

# Terpenoid-Based Nanoemulgels as Matrix Metalloproteinase (MMP) Inhibitors in Melanoma Therapy: Mechanistic Insights, Formulation Strategies, and Therapeutic Potential

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## Abstract

Melanoma is an aggressive skin cancer with high metastatic potential driven by rapid progression, extracellular matrix (ECM) degradation, and therapy resistance. Matrix metalloproteinases (MMP-2 and MMP-9) are key mediators of invasion, angiogenesis, and metastasis through basement membrane breakdown and facilitation of tumor cell dissemination. Despite advances in targeted therapies and immunotherapy, clinical outcomes remain limited due to systemic toxicity, poor tumor selectivity, and acquired resistance, highlighting the need for novel molecularly targeted strategies. Terpenoids, plant-derived bioactive compounds, exhibit significant anticancer potential through antioxidant, anti-inflammatory, pro-apoptotic, and anti-metastatic effects. They modulate multiple signaling pathways, including NF- $\kappa$ B, MAPK, PI3K/AKT, and AP-1, resulting in downregulation of MMP expression and suppression of melanoma invasion and metastasis. However, their clinical application is constrained by poor aqueous solubility, instability, and low bioavailability. To address these limitations, nanoemulgel-based delivery systems have emerged as a promising topical platform. Nanoemulgels integrate the advantages of nanoemulsions and hydrogels, providing enhanced skin permeation, sustained release, improved stability, and localized drug delivery. Terpenoid-loaded nanoemulgels improve dermal penetration, increase tumor site accumulation, and enable controlled inhibition of MMP-mediated ECM degradation. Additionally, they enhance antioxidant defenses, reduce inflammatory mediators, and promote apoptosis in melanoma cells. Overall, terpenoid-based nanoemulgels offer a multifunctional and targeted therapeutic approach by combining MMP inhibition, anti-inflammatory activity, and advanced drug delivery. This review discusses the mechanistic role of MMPs in melanoma progression, the therapeutic

potential of terpenoids, and recent advances in nanoemulgel systems as next-generation strategies for effective melanoma treatment and metastasis suppression for improved patient outcomes overall therapy efficacy.

**Keywords:** Melanoma, Matrix metalloproteinases, Nanoemulgel, Terpenoids, Topical drug delivery, Nanotechnology

## I. Introduction

Melanoma represents one of the most aggressive and therapeutically challenging forms of skin cancer, originating from the malignant transformation of melanocytes. Although it accounts for a smaller proportion of cutaneous malignancies than basal cell carcinoma and squamous cell carcinoma, melanoma is responsible for the majority of skin cancer-related deaths because of its rapid progression, high metastatic potential, and resistance to therapy [1]. The global incidence of melanoma has increased significantly over recent decades, particularly in populations with high ultraviolet (UV) exposure and genetic susceptibility. Environmental factors, excessive UV radiation, oxidative stress, and molecular alterations collectively contribute to melanoma initiation and progression [2]. Advanced melanoma frequently metastasizes to vital organs such as the lungs, liver, brain, and bones, resulting in poor prognosis and reduced survival rates. The aggressive nature of melanoma is associated with dysregulated cellular proliferation, angiogenesis, immune evasion, and extracellular matrix (ECM) remodeling, all of which facilitate tumor invasion and dissemination [3].

Despite substantial progress in melanoma treatment, major therapeutic limitations still persist. Surgical excision remains effective for localized melanoma; however, treatment success decreases considerably in metastatic stages. Conventional chemotherapeutic agents, including dacarbazine and temozolomide, often demonstrate limited efficacy

because of systemic toxicity, poor tumor selectivity, and multidrug resistance [4]. Similarly, targeted therapies against BRAF and MEK mutations have improved clinical outcomes in selected patients, yet resistance commonly develops through pathway reactivation and tumor heterogeneity. Immune checkpoint inhibitors such as anti-PD-1 and anti-CTLA-4 antibodies have revolutionized melanoma therapy by enhancing antitumor immunity, but incomplete response rates, immune-related adverse effects, and acquired resistance continue to limit long-term effectiveness. Furthermore, the dense tumor microenvironment and abnormal vascular architecture reduce drug penetration into melanoma tissues, emphasizing the need for more effective and targeted therapeutic strategies [5].

Among the molecular factors involved in melanoma progression, matrix metalloproteinases (MMPs) play a critical role in tumor invasion, angiogenesis, and metastasis. MMPs are zinc-dependent proteolytic enzymes that degrade ECM components and basement membranes, thereby enabling melanoma cells to migrate and invade surrounding tissues. In particular, MMP-2 and MMP-9 are highly overexpressed in metastatic melanoma and are strongly associated with poor clinical outcomes [6]. Increased MMP activity promotes ECM degradation, epithelial-mesenchymal transition (EMT), inflammatory signaling, and angiogenesis, all of which accelerate metastatic dissemination. Consequently, inhibition of MMP-mediated pathways has emerged as a promising therapeutic strategy aimed at suppressing melanoma invasion and metastasis rather than merely eliminating tumor cells [7].

Natural bioactive compounds, especially terpenoids, have gained increasing attention for their potential anticancer properties and favorable safety profiles. Terpenoids are structurally diverse plant-derived secondary metabolites known to exhibit antioxidant, anti-inflammatory, antiproliferative, pro-apoptotic, and anti-metastatic activities. Several terpenoids, including ursolic acid, betulinic acid, limonene, carvacrol, thymol, and farnesol, have demonstrated the ability to regulate melanoma-associated signaling pathways such as MAPK, PI3K/Akt, NF- $\kappa$ B, and MMP-mediated ECM degradation. Importantly, these compounds can suppress MMP-2 and MMP-9 expression, thereby reducing melanoma cell migration, invasion, and angiogenesis. However, the therapeutic application of terpenoids is frequently limited by poor aqueous solubility, low bioavailability, rapid degradation, and insufficient skin penetration [8].

To overcome these limitations, nanotechnology-based drug delivery systems have emerged as promising approaches for melanoma-targeted therapy. Nanoformulations such as nanoemulsions, liposomes, solid lipid nanoparticles, polymeric nanoparticles, and nanoemulgels can enhance the stability, solubility, permeability, and bioavailability of terpenoid compounds. Among these systems, nanoemulgels are particularly attractive for topical melanoma treatment because they combine the advantages of nanoemulsions and hydrogels, enabling improved dermal penetration, prolonged skin retention, controlled drug release, and localized therapeutic action [9]. Additionally, nanoscale delivery systems may enhance selective accumulation of terpenoids within melanoma tissues while improving MMP inhibitory activity and reducing systemic toxicity. Recent studies also indicate that terpenoid-loaded nanocarriers can modulate oxidative stress, inflammatory mediators, apoptotic pathways, and ECM remodeling, thereby providing a multifaceted therapeutic approach against melanoma progression and metastasis [10].

