Die Pharmazie

Pharmazie **2026**; 81(8): 52238
https://doi.org/10.31083/Pharmazie52238

Review

Nanotechnology-Based Strategies for Treating Skin Hyperpigmentation: A Review of Current Advances and Challenges

Gabriela Fátima de Lima Flores[1], Gabriela Fusinatto de Oliveira[1], Debora Cristine Chrisostomo Dias[2], Ana Paula Horn[3], Cristiana Lima Dora[2], Letícia Scherer Koester[1], Flávia Nathiely Silveira Fachel[1], Helder Ferreira Teixeira[1,*]

[1]School of Pharmacy, Federal University of Rio Grande do Sul (UFRGS), Porto Alegre, RS 90610-000, Brazil
[2]School of Medicine, Federal University of Rio Grande (FURG), Rio Grande, RS 96203-900, Brazil
[3]Institute of Biological Sciences, Federal University of Rio Grande (FURG), Rio Grande, RS 96203-900, Brazil
*Correspondence: helder.teixeira@ufrgs.br (Helder Ferreira Teixeira)
Academic Editor: Hirofumi Takeuchi
Submitted: 25 March 2026 Revised: 13 June 2026 Accepted: 22 June 2026 Published: 20 August 2026

Abstract

Skin hyperpigmentation is a common dermatological condition characterized by excessive melanin accumulation in the epidermis, dermis, or both, resulting from disorders such as melasma, post-inflammatory hyperpigmentation, drug-induced hyperpigmentation, and solar lentigo. Conventional treatments are mainly based on tyrosinase inhibition; however, many depigmenting agents have limitations, including low stability, poor skin permeation, prolonged treatment durations, and adverse effects such as irritation and dermatitis. In this context, nanotechnology-based delivery systems have emerged as promising alternatives for the topical administration of depigmenting compounds. Therefore, this review discusses recent advances in nanotechnology-based strategies for treating skin hyperpigmentation, with a primary focus on lipid-based nanosystems, including liposomes, nanoemulsions, solid lipid nanoparticles, and nanostructured lipid carriers. A total of 33 studies published between 2000 and 2025 were analyzed. The reviewed studies demonstrated that nanoencapsulation may improve the physicochemical stability, enable controlled release, enhance skin permeation/retention, and increase the therapeutic performance of depigmenting agents while reducing toxicity and adverse effects. *In vitro* studies also reported enhanced tyrosinase inhibition, high cell viability, and increased accumulation of active compounds in different skin layers. Overall, nanotechnology-based delivery systems represent a promising and versatile approach for improving the efficacy and safety of topical treatments for skin hyperpigmentation.

Keywords: skin; melanin; hyperpigmentation; treatment; nanotechnology-based delivery systems

1. Introduction

The skin plays a critical role as a protective barrier against foreign bodies like microorganisms, chemical agents, or ultraviolet radiation, and contributes significantly to human appearance. The skin color reflects melanin production, distribution and degradation, which varies according to phototype and environmental factors such as sun exposure [1,2,3,4,5,6]. Alterations in these processes can lead to hyperpigmentation, a common skin condition that exacerbates skin pigmentation and results in excessive melanin accumulation in the epidermis and dermis [7,8,9,10,11].

Current treatment options for hyperpigmentation focus on inhibiting melanogenesis, particularly through tyrosinase inhibition. However, these treatments are associated with adverse effects such as contact dermatitis, post-inflammatory pigmentation, exogenous ochronosis, among others, as well as variable therapeutic effectiveness [12,13,14,15]. These limitations highlight the need for safer and more effective treatment strategies.

In recent years, nanotechnology-based delivery systems have emerged as promising alternatives for the topical delivery of drugs used in the treatment of skin disorders, including hyperpigmentation. The incorporation of depigmenting agents into nanostructured systems may improve their aqueous solubility, physicochemical stability, release kinetics, and skin permeation/retention, thereby enhancing their cutaneous availability [16,17]. Among the most extensively investigated lipid-based nanosystems for topical administration are liposomes, nanoemulsions, solid lipid nanoparticles, and nanostructured lipid carriers [18,19,20,21]. Thus, the incorporation of depigmenting compounds into these nanocarriers may improve their therapeutic efficacy while helping to overcome or minimize adverse effects associated with conventional formulations.

In this review, a brief overview of melanogenesis, the pathophysiology of hyperpigmentation, and current therapeutic approaches is first presented to provide contextual background for the topic. Subsequently, key aspects of nanotechnology-based systems as carriers for depigmenting compounds are discussed, with emphasis on their composition, physicochemical properties, and *in vitro* findings related to toxicity, skin permeation/retention, and tyrosinase inhibitory activity, among others.

1.1 Melanogenesis Process and Hyperpigmentation in the Skin

The skin is composed of layers, subdivided into epidermis, dermis, and hypodermis [5]. Certain functions can be defined from these layers, such as skin color. The constituent skin color depends on the phototype and ultraviolet (UV radiation) exposure because of the interactions of light (primarily absorption) with the epidermis and dermis [22].

