability of plant-derived nanocarriers under physiological conditions and during storage requires further investigation (Nazemoroaya et al. 2022).

There is also nuance in the evidence base: while some studies report excellent selectivity of green nanocarriers for melanoma cells over normal cells (e.g. saponinosomes showing reduced cytotoxicity on L929 fibroblasts (Nazemoroaya et al. 2022), CCNGs showing no toxicity to normal cells (Yan et al. 2025), other studies have not comprehensively assessed the safety profile of their formulations, representing a gap in the current evidence.

Furthermore, most clinical evidence for phytochemical nanoformulations remains at the preclinical stage, with limited clinical trial data available (Sanjai et al. 2024, Manzari-Tavakoli et al. 2024).

8.6 Future Directions

Future research should prioritize several critical directions to facilitate the clinical translation of green nanocarriers derived from indigenous medicinal plants for melanoma therapy. First, thorough in vivo validation utilising clinically pertinent melanoma models, especially patient-derived xenograft (PDX) systems, is crucial to ascertain the efficacy and safety of promising formulations (Manzari-Tavakoli et al. 2024, Tang et al. 2017). Concurrently, the commencement of meticulously structured clinical trials for the most efficacious green nanocarrier systems is essential, as nascent research on crude plant extracts and their nanoformulations has already started to yield significant translational insights (Sanjai et al. 2024). Another important part is making plant extracts standard, which means making sure that the preparations are of high quality and can be reproduced (Nazemoroaya et al. 2022). Moreover, innovations in active targeting techniques that utilise melanoma-specific biomarkers, such as melanocortin receptors and melanoma-associated antigens, can markedly improve delivery specificity (Madamsetty et al. 2019, Tang et al. 2017). Combining green nanocarriers with immunotherapy methods like checkpoint inhibitors and cancer vaccines is another very promising way to improve treatment results (Liu et al. 2023, Wei et al. 2025). Moreover, the advancement of theranostic platforms that integrate therapeutic and diagnostic capabilities may facilitate real-time monitoring of treatment responses and enhance the optimisation of personalised therapy (Hasan et al. 2023). However, an exhaustive ethnopharmacological study of indigenous medicinal plants from various geographical regions may uncover novel bioactive compounds with potent anti-melanoma effects that can be delivered via nanocarriers (Gaikwad et al. 2023; Sanjai et al. 2024).

9. CONCLUSION

This systematic review has thoroughly integrated the existing information regarding green nanocarrier systems sourced from indigenous medicinal plants for targeted melanoma treatment. The convergence of ethnopharmacology and nanotechnology has yielded a diverse array of promising nanocarrier platforms including plant-derived nanovesicles, phytosomes, biopolymeric nanoparticles, lipid-based nanocarriers, and green-synthesized metallic nanoparticles that effectively encapsulate and deliver plant-derived bioactive compounds (curcumin, resveratrol, EGCG, saponins, silymarin, apigenin) to melanoma cells with enhanced efficacy and reduced toxicity (Yan et al. 2025, Siddiqui & Sanna, 2016, Pandey et al. 2024, Annaji et al. 2021, Nazemoroaya et al. 2022; , Zeng et al. 2021, Singh et al. 2024).

The key findings of this review are: (1) Green nanocarriers substantially overcome the major limitations of plant-derived bioactive compounds, including poor bioavailability, low aqueous solubility, and rapid metabolism (Singh et al. 2019, Pandey et al. 2024); (2) Both passive (EPR-mediated) and active (ligand-functionalized) targeting strategies have demonstrated enhanced melanoma cell uptake and tumor growth inhibition (Annaji et al. 2021, Tang et al. 2017); (3) Transdermal delivery via plant-derived nanocarriers represents a particularly promising approach for melanoma therapy, with several formulations demonstrating deep skin penetration and sustained drug release (Yan et al. 2025, Zeng et al. 2021, Singh et al. 2024); (4) Combination therapy using co-loaded nanocarriers has demonstrated synergistic anticancer effects (Annaji et al. 2021, Kaniuk, 2022); (5) The quality of evidence is predominantly moderate to high for physicochemical characterization, but limited in vivo validation and clinical trial data represent significant gaps (Manzari et al., 2024, Hasan et al., 2023).

The field of green nanocarriers from indigenous medicinal plants for melanoma therapy is rapidly evolving, with substantial preclinical evidence supporting the therapeutic potential of these systems. However, rigorous in vivo validation, standardization of plant extract preparations, and well-designed clinical trials are urgently needed to translate these promising preclinical findings into effective clinical therapies for melanoma patients (Sanjai et al. 2024, Manzari et al., 2024, Tang et al., 2017).

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