Therefore, the integration of terpenoid therapeutics with advanced nanocarrier systems represents a promising strategy for targeted anti-invasive melanoma therapy. This review focuses on the pathological role of MMPs in melanoma progression, the anti-metastatic potential of terpenoids, and recent advances in terpenoid-based nanoformulations, particularly nano-emulgels, for MMP-targeted melanoma treatment.

## II. Melanoma Pathophysiology and Molecular Progression

Melanoma is a highly aggressive skin malignancy that develops through a multistep process involving genetic mutations, oxidative stress, and complex interactions within the tumor microenvironment. Chronic UV radiation is the primary etiological factor responsible for melanocyte transformation, as it induces DNA damage, genomic instability, and oxidative stress. Mutations in oncogenes and tumor suppressor genes such as *BRAF*, *NRAS*, *KIT*, *PTEN*, and *CDKN2A* contribute significantly to melanoma initiation and progression [11]. Among these, the *BRAF<sup>V600E</sup>* mutation is one of the most frequently observed molecular alterations and leads to constitutive activation of the mitogen-activated protein kinase (MAPK) signaling pathway, thereby promoting melanoma cell proliferation, survival, and invasion. Additionally, loss of *PTEN* expression activates the phosphatidylinositol-3 kinase/protein kinase B

(PI3K/AKT) pathway, which enhances tumor growth, metabolic adaptation, angiogenesis, and therapeutic resistance. The combined dysregulation of MAPK and PI3K/AKT signaling pathways is strongly associated with melanoma aggressiveness and metastatic potential [12].

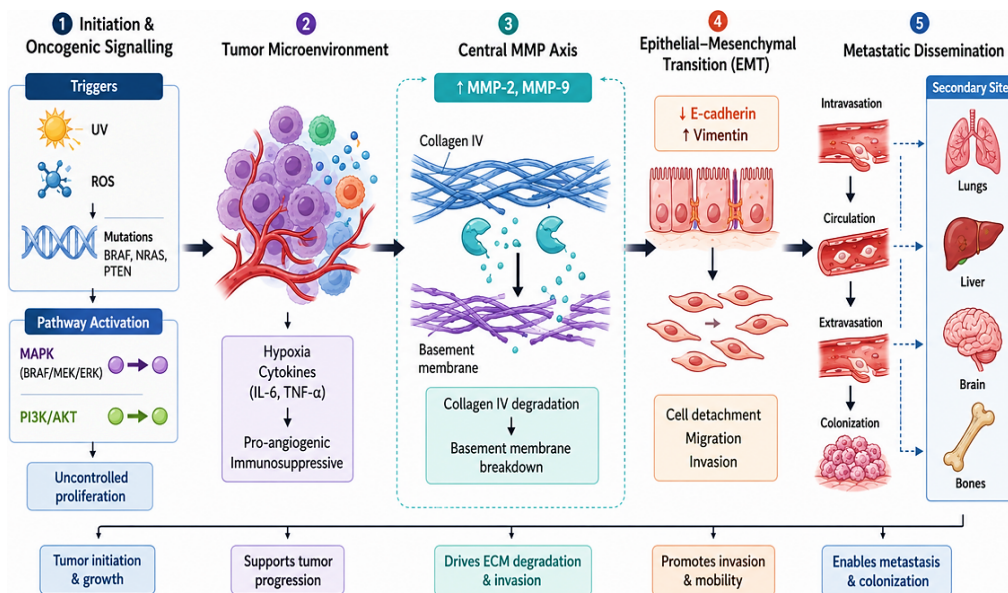
Melanoma progression occurs through sequential pathological stages characterized by increasing invasiveness. Initially, melanoma develops in the radial growth phase, during which atypical melanocytes proliferate horizontally within the epidermis and superficial dermis with limited metastatic capability. As the disease advances to the vertical growth phase, melanoma cells invade deeper dermal layers and acquire enhanced proliferative and metastatic properties. Eventually, metastatic melanoma develops when malignant cells disseminate through lymphatic and hematogenous routes to distant organs such as the lungs, liver, brain, and bones. This progression is driven by cumulative molecular alterations, extracellular matrix remodeling, and adaptive changes within the tumor microenvironment [13].

The tumor microenvironment plays a crucial role in melanoma progression and therapeutic resistance. Melanoma cells interact with fibroblasts, endothelial cells, immune cells, inflammatory mediators, and extracellular matrix components, creating a highly dynamic and immunosuppressive environment favorable for tumor growth. Tumor-associated macrophages, cancer-associated fibroblasts, and regulatory T cells secrete cytokines, chemokines, and growth factors that promote angiogenesis, immune evasion, and tumor invasion. Chronic inflammation within the tumor microenvironment also increases the production of reactive oxygen species (ROS), which contribute to oxidative stress, DNA damage, and activation of oncogenic signaling pathways. Elevated ROS levels activate transcription factors such as NF- $\kappa$ B, AP-1, and HIF-1 $\alpha$ , thereby stimulating melanoma proliferation, angiogenesis, EMT, and metastatic dissemination [14].

Angiogenesis is another critical hallmark of melanoma progression, enabling tumors to obtain oxygen and nutrients necessary for rapid growth and metastasis. Melanoma cells secrete pro-angiogenic factors including vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), and transforming growth factor- $\beta$  (TGF- $\beta$ ), which collectively stimulate endothelial cell proliferation and neovascularization. Hypoxic tumor conditions further enhance angiogenic signaling through HIF-

1 $\alpha$ -mediated VEGF expression. Newly formed tumor blood vessels are structurally abnormal and highly permeable, facilitating melanoma cell intravasation and systemic dissemination [15].