The melanin synthesis and the process of activating the skin are demonstrated in Fig. 1. Melanin synthesis occurs in melanocytes, cells predominantly located in the basal layer of the epidermis, where melanin is produced and transferred to neighboring keratinocytes through dendritic projections [9,23]. Melanocytes are positioned among the basal cells of the epidermis, which divide and give rise to the upper layers, such as the stratum spinosum [23,24]. Melanin acts as a photoprotective agent by absorbing UV radiation and dissipating more than 99.9% of the absorbed energy, thereby shielding the nuclear DNA of keratinocytes from mutations such as pyrimidine dimer formation. Additionally, melanin helps neutralize reactive oxygen species (ROS) produced by UV exposure [25,26].

In addition to the epidermis, melanocytes are also found in the dermis, especially near the hair bulb matrix within hair follicles. These follicular melanocytes are responsible for hair pigmentation and differ from epidermal melanocytes because they have a more dendritic morphology, are larger, and produce bigger melanosomes. As a result, melanocytes are distributed in both the epidermis and deeper dermal structures like hair follicles, where they serve different pigmentary functions [5,27,28].

Tyrosinase is the central enzyme involved in defining skin color and synthesizing eumelanin and pheomelanin, reason why its dysfunction leads to visible dermatological changes during the tyrosinase activity process [29,30]. It is important to recognize that reducing melanin synthesis in any dermal skin condition requires developing treatments that decrease tyrosinase activity [31]. To control tyrosinase activity, it is necessary to act on the catalysis of the conversion of tyrosine into dopaquinone, as this reaction is a rate-limiting step in melanin synthesis. Therefore, the use of tyrosinase activity as a marker or indicator was established [32].

Skin pigmentation is regulated by homeostatic mechanisms involving the interaction between melanocytes, keratinocytes, and fibroblasts. Under physiological conditions, melanocytes do not undergo continuous renewal, as they are differentiated and non-proliferative cells, except during pathological conditions [33]. The maintenance of pigmentary homeostasis depends on stimuli such as UV radiation, inflammation, and hormonal factors, which primarily influence the enzymatic activity of melanocytes, especially tyrosinase [7]. The degree of hyperpigmentation is directly connected to the intensity and duration of these stimuli, leading to three main stages in the epidermal melanogenic process: increased tyrosinase activity, higher melanin production, and increased transfer of melanosomes to keratinocytes [34,35]. In addition, skin coloration is also influenced by the rate of melanosome degradation within keratinocytes, which is slower in higher phototypes, contributing to more intense and longer-lasting pigmentation [32,36].

Recent advances in the biology of pigmentation have shown that hyperpigmentation is a multifactorial process that goes beyond melanogenesis and tyrosinase activity. In addition to the direct regulation of melanin synthesis, inflammatory mediators, oxidative stress, and complex interactions between melanocytes, keratinocytes, fibroblasts, and immune cells play crucial roles in the initiation and persistence of pigmentation disorders [6,37,38]. Pro-inflammatory cytokines and reactive oxygen species can activate melanogenic pathways and increase melanocyte activity, while alterations in the dermal microenvironment contribute to abnormal pigment deposition and maintenance [37]. At the molecular level, melanogenesis is regulated by a network of intracellular signaling pathways that collectively control the proliferation, differentiation, and melanin production of melanocytes [37,38].

1.2 Pathophysiology of Skin Hyperpigmentation

Cutaneous hyperpigmentation is a condition characterized by the abnormal accumulation of melanin in the epidermis, dermis, or both, and can occur through different mechanisms [39]. Among these mechanisms are increased tyrosinase activity, enhanced transfer of melanosomes to keratinocytes, decreased rate of melanosome degradation, and chronic skin inflammation. These changes can result from various causes, leading to different clinical signs, most commonly: post-inflammatory hyperpigmentation (PIH), drug-induced hyperpigmentation, melasma, and solar lentigo, among others [40,41]. The leading causes and pathophysiology of skin hyperpigmentation will be discussed below.

1.2.1 Post-Inflammatory Hyperpigmentation (PIH)

Post-inflammatory hyperpigmentation (PIH) is an acquired pigmentation disorder caused by the overproduction or irregular dispersion of melanin in the skin [39]. It is characterized by the appearance of dark spots on the skin following inflammation or local trauma, such as acne, other inflammatory dermatoses, or burns, where melanin can be deposited in the epidermis, dermis, or both [10,42]

This acquired condition can affect both men and women, and it is more frequently observed in individuals with higher phototypes. The dark spots may be worsened by sun exposure and the use of irritating substances or drugs applied to the skin. PIH can be classified into two main patterns: epidermal and dermal [39]. In the epidermal pattern, pigmentation is confined to the epidermis, where increased melanin production and transfer to neigh-

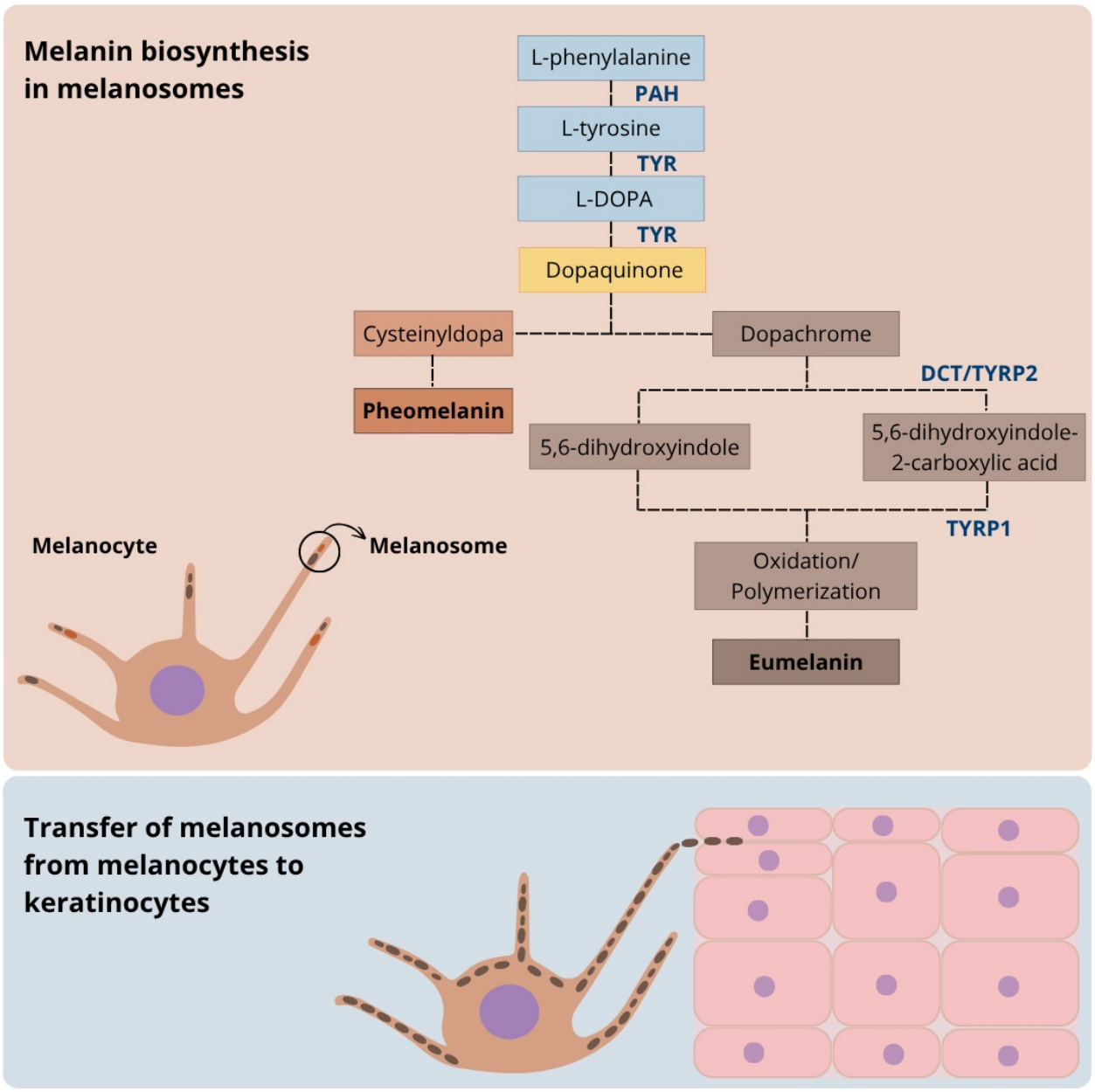

Fig. 1. Flowchart illustrating melanogenesis within melanosomes, highlighting the biosynthetic pathways leading to eumelanin and pheomelanin production, and the subsequent transfer of mature melanosomes from melanocytes to keratinocytes in the epidermis. Key melanogenic enzymes: PAH, phenylalanine hydroxylase; TYR, tyrosinase; DCT/TYRP2, dopachrome tautomerase (tyrosinase-related protein 2); TYRP1, tyrosinase-related protein 1. These enzymes participate in the sequential biochemical reactions that regulate melanin synthesis and determine the production of eumelanin and pheomelanin (©Helder Ferreira Teixeira via Canva.com).

boring keratinocytes occur, mediated by inflammatory cytokines and reactive oxygen species, resulting in brownish-colored spots. In the dermal pattern, inflammation or injury causes damage to the basal layer keratinocytes, leading to the release of large amounts of melanin into the dermis. This melanin is phagocytosed by macrophages, forming melanophages that accumulate in the upper dermis and clinically manifest as blue-gray discoloration that can persist for years. This dermal PIH pattern is the most difficult to treat [39,43,44,45].

1.2.2 Hyperpigmentation Caused by Drugs

Hyperpigmentation caused by drugs is manifested when adverse effects occur during the administration of certain drugs, characterized by the appearance of pigmented spots in areas exposed or not exposed to sunlight [39]. The mechanisms involved include increased melanogenesis, the formation of drug–melanin complexes, the deposition of the drug or its metabolites in the skin, and, in some cases, the deposition of endogenous pigments activated by the drug's

action [46]. The agents related to this type of hyperpigmentation include amiodarone, minocycline, tricyclic antidepressants, phenothiazines, antimalarials, clofazimine, gold, silver, bismuth, oral contraceptives, anticancer drugs, and others [43]. The coloration of the lesions varies according to the causative agent and the individual's phototype, and may appear as gray-blue, brownish-purple, or tan. These lesions are often distributed in areas exposed to ultraviolet radiation. Treatment is challenging, and discontinuation of the drug does not always result in the immediate reversal of the pigmentary changes [47].