ECM degradation is a major event in melanoma invasion and metastasis. Melanoma cells overexpress MMPs, particularly MMP-2 and MMP-9, which degrade collagen, laminin, fibronectin, and basement membrane components. This degradation facilitates tumor cell migration and releases growth factors that further support angiogenesis and tumor progression. The EMT-like process additionally enhances melanoma invasiveness through downregulation of E-cadherin and upregulation of mesenchymal markers such as N-cadherin and vimentin [16]. EMT-associated transcription factors including Snail, Slug, Twist, and ZEB promote cytoskeletal remodeling, extracellular matrix degradation, and metastatic dissemination. Collectively, melanoma pathophysiology involves a complex interplay among genetic mutations, oxidative stress, oncogenic signaling pathways, angiogenesis, EMT, and extracellular matrix remodeling, all of which contribute to the highly aggressive and therapy-resistant nature of this malignancy [17]. The integrated molecular events involved in melanoma initiation, progression, extracellular matrix remodeling, and metastatic dissemination are summarized in Figure 1.



**Figure 1.** Molecular Pathophysiology and MMP-Driven Melanoma Progression

### III.

#### IV. MMPs in Melanoma

MMPs are a family of zinc-dependent endopeptidases that play fundamental roles in ECM remodeling, tissue repair, angiogenesis, embryogenesis, and cellular migration. More than twenty-five MMPs have been identified in humans and are classified into collagenases, gelatinases, stromelysins, matrilysins, membrane-type MMPs, and other specialized subgroups according to substrate specificity and structural organization [18]. Structurally, MMPs generally consist of a signal peptide, a pro-domain responsible for maintaining enzyme latency, a catalytic zinc-binding domain, and a hemopexin-like domain involved in substrate recognition and protein interactions. Under normal physiological conditions, MMP activity is tightly regulated by transcriptional control, proteolytic activation, and endogenous tissue inhibitors of metalloproteinases (TIMPs), thereby maintaining tissue homeostasis and controlled extracellular matrix turnover [19].

Physiologically, MMPs participate in wound healing, immune responses, angiogenesis, and cellular differentiation. However, dysregulated MMP expression contributes significantly to pathological conditions including chronic inflammation, fibrosis, arthritis, cardiovascular disorders, and cancer progression. In melanoma, abnormal activation of MMPs facilitates degradation of extracellular matrix components and basement membranes, thereby enabling melanoma cells to invade adjacent tissues and metastasize to distant

organs [20]. Among the various MMP family members, MMP-2 and MMP-9 are considered the most critical in melanoma progression because of their potent ability to degrade type IV collagen, which constitutes a major structural component of the basement membrane. Elevated expression of these gelatinases is strongly associated with increased melanoma invasiveness, angiogenesis, metastatic dissemination, and poor clinical prognosis. Furthermore, MMP-mediated matrix degradation releases sequestered cytokines, chemokines, and growth factors that further stimulate tumor growth and inflammatory signaling within the tumor microenvironment [21].

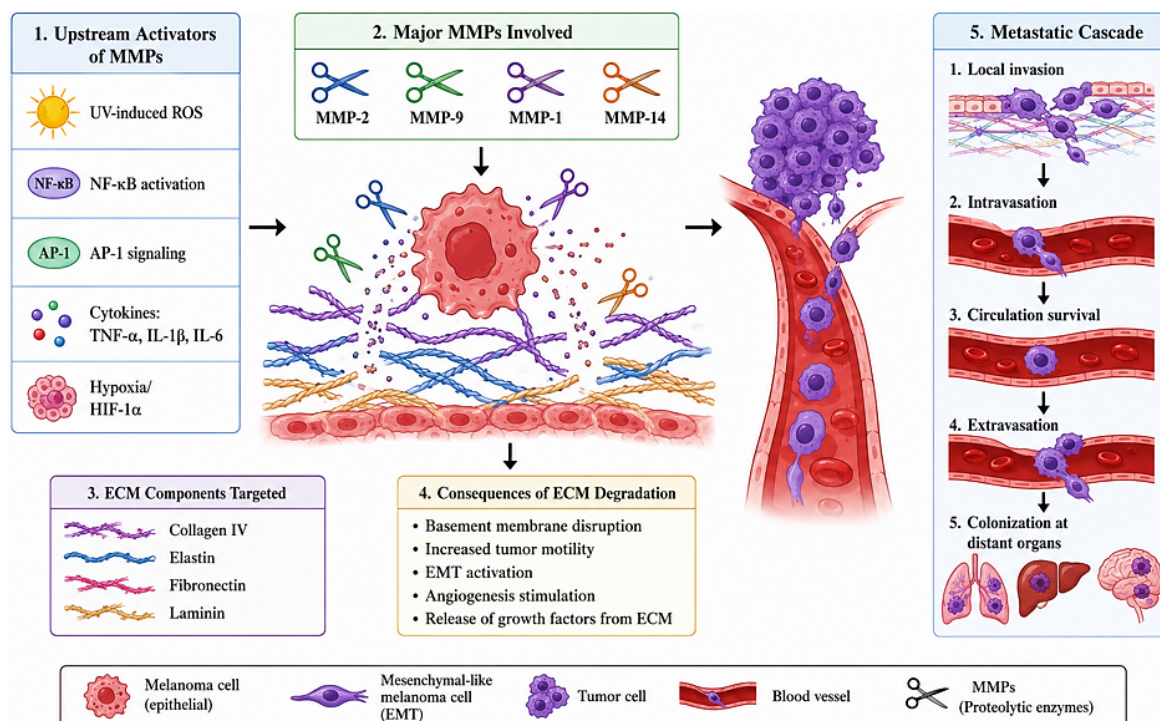
#### 3.1. MMP Signaling Pathways

The regulation of MMP expression in melanoma involves multiple oncogenic signaling pathways that collectively enhance tumor progression, invasion, and metastasis. One of the major regulatory mechanisms involves activation of the mitogen-activated protein kinase (MAPK) pathway through mutations in BRAF and NRAS oncogenes. Constitutive activation of MAPK signaling stimulates transcription factors such as activator protein-1 (AP-1) and nuclear factor-kappa B (NF-κB), which directly upregulate MMP gene transcription. Simultaneously, activation of the PI3K/AKT pathway enhances melanoma cell survival and promotes MMP-mediated extracellular matrix remodeling [22]. Additional pathways including transforming growth factor-beta (TGF-β),

Wnt/ $\beta$ -catenin, focal adhesion kinase (FAK), and hypoxia-inducible factor-1 alpha (HIF-1 $\alpha$ ) signaling further contribute to MMP overexpression and melanoma aggressiveness. Oxidative stress also plays a pivotal role in MMP activation, as elevated ROS stimulate redox-sensitive transcription factors that increase MMP synthesis and enzymatic activity. Moreover, inflammatory mediators such as TNF- $\alpha$ , interleukin-1 beta (IL-1 $\beta$ ), and interleukin-6 (IL-6) amplify MMP expression within the melanoma microenvironment, thereby accelerating tumor invasion and angiogenesis [23].