1.2.3 Melasma

Melasma is a chronic alteration in skin pigmentation, resulting from a pigmentary dermatosis. It is characterized by hyperpigmented macules with irregular borders and brown coloration, usually symmetrically located on the face—especially on the cheeks, forehead, upper lip, and chin [48]. Its etiology is multifactorial, involving ultraviolet radiation, hormonal factors (such as oral contraceptives and pregnancy), genetic predisposition, and low-grade chronic inflammation [49].

Melasma can be classified into three patterns based on the depth of melanin: epidermal, dermal, and mixed, as previously described in PIH. Additionally, melasma shows a variable response to treatment, and recurrence after sun exposure is common [50]. Wood's lamp and dermoscopy are valuable tools for assessing the depth of pigmentation and guiding therapeutic decisions [36].

1.2.4 Solar Lentigo

Solar lentigo, also called an age spot or liver spot, is a type of acquired hyperpigmentation linked to prolonged exposure to ultraviolet radiation and is seen as a result of skin photoaging. It appears as well-defined, flat patches in various shades of light to dark brown, typically found on sun-exposed areas like the backs of the hands, face, neck, and forearms [51].

Histologically, it is characterized by a focal increase in basal melanocyte density and accumulation of melanin in the epidermis, without significant atypia or inflammation. It is a relatively simple form of hyperpigmentation to treat, with a good response to available therapies, especially when compared to deeper or recurrent forms [52].

1.3 Treatments

Currently, a variety of treatments and procedures are available for skin hyperpigmentation [53]. Topical depigmenting agents, such as tyrosinase inhibitors (including arbutin, hydroquinone (HQ), kojic acid, L-ascorbic acid, and azelaic acid), are widely employed as therapeutic strategies for skin hyperpigmentation [54]. Overall, skin hyperpigmentation treatment works by inhibiting tyrosinase and TYRP2, which suppresses melanogenesis and reduces the melanogenic process [55,56].

Nevertheless, these compounds are highly associated with instability and adverse effects, such as a burning sensation on the skin [56,57]. Among some adverse effects related to kojic acid and hydroquinone are skin irritation, contact dermatitis, erythema, and, in cases of prolonged use, exogenous ochronosis [58,59]. It is noteworthy that in countries such as South Africa and Thailand, the use of hydroquinone is prohibited due to its harmful activity on the skin and its adverse effects that are correlated. In addition, tyrosinase inhibitors are associated with prolonged treatments, exhibiting medium-long-term effectiveness and variable clinical outcomes [60].

2. Data Collection

The data collection was carried out across four databases: Embase® (Elsevier), Scopus (Elsevier), PubMed® (MEDLINE/National Library of Medicine), and Web of Science (Clarivate Analytics). The search period was limited from 2000 to 2025, with all results retrieved by March 09, 2025. The search used a combination of terms: nano* (title) AND skin (title, abstract, keywords) AND hyperpigmentation (title, abstract, keywords). Study selection and eligibility were based on an initial screening. The inclusion criteria comprised studies focused on skin hyperpigmentation, its treatments, and nanotechnology-based delivery systems applied via the topical route. Eligible studies were required to present complete and accessible original research data in English and include either *in vitro* or *in vivo* experiments. Exclusion criteria encompassed studies that did not meet these requirements, duplicate records, unavailable publications, and review articles. A flowchart illustrating the methodology for selecting relevant papers from the databases is shown in Fig. 2. Using the search terms, Embase yielded 81 papers, with 45 excluded and 36 selected; Scopus resulted in 131 papers, with 64 excluded and 67 selected; PubMed® produced 72 papers, with 29 excluded and 43 selected; and Web of Science provided 87 papers, with 42 excluded and 45 selected. In total, 191 papers were identified across all databases. Among these, 110 were duplicates, 11 were unavailable, and 37 were review articles, leaving 33 papers for final review.

After data collection, the selected papers from the combined search terms were imported into a reference manager for organization. The files were then converted into 'RIS' format for import into VOSviewer. This free text mining software creates bibliometric maps of scientific fields. Once the files were loaded, bibliographical data—such as abstracts and keywords—were mapped to identify the most relevant keywords with at least two occurrences. Unrelated words, such as organization names and common terms, were removed, and repetitive words (singular, plural, and abbreviations) were merged.

After compiling the keyword list, VOSviewer generated a map that grouped the most frequently cited terms in

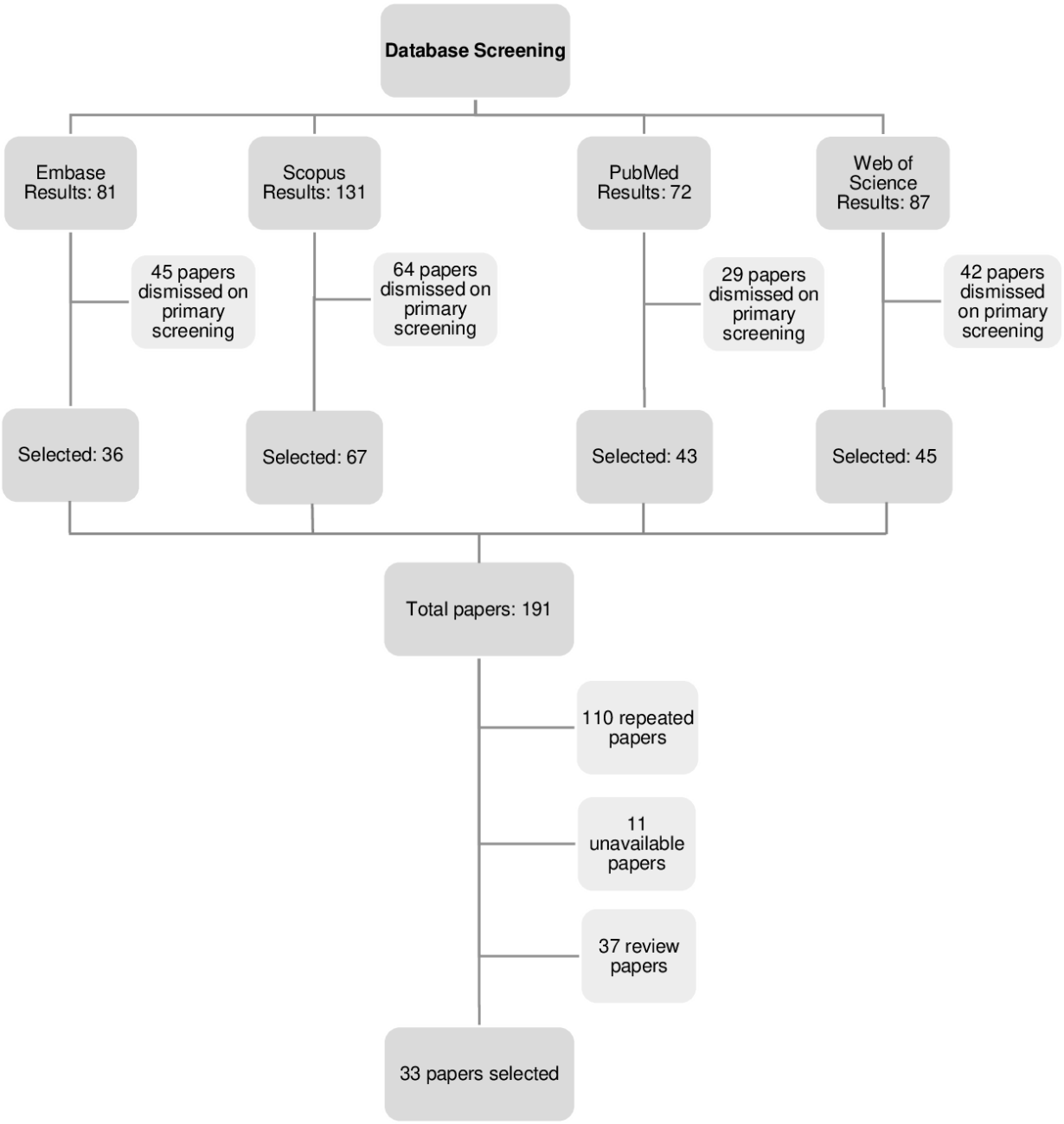

Fig. 2. Flowchart illustrating the article selection process conducted in the Embase® (Elsevier), Scopus (Elsevier), PubMed® (MEDLINE/National Library of Medicine), and Web of Science (Clarivate Analytics) databases using the search terms nano* (title) AND skin (title, abstract, keywords) AND hyperpigmentation (title, abstract, keywords) published between 2000 and 2025.

the papers; the size of each word reflected its citation frequency. This process enabled a systematic and automated analysis, highlighting the most commonly cited words in the selected papers. As shown in Fig. 3, the most cited words were "hyperpigmentation", "solid lipid nanoparticles", and "nanostructured lipid carriers".

3. Nanotechnology-Based Delivery Systems

Nanotechnology-based delivery systems have been widely explored for topical drug delivery. The incorporation of drugs or bioactive compounds into nanostructured systems for skin application has emerged as a promising strategy to improve compound stability, skin permeation and retention, controlled release, and therapeutic efficacy, while potentially reducing local irritation and systemic adverse effects [19,61,62].

Several nanostructured systems have been investigated for the topical delivery of depigmenting compounds, including nanostructured lipid carriers (NLCs), solid lipid nanoparticles (SLNs), nanoemulsions, lipo-