### 3.2. MMPs and Tumor Metastasis

MMPs are central mediators of melanoma metastasis because of their capacity to degrade extracellular matrix barriers and facilitate tumor cell migration. During melanoma progression, malignant cells acquire invasive phenotypes through EMT-like processes characterized by reduced E-cadherin expression and increased mesenchymal markers such as N-cadherin and vimentin. MMP-mediated degradation of collagen, laminin, fibronectin, and proteoglycans creates migratory pathways that permit melanoma cells to infiltrate stromal tissues and intravasate into blood and lymphatic vessels [24]. MMP-2 and MMP-9 are particularly important during metastatic dissemination due to their ability to destroy basement membrane integrity and promote vascular invasion. In addition to extracellular matrix degradation, MMPs contribute to angiogenesis by releasing pro-angiogenic molecules including VEGF and basic fibroblast growth factor (bFGF). Newly formed tumor vasculature supplies nutrients and oxygen to rapidly proliferating melanoma cells while simultaneously providing routes for distant metastasis. Increased expression of membrane-type MMPs further enhances pericellular proteolysis and invasive tumor behavior. Clinical studies have demonstrated that metastatic melanoma lesions exhibit significantly higher MMP expression compared with primary tumors, highlighting the strong association between MMP dysregulation and advanced disease progression [25]. The integrated role of upstream signaling, MMP activation, ECM degradation, and metastatic dissemination is summarized schematically in Figure 2.



**Figure 2.** MMP- Mediated Extracellular matrix remodelling and metastatic cascade in melanoma

### 3.3. Therapeutic Targeting of MMPs

Due to their significant involvement in melanoma invasion and metastasis, MMPs have emerged as promising therapeutic targets for anti-metastatic intervention. Early synthetic MMP inhibitors demonstrated encouraging preclinical efficacy by suppressing extracellular matrix degradation and tumor invasion; however, their clinical application was limited by poor selectivity, musculoskeletal toxicity, low bioavailability, and insufficient therapeutic responsiveness. Consequently, recent therapeutic approaches focus on the development of selective MMP inhibitors with improved specificity and reduced adverse effects [24,27]. Monoclonal antibodies, small interfering RNA (siRNA), and gene-silencing strategies targeting MMP signaling pathways are currently being explored to inhibit melanoma progression more effectively. In addition, naturally derived phytochemicals such as terpenoids, flavonoids, alkaloids, and polyphenols have gained considerable attention because of their ability to suppress MMP-2 and MMP-9 expression through modulation of MAPK, PI3K/AKT, and NF-κB signaling pathways. Several terpenoids have demonstrated potent anti-invasive and anti-angiogenic activities by reducing oxidative stress, inhibiting inflammatory mediators, and preventing extracellular matrix degradation. Furthermore,

nanotechnology-based delivery systems including nanoemulsions, liposomes, polymeric nanoparticles, and nanoemulgels are increasingly being investigated to improve the stability, skin penetration, targeted delivery, and therapeutic efficacy of MMP inhibitors in melanoma treatment [27]. These advanced nanoformulations may enhance localized drug accumulation within melanoma tissues while minimizing systemic toxicity, thereby offering a promising strategy for the management of metastatic melanoma.

## V. Terpenoids as Natural MMP Inhibitors

Terpenoids are a diverse class of naturally occurring secondary metabolites synthesized from isoprene units and widely distributed in medicinal plants, aromatic herbs, fruits, and essential oils. Due to their potent antioxidant, anti-inflammatory, anticancer, and anti-metastatic properties, terpenoids have gained significant attention as natural therapeutic agents against melanoma progression. Recent studies have demonstrated that terpenoids can suppress melanoma invasion and metastasis by modulating MMPs, particularly MMP-2 and MMP-9, which are critically involved in extracellular matrix degradation and tumor dissemination [28].

### 4.1. Classification of Terpenoids

The classification, natural sources, representative compounds, and multitargeted anticancer mechanisms of terpenoids against melanoma are summarized in Figure 3.

*Monoterpenes:* Monoterpenes consist of two isoprene units and are commonly found in essential oils of aromatic plants and citrus fruits. Important monoterpenes include limonene, thymol, and carvacrol, which exhibit antioxidant, anti-inflammatory, and anticancer activities. These compounds suppress melanoma cell proliferation and migration through modulation of oxidative stress and inflammatory signaling pathways [29].

*Sesquiterpenes:* Sesquiterpenes contain three isoprene units and possess significant pharmacological properties. Artemisinin and its derivatives are among the most extensively studied sesquiterpenes due to their potent anticancer activity. These compounds inhibit angiogenesis, induce apoptosis, and suppress MMP-mediated invasion in melanoma cells [30].

*Diterpenes:* Diterpenes are composed of four isoprene units and demonstrate diverse biological activities including antioxidant, anti-inflammatory, and antiproliferative effects. Several diterpenes modulate intracellular signaling pathways associated with melanoma progression and extracellular matrix remodeling [31].

*Triterpenes:* Triterpenes consist of six isoprene units and include highly bioactive compounds such as ursolic acid, betulinic acid, and lupeol. These compounds exhibit potent anti-invasive, anti-angiogenic, and pro-apoptotic activities through inhibition of MMP expression and suppression of oncogenic signaling pathways [32].

#### 4.2. Natural Sources

Terpenoids are abundantly present in medicinal plants and dietary sources. Ursolic acid is commonly found in apples, rosemary, basil, and holy basil, whereas betulinic acid is isolated primarily from birch bark. Limonene is abundant in citrus peel oils, while thymoquinone is the principal active constituent of *Nigella sativa*. Carvacrol is present in oregano and thyme essential oils, and lupeol is found in fruits, vegetables, aloe vera, and medicinal herbs. Artemisinin derivatives are obtained from *Artemisia annua*. These natural sources have been extensively investigated for their therapeutic potential in cancer management [33].

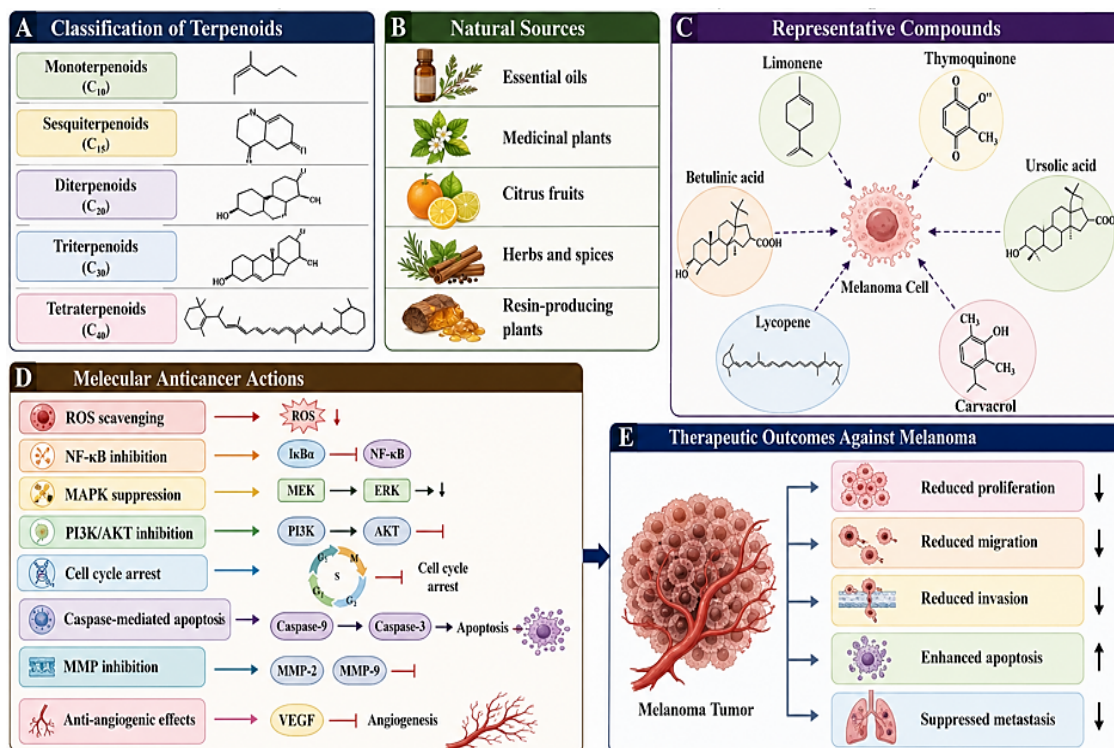


Figure 3. Types, sources, and pharmacological actions of terpenoids against melanoma

### 4.3. Pharmacological Properties

Terpenoids possess broad pharmacological activities including antioxidant, anti-inflammatory, antimicrobial, antiproliferative, anti-angiogenic, and pro-apoptotic effects. Their anticancer activity is mainly associated with modulation of oxidative stress, inhibition of inflammatory mediators, suppression of tumor proliferation, induction of apoptosis, and inhibition of extracellular matrix degradation. Several terpenoids also demonstrate immunomodulatory effects and can interfere with signaling pathways involved in melanoma progression and metastasis [34].

### 4.4. Mechanisms of MMP Inhibition

**NF-κB Suppression:** NF-κB is a key transcription factor involved in inflammation, tumor progression, angiogenesis, and MMP expression. Persistent activation of NF-κB promotes melanoma invasion and metastatic dissemination. Terpenoids inhibit NF-κB signaling by suppressing phosphorylation and nuclear translocation of NF-κB subunits, thereby reducing MMP transcription and inflammatory responses [35].

**AP-1 Modulation:** AP-1 is another important transcription factor regulating MMP gene expression through MAPK signaling pathways. Terpenoids suppress AP-1 activation by modulating

ERK, JNK, and p38 MAPK pathways, resulting in reduced melanoma cell migration, invasion, and extracellular matrix degradation [36].

**ROS Scavenging:** Oxidative stress contributes significantly to melanoma progression and MMP activation through excessive production of ROS. Terpenoids possess strong antioxidant properties and effectively scavenge ROS, thereby reducing oxidative stress-mediated activation of NF-κB, AP-1, and HIF-1α signaling pathways [37].

**Downregulation of MMP-2 and MMP-9:** Many terpenoids directly suppress the expression and activity of MMP-2 and MMP-9 while increasing TIMPs. This inhibition prevents extracellular matrix degradation, basement membrane disruption, angiogenesis, and metastatic dissemination [38].

**Anti-inflammatory and Apoptotic Effects:** Terpenoids reduce the production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, thereby suppressing inflammatory signaling associated with melanoma progression. Additionally, they induce apoptosis through mitochondrial dysfunction, caspase activation, Bax/Bcl-2 modulation, and inhibition of survival pathways including PI3K/AKT and STAT3 signaling [39]. The combined mechanisms underlying terpenoid-mediated MMP inhibition and the improved therapeutic delivery achieved through nanoemulgel

systems in melanoma treatment are depicted in Figure 4.