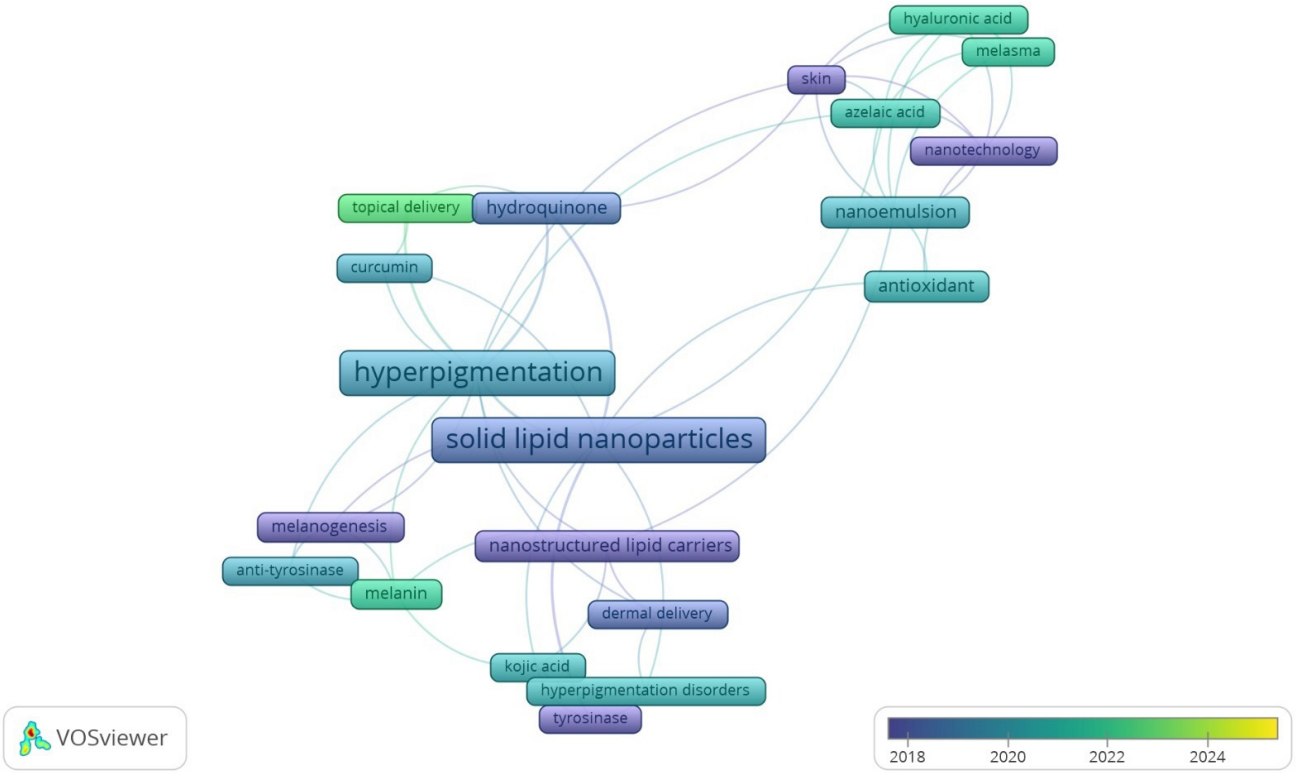

Fig. 3. Keyword mapping of the selected studies retrieved using the search strategy nano* (title) AND skin (title, abstract, keywords) AND hyperpigmentation (title, abstract, keywords), covering publications from 2000 to 2025.

somes, niosomes, nanovesicles, nanocrystals, ethosomes, nanosponges, and polymeric nanoparticles. Among the 33 studies selected in this review, lipid-based nanosystems were the most frequently reported, particularly NLCs and SLNs, which accounted for 17 studies, followed by nanoemulsions (6 studies). In contrast, liposomes, niosomes, and nanovesicles were each described in 2 studies, whereas nanocrystals, ethosomes, nanosponges, and polymeric nanoparticles were reported in only 1 study each. Overall, the reviewed literature demonstrates a clear predominance of lipid-based nanocarriers for the management of skin hyperpigmentation, likely due to their versatility, biocompatibility, and ability to incorporate a varied range of pharmaceutical and bioactive compounds, as illustrated in Fig. 3.

According to Table 1 (Ref. [4,12,13,20,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91]), a wide variety of nanotechnology-based systems have been developed for the delivery of depigmenting compounds. The composition of these nanosystems was highly diverse and strongly dependent on the type of nanostructure and the preparation method employed. Different lipids, surfactants, phospholipids, polymers, oils, and stabilizing agents were combined to optimize physicochemical properties, stability, drug incorporation, and skin delivery performance. Likewise, several preparation methods were reported, including thin-film hydration, solvent evaporation, ultrasonication, hot melt homogenization, high-pressure homogenization, high-shear homogenization, microfluidization, ethanol injection, spontaneous emulsification, and low- or high-energy emulsification techniques.

Physicochemical characterization demonstrated marked variability among the developed formulations. Overall, particle sizes ranged from approximately 13 nm in nanoemulsions to about 507 nm in liposomal systems [4,63]. Most formulations presented nanometric dimensions below 300 nm, which are considered favorable for topical application and skin interaction. Polydispersity index (PDI) values varied considerably among the analyzed studies, ranging from 0.085 to 0.480. Nevertheless, most formulations exhibited PDI values below 0.2–0.3, suggesting an acceptable degree of particle size homogeneity and relatively narrow size distribution [4,64]. Zeta potential values varied substantially according to the composition and surface characteristics of the nanosystems, ranging from approximately +22 mV to −46 mV [65,66]. Most formulations displayed negative surface charges, which may contribute to improved colloidal stability by reducing particle aggregation.

Association or encapsulation efficiency also varied considerably depending on the active compound and the carrier composition. Reported values ranged from approximately 9% in some SLN formulations containing curcumin

Table 1. Summary of literature survey in Embase® (Elsevier), Scopus (Elsevier), PubMed® (MEDLINE/National Library of Medicine), and Web of Science (Clarivate Analytics) using the keywords nano* (title) AND skin (title, abstract, keywords) AND hyperpigmentation (title, abstract, keywords).