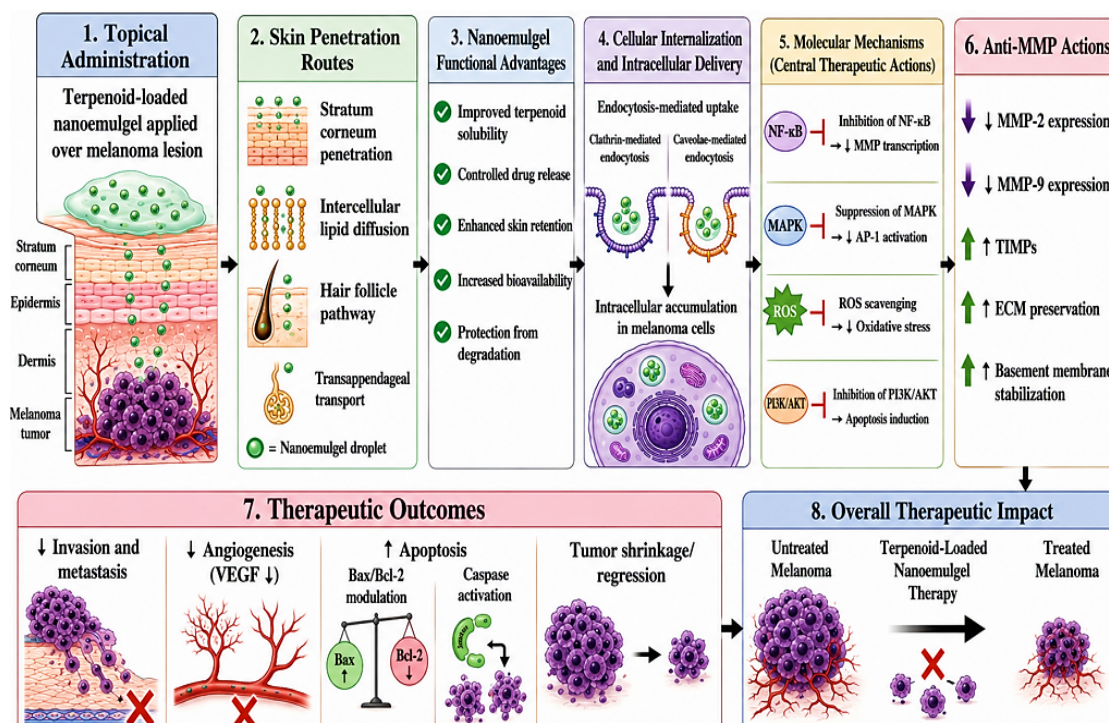


Figure 4. Multifunctional Mechanism of Terpenoid-Loaded Nanoemulgels in Targeted Melanoma Therapy

#### 4.5. Important Terpenoids

**Ursolic Acid:** Ursolic acid is a pentacyclic triterpene with potent anti-metastatic and anti-angiogenic properties. It inhibits NF- $\kappa$ B, STAT3, and MMP-9 signaling pathways, thereby reducing melanoma invasion and tumor progression [40].

**Betulinic Acid:** Betulinic acid exhibits strong anticancer activity through induction of mitochondrial apoptosis and suppression of MMP-2 and MMP-9 expression. It also inhibits angiogenesis and melanoma cell migration [41].

**Limonene:** Limonene demonstrates antioxidant and anti-inflammatory activities and suppresses melanoma proliferation through modulation of Ras/MAPK signaling pathways and oxidative stress [42].

**Thymoquinone:** Thymoquinone possesses significant anticancer activity mediated through inhibition of oxidative stress, angiogenesis, inflammatory mediators, and MMP expression [43].

**Carvacrol:** Carvacrol exhibits anti-invasive and anti-inflammatory effects by suppressing NF- $\kappa$ B signaling, reducing MMP activity, and inhibiting melanoma cell migration [44].

**Lupeol:** Lupeol inhibits melanoma progression through suppression of PI3K/AKT signaling,

angiogenesis, extracellular matrix degradation, and inflammatory responses [45].

**Artemisinin Derivatives:** Artemisinin derivatives exhibit promising anticancer properties by inducing oxidative stress selectively in tumor cells, suppressing angiogenesis, and inhibiting MMP-mediated invasion and metastasis [46].

#### VI. Nanoemulgel Drug Delivery System

Nanoemulgels are advanced topical drug delivery systems that combine the unique advantages of nanoemulsions and hydrogels to enhance the solubility, stability, skin permeation, and therapeutic efficacy of poorly water-soluble drugs. Nanoemulsions are nanosized oil-in-water colloidal systems stabilized by surfactants, while gels provide viscosity, bioadhesion, and prolonged residence at the application site. Their integration results in a dual-functional system that improves physicochemical stability, enables controlled and sustained drug release, enhances dermal penetration, and improves patient compliance. Due to these properties, nanoemulgels are particularly suitable for delivering lipophilic anticancer agents such as terpenoids in melanoma therapy, where deep skin

penetration and localized action are essential for therapeutic efficacy [47,48].

Nanoemulgels are formulated using an oil phase, surfactants, co-surfactants, and gelling agents, each contributing to system stability and performance. The oil phase dissolves lipophilic drugs and may include natural oils, essential oils, or medium-chain triglycerides, while surfactants such as Tween 80, Span 80, and lecithin reduce interfacial tension and stabilize nanosized droplets. Co-surfactants like ethanol, propylene glycol, and polyethylene glycol enhance emulsification efficiency and droplet flexibility, whereas gelling agents such as carbopol, HPMC, xanthan gum, and poloxamers impart viscosity, bioadhesion, and sustained release characteristics. These components collectively govern droplet size, stability, drug encapsulation, and skin permeation behavior [49]. Nanoemulgels are prepared using high-energy methods such as high-pressure homogenization, ultrasonication, and microfluidization, or low-energy approaches including spontaneous emulsification and phase inversion techniques, after which the nanoemulsion is incorporated into a gel matrix to obtain the final formulation. Key advantages include enhanced skin permeation, improved drug solubilization, controlled and sustained release, reduced systemic toxicity, protection of labile compounds, and prolonged skin retention. Physicochemical evaluation involving particle size, PDI, zeta potential, drug loading, rheology, spreadability, and *in vitro* release studies is essential to ensure formulation quality, stability, and therapeutic performance, making nanoemulgels a highly promising platform for targeted melanoma therapy [50].

## VII. Terpenoid-Based Nanoemulgels for Melanoma Therapy

Terpenoid-based nanoemulgels have emerged as a promising topical and transdermal drug delivery approach for melanoma therapy by integrating the biological activity of terpenoids with the physicochemical advantages of nanoemulsion and hydrogel systems [51]. Terpenoids, a diverse class of plant-derived isoprenoids, exhibit well-established anticancer properties including inhibition of cell proliferation, induction of apoptosis, suppression of angiogenesis, and modulation of metastatic signaling pathways [52]. However, their clinical utility is limited by poor aqueous solubility, volatility, instability, and low systemic bioavailability. Nanoemulgel systems effectively overcome these limitations by enhancing

solubilization, improving dermal retention, and enabling sustained and controlled drug release, thereby providing a rational platform for localized melanoma management with reduced systemic toxicity [53].

A key advantage of terpenoid-based nanoemulgels is their ability to enhance skin permeation and tumor-localized drug delivery. The nanoscale droplet size of nanoemulsions facilitates close interaction with the stratum corneum lipid matrix, promoting penetration through follicular and intercellular pathways. When incorporated into a hydrogel matrix, the formulation ensures prolonged residence time at the application site, minimizing drug loss and increasing local drug concentration within melanoma-infiltrated skin layers. This enhanced permeation is particularly relevant in melanoma, where aggressive dermal invasion and heterogeneous vascularization limit the effectiveness of conventional topical therapies [54]. Consequently, higher intracellular accumulation of terpenoids improves anticancer efficacy at the tumor site.

Terpenoid-based nanoemulgels also exhibit strong anti-invasive potential through sustained inhibition of matrix metalloproteinases, particularly MMP-2 and MMP-9, which are key mediators of extracellular matrix degradation and melanoma metastasis. Terpenoids such as limonene, thymol, carvacrol, geraniol, and ursolic acid have been reported to downregulate MMP expression via suppression of NF- $\kappa$ B and AP-1 signaling pathways. Nanoemulgel delivery further enhances this effect by providing prolonged drug release and maintaining therapeutic concentrations in tumor tissues, thereby reducing melanoma cell migration, invasion, and angiogenesis [55].

In addition to anti-metastatic effects, these systems exert potent antioxidant and pro-apoptotic activities that are crucial in melanoma pathophysiology. Terpenoids neutralize reactive oxygen species and enhance endogenous antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, thereby reducing oxidative stress-mediated activation of MAPK and PI3K/AKT survival pathways [56]. Simultaneously, they induce apoptosis through mitochondrial dysfunction, caspase activation, and modulation of Bax/Bcl-2 expression balance. Nanoemulgel systems improve stability and dermal bioavailability of these compounds, amplifying their multi-targeted anticancer effects [57].

From a delivery perspective, nanoemulgels offer both topical and transdermal advantages in

melanoma treatment. Topical application is particularly suitable for early-stage lesions, enabling localized drug action with minimal systemic exposure, whereas transdermal delivery facilitates deeper penetration into invasive tumor regions. This dual capability ensures controlled drug diffusion across multiple skin layers while minimizing off-target toxicity. Such localized targeting is especially valuable in melanoma due to its invasive behavior and metastatic potential [58].

Tumor-targeted nanoemulgels further enhance therapeutic precision through passive and active targeting strategies. Passive targeting is supported by tumor-associated vascular permeability, while active targeting can be achieved by ligand modification (e.g., folic acid, peptides, or antibodies) to improve selective uptake by melanoma cells [59]. This improves intracellular delivery and reduces toxicity to surrounding healthy tissues. Additionally, combination therapy approaches involving co-delivery of terpenoids with chemotherapeutic agents or other phytochemicals enhance synergistic anticancer activity, overcome drug resistance, and strengthen inhibition of MAPK and PI3K/AKT signaling pathways [60].

Preclinical studies support the efficacy of terpenoid-loaded nanoemulgels, demonstrating reduced melanoma cell proliferation, enhanced apoptosis, decreased tumor volume, inhibition of angiogenesis, and downregulation of MMP expression in experimental models. Histopathological findings further indicate restoration of normal dermal architecture and reduced inflammatory infiltration following treatment. Emerging smart-responsive nanoemulgels, designed to release drugs in response to tumor-specific stimuli such as acidic pH, oxidative stress, or enzymatic activity, represent an advanced evolution of this delivery system, enabling site-specific and controlled therapeutic action [61,62].

Overall, terpenoid-based nanoemulgels provide a multifunctional platform for melanoma management by combining enhanced skin delivery, sustained MMP inhibition, oxidative stress modulation, and multi-pathway anticancer activity. Their integration of nanoscale precision with topical convenience positions them as a highly promising strategy for future melanoma therapy, particularly when combined with targeted, combination, and stimuli-responsive drug delivery approaches.

### VIII. Mechanisms of Nanoemulgel-Mediated MMP Suppression

Nanoemulgel-based drug delivery systems exert anti-melanoma effects primarily through multi-targeted modulation of MMPs and their upstream regulatory networks within the tumor microenvironment. At the cellular level, nanoemulgels enhance dermal penetration and tumor accumulation via follicular transport, intercellular lipid disruption, and endocytosis-mediated uptake (clathrin- and caveolae-dependent pathways), leading to efficient intracellular delivery of encapsulated phytoconstituents or chemotherapeutics [53]. Once internalized, these nanosystems modulate key signaling cascades responsible for MMP overexpression in melanoma cells. A central mechanism involves inhibition of NF- $\kappa$ B and MAPK signaling pathways, which are well-established transcriptional regulators of MMP-2 and MMP-9 expression. Suppression of NF- $\kappa$ B nuclear translocation leads to downregulation of pro-inflammatory cytokines such as TNF- $\alpha$  and IL-6, thereby attenuating inflammatory-driven tumor progression and ECM degradation [55,63].

Within the tumor microenvironment, nanoemulgels contribute to stromal normalization by reducing oxidative stress and reprogramming tumor-associated fibroblasts and immune cells. This results in decreased secretion of pro-angiogenic factors, particularly VEGF, which indirectly suppresses MMP activation required for basement membrane breakdown and neovascularization. The inhibition of angiogenesis further limits nutrient supply and metastatic dissemination. Concurrently, nanoemulgel-mediated delivery of bioactives promotes apoptosis through mitochondrial dysfunction, increased Bax/Bcl-2 ratio, and activation of caspase-dependent pathways, which collectively reduce melanoma cell survival and invasive potential [64,65].

At the metastatic level, suppression of MMP-2 and MMP-9 is critical, as these enzymes facilitate degradation of type IV collagen in the basement membrane, enabling tumor invasion. By downregulating upstream mediators such as NF- $\kappa$ B, MAPK, VEGF, TNF- $\alpha$ , and IL-6, nanoemulgels effectively disrupt EMT-associated signaling, thereby limiting cellular migration and metastasis [66]. Overall, the synergistic interaction between enhanced intracellular delivery, anti-inflammatory modulation, anti-angiogenic effects, and apoptosis induction positions nanoemulgels as a promising strategy for comprehensive MMP suppression in melanoma therapy.

### IX. Challenges and Limitations

Despite their significant therapeutic promise, nanoemulgel systems face several translational and clinical limitations that hinder widespread application in melanoma management. A primary concern is physical and chemical stability, as nanoemulsions are inherently thermodynamically unstable systems prone to Ostwald ripening, phase separation, coalescence, and droplet aggregation during storage. These instabilities can compromise drug loading efficiency, release kinetics, and overall therapeutic reproducibility. In addition, achieving large-scale production with consistent droplet size distribution and zeta potential remains challenging due to limitations in high-energy emulsification techniques and batch-to-batch variability [58,67].