System	Pharmaceutical compounds	Preparation technique	Components	Particle size (nm)	Polydispersity index (PDI)	ζ-potential (mV)	Association efficiency (%)	Ref
Liposomes	Vitamin K1	Thin-Layer Evaporation Method	Phospholipid, Cholesterol, Chloroform, Ethanol, Phosphate Buffer Saline	126.5 ± 2.3	0.163 ± 0.003	+22.5 ± 1.2	96.2	[66]
Liposomes	Arbutin	Reversed-Phase Evaporation Method	Fish Collagen, Hyaluronic Acid Sodium Salt, Soybean Phosphatidylcholine, Carbopol 940, Triethanolamine, 1,8-Cineole, (R)-(+)-Limonene, Caffeine, Transcutol, and Labrasol	151.9 ± 23.8 to 507.0 ± 15.3	0.29 ± 0.03 to 0.40 ± 0.07	–16.37 ± 0.19 to –28.2 ± 1.8	80.59 ± 0.72 to 99.53 ± 0.77	[63]
Nanocrystals	Hydroquinone	Acid Hydrolysis	Sulfuric Acid Solution, Distilled Water, Microcrystalline Cellulose	301 ± 10	0.36 ± 0.05	–46.1 ± 0.1	79.3 ± 2	[65]
Nanoemulsions	4-n-Butylresorcinol	Low-Energy Emulsification Method	PEG-40 Hydrogenated Castor Oil, Distilled Water	13.3 ± 0.2	0.08 ± 0.02	-	80.05 ± 0.75	[4]
Nanoemulsions	Kojic Monooleate	High and Low Energy Emulsification Techniques	Lemon Essential Oil, Castor Oil, Polysorbate 80, Xanthan Gum, Deionized Water	110.0 ± 0.1	0.25 ± 0.01	−43.60 ± 0.23	-	[12]
Nanoemulsions	Kojic Dipalmitate and Rosehip Oil	High-Energy Method (Ultra-Turrax®)	Polysorbate 80, Purified Water, Sorbitan Oleate	74 ± 1	0.269 ± 0.004	–9.44 ± 0.53	97.79 ± 2.01	[83]
Nanoemulsions	Kojic Acid and Kojyl 3-Aminopropylphosphonic Acid	Spontaneous Formation	Polysorbate 80, Monooleate 80, Isopropyl Myristate, Polyethylene Glycol 200	141 ± 11	-	-	-	[88]
Nanoemulsions	Azelaic Acid	High Speed Stirring	Ethanol, Triethanolamine, Sorbitan Monooleate, Poloxamer 407, BHT, Rice Bran Oil, Phenoxyethanol, Caprylyl Glycol, Sodium Edetate, HA	419 ± 23	-	–10.9 ± 0.44	84.65	[84]
Nanoemulsions	Quercetin and Olive Oil	High-Energy Emulsification Method	Span®80, Tween®80, Distilled Water, Ethanol	183.4 ± 9.5	0.19 ± 0.03	–17.13 ± 0.61	99.62 ± 0.27	[67]
Nanosized Etho-somal Gel	Kojic Acid Dipalmitate	Cold Method	Soy Phosphatidylcholine, Ethanol, Propylene Glycol, Water	148 ± 3.6	0.158 ± 0.07	–23.4	90.00	[86]
Nanosponges	Azelaic acid	Melt Method	β-Cyclodextrin, Diphenyl Carbonate, Distilled Water	228.3 ± 12.3	0.141 ± 0.096	−21.43 ± 1.54	88.20 ± 0.12	[89]
NLCs	MHY908-Loaded	Reverse Injection Technique of Melt and Ultrasonication	Compritol®, Miglyol, Poloxamer 188	198 ± 6	0.3 ± 0.2	−32 ± 1.2	89 ± 1.4	[13]
NLCs	N-Acetyl Glucosamine	Hot Homogenization Technique	Glyceryl palmitostearate, Poloxamer®, Polysorbate 80, Miglyol®	191 ± 4.0	-	-	44 ± 3.6	[72]

Table 1. Continued.