From a dermatological standpoint, excipient selection particularly surfactants and co-surfactants raises concerns regarding potential skin irritation, hypersensitivity reactions, and long-term safety upon repeated topical application. Regulatory approval is further complicated by the lack of standardized guidelines specifically tailored for nanocarrier-based topical systems, resulting in ambiguous classification between cosmetics, drug delivery systems, and combination products [68]. Another critical limitation is the paucity of robust clinical evidence; most studies remain confined to in vitro assays and animal models, limiting direct extrapolation to human melanoma patients [69].

Reproducibility and formulation standardization also remain major bottlenecks, as variations in lipid composition, polymer concentration, and manufacturing conditions significantly influence physicochemical properties and biological performance. Furthermore, long-term stability under real-world storage conditions and interaction with biological fluids are not yet fully understood. Collectively, these challenges highlight the need for optimized manufacturing protocols, regulatory harmonization, and comprehensive clinical validation to ensure safe and effective translation of nanoemulgel systems into melanoma therapy [70].

## X. Future Perspectives and Research Opportunities

The future development of nanoemulgel-based melanoma therapies is expected to be driven by advances in precision nanomedicine, artificial intelligence, and targeted drug delivery strategies. AI-assisted nano-formulation design is emerging as a powerful tool to optimize critical quality attributes such as droplet size, surfactant ratio, drug loading

efficiency, and release kinetics, thereby accelerating formulation development and reducing experimental variability. Machine learning algorithms can also predict stability profiles and biological performance, enabling rational design of highly efficient nanoemulgel systems [71,72].

Another promising direction involves ligand-targeted nanoemulgels, where surface modification with antibodies, peptides, or aptamers enables selective binding to melanoma-specific receptors such as integrins, melanocortin-1 receptor (MC1R), or CD44. This targeted approach enhances tumor specificity, minimizes off-target toxicity, and improves intracellular drug accumulation. Combination strategies integrating nanoemulgels with immunotherapeutic agents, such as immune checkpoint inhibitors (e.g., anti-PD-1/PD-L1), represent a particularly compelling avenue for synergistic tumor suppression by simultaneously targeting cancer cells and restoring anti-tumor immune responses [73,74].

Personalized melanoma therapy is another emerging frontier, where patient-specific tumor genomics and microenvironmental profiles could guide the selection of tailored nanoemulgel formulations. Such precision approaches may significantly improve therapeutic outcomes in heterogeneous melanoma populations [75]. Furthermore, ongoing advancements in scalable nanomanufacturing, regulatory science, and translational nanotoxicology are expected to facilitate clinical translation. Overall, the integration of smart targeting, computational design, and combination therapy strategies positions nanoemulgels as next-generation platforms in melanoma management [76].

## XI. Conclusion

Nanoemulgel-based drug delivery systems represent a highly promising and multifunctional approach for melanoma therapy, particularly through their ability to suppress MMP-mediated tumor invasion and metastasis. The available preclinical evidence indicates that these systems enhance drug permeation, improve intracellular delivery, and effectively modulate key molecular pathways including NF- $\kappa$ B, MAPK, VEGF, TNF- $\alpha$ , IL-6, MMP-2, and MMP-9. Collectively, these effects result in reduced extracellular matrix degradation, inhibition of angiogenesis, suppression of inflammatory signaling, and induction of apoptosis in melanoma cells.

The therapeutic significance of nanoemulgels lies in their capacity to integrate

multiple mechanisms of action within a single topical platform, thereby addressing the complex biology of melanoma progression. Their dual role in enhancing local bioavailability while simultaneously targeting molecular drivers of metastasis offers a strong rationale for continued development. However, despite encouraging experimental outcomes, clinical translation remains limited and requires further validation through well-designed clinical trials and standardized formulation protocols.

In conclusion, nanoemulgel systems hold substantial translational potential as next-generation topical nanomedicines for melanoma management. With continued advancements in targeted delivery, formulation science, and clinical evaluation, they may evolve into effective and clinically viable strategies for controlling melanoma progression and improving patient outcomes.

#### Abbreviations

AKT – Protein kinase B  
AP-1 – Activator protein-1  
BRAF – v-Raf murine sarcoma viral oncogene homolog B  
CD44 – Cluster of differentiation 44  
CDKN2A – Cyclin-dependent kinase inhibitor 2A  
CTLA-4 – Cytotoxic T-lymphocyte-associated protein 4  
ECM – Extracellular matrix  
EMT – Epithelial–mesenchymal transition  
ERK – Extracellular signal-regulated kinase  
FAK – Focal adhesion kinase  
FGF – Fibroblast growth factor  
HIF-1 $\alpha$  – Hypoxia-inducible factor-1 alpha  
HPMC – Hydroxypropyl methylcellulose  
IL-1 $\beta$  – Interleukin-1 beta  
IL-6 – Interleukin-6  
JNK – c-Jun N-terminal kinase  
KIT – KIT proto-oncogene receptor tyrosine kinase  
MAPK – Mitogen-activated protein kinase  
MC1R – Melanocortin-1 receptor  
MEK – Mitogen-activated protein kinase kinase  
MMP – Matrix metalloproteinase  
MMP-2 – Matrix metalloproteinase-2  
MMP-9 – Matrix metalloproteinase-9  
NF- $\kappa$ B – Nuclear factor kappa B  
NRAS – Neuroblastoma RAS viral oncogene homolog  
PD-1 – Programmed cell death protein 1

PDGF – Platelet-derived growth factor  
PD-L1 – Programmed death-ligand 1  
PEG – Polyethylene glycol  
PI3K – Phosphatidylinositol-3 kinase  
PDI – Polydispersity index  
PTEN – Phosphatase and tensin homolog  
ROS – Reactive oxygen species  
siRNA – Small interfering RNA  
STAT3 – Signal transducer and activator of transcription 3  
TGF- $\beta$  – Transforming growth factor-beta  
TIMPs – Tissue inhibitors of metalloproteinases  
TNF- $\alpha$  – Tumor necrosis factor-alpha  
UV – Ultraviolet  
VEGF – Vascular endothelial growth factor

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#### Competing Interest

Authors declare that there is no potential conflict of interest in this paper.

#### Author Contribution

Marimuthu Yuvaraja was involved in the conception, planning of the study and drafted the original version of the manuscript. Satheesh Babu Natarajan reviewed the manuscript. All authors read and approved the final version of the manuscript.

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