System	Pharmaceutical compounds	Preparation technique	Components	Particle size (nm)	Polydispersity index (PDI)	ζ-potential (mV)	Association efficiency (%)	Ref
NLCs	Kojic Acid	Ultra-Probe Sonication Method	Glyceryl Monostearate, Cholesterol, Span®60, Deionized Water, Tween®20, Oleic Acid	172.9 ± 7.1	0.3 ± 0.1	–39.1 ± 2.7	76.4 ± 0.1	[75]
NLCs	Ginger Oil and Hexylresorcinol	High-Shear Homogenization Technique	Precirol® ATO 5, Poloxamer 188, Sucrose Distearate, Span®85, Water	113 ± 1.2	0.219 ± 0.010	–24.2 ± 1.0	92.0 ± 1.0	[69]
NLCs	Deoxyarbutin	High-Shear Homogenization	Cetyl Palmitate, Myristyl Myristate, Poloxamer 188, PEG-400, Sodium Sulfite, Deionised Water	434.9 ± 21.5	0.219 ± 0.004	-	99.821 ± 0.004	[70]
NLCs	Auraptene	High Shear Homogenization and Ultrasound Method	Span®80, Poloxamer 188	103.1 ± 4.9	0.29 ± 0.06	–21.2 ± 1.2	89.56 ± 3.75	[80]
NLCs	Glycyrrhiza Glabra Extract	High-Shear Homogenization and Ultrasonication Methods	Compritol®, MCT Oil, Polysorbate 80, Sodium Cholate	196.3 ± 0.9	0.295 ± 0.006	–15.7 ± 0.33	79.01 ± 2.37	[81]
NLCs	Dihydrooxyresveratrol	Hot and High-Pressure Homogenization Techniques	Olivem 1000®, Miglyol C-T7, Tween 80, Microcare PHC®, Deionized Water	110.3 ± 1.7	0.20 ± 0.03	–35.3 ± 0.96	97.79 ± 0.09	[82]
Nanovesicles	Curcumin	Modified Ethanol Injection Method	Soy Phosphatidylcholine, DMSO, Ethanol, Chloroform, Distilled Water	182.9 ± 6.3	0.214 ± 0.002	–21.4 ± 0.72	89.1 ± 0.42	[90]
Nanovesicles	Hydroquinone	Thin-Film Hydration Method	Phospholipon®90 G, Sodium Cholate, Chloroform, Methanol, Sodium Metabisulfite	210.0 ± 5.2	0.24	–15.1	67.61	[87]
Niosomes	Arbutin	Ultrasonication Technique	Cholesterol, Polysorbate 20, Sorbitan Monolaurate, Water, Carbopol 941	114.8 ± 13.7	0.48 ± 0.05	−18.9 ± 9.5	35.55 ± 1.59	[64]
Niosomes	Glutathione	Micro Fluidization Technique	Cholesterol, Span®60, Ultrapure Water	349.5 ± 2.3	0.23 ± 0.01	–37.4 ± 2.4	98.24 ± 0.04	[91]
Polymeric Nanoparticles	Vitamin C	Solvent-Evaporation Method	Ethyl Cellulose, Methanol, Pluronic F127, Distilled Water, Polymer Ratio	258 ± 12	0.265	+9.30	87.3 ± 0.84	[85]
SLNs	Trans-Resveratrol-Loaded	Ultrasonication Technique	Stearic Acid, Poloxamer 407, Soy Lecithin, Methylparaben, Propylparaben, Distilled Water	155.5 ± 0.3	0.140 ± 0.02	–2.60 ± 1.27	-	[20]
SLNs	MHY498-Loaded	Solvent-Evaporation Method	Glyceryl behenate, Phosphatidylcholine, Ethanol, Poloxamer 188	207 ± 39	0.269	−29.8 ± 1.2	77.6 ± 4.7	[71]

Table 1. Continued.

System	Pharmaceutical compounds	Preparation technique	Components	Particle size (nm)	Polydispersity index (PDI)	ζ-potential (mV)	Association efficiency (%)	Ref
SLNs	N-Acetyl-D-Glucosamine	High Shear Homogenization	Cetyl Palmitate, Phosphatidylcholine, Peg-25 Hydrogenated Castor Oil, C12–13 Alkyl Ethylhexanoate, Di C12–13 Alkyl Tartrate, Hydrophilic Fumed Silica, various PEG-derivatives, Hydroxypropyl Methylcellulose	252 ± 24	0.43 ± 0.08	–28 ± 1	12.8 ± 4.2	[73]
SLNs	Curcumin	Ultrasonic Probe Sonication Method	Polysorbate 80, Sorbitan Monooleate, Glyceryl Distearate	213 ± 17	0.31 ± 0.06	–27 ± 1	8.9 ± 3.5	[68]
SLNs	Kojic Acid	Ultrasonic Probe Sonication Method	Cholesterol, Glyceryl Monostearate, Polysorbate 20, Sorbitan Monostearate, Deionised Water	156.9 ± 7.1	0.388 ± 0.004	–27.67 ± 1.89	59.02 ± 0.74	[74]
SLNs	Ethanol Leaves Extract of Prunus persica (L.)	Solvent Evaporation and Homogenization	Glyceryl Monostearate, Chloroform–Methanol, Polysorbate 80	170 to 176	0.230 to 0.450	–21.8 to –22.0	70 to 77	[76]
SLNs	Hydroquinone	Ultrasonication Method	Stearic Acid, Ionic Surfactants Cetyltrimethylammonium Bromide, Sodium Lauryl Sulphate, Water	151.3	0.33	–27.3	89.4	[77]
SLNs	Azelaic Acid	Ethanol Evaporation and High-Pressure Homogenization	Stearic Acid, Poloxamer 188, Ethanol, Distilled Water	282.9	0.319	–15.2	97.18	[78]
SLNs	Hydroquinone	Hot Melt Homogenization Technique	Ethanol, Water, Poloxamer 407, Glyceryl Distearate, Sorbitan Monolaurate	86	-	-	89.5 ± 4.5	[79]
SLNs	Ginger Oil and Hexylresorcinol	High-Shear Homogenization Technique	Precirol® ATO 5, Poloxamer 188, Sucrose Distearate, Span®85, Water	96.0 ± 1.1	0.192 ± 0.015	–21.7 ± 1.8	99.0 ± 0.7	[69]

Data collected from 2000 to 2025.

to values close to 100% in several nanoemulsions, liposomes, SLNs, and NLCs [63,67,68,69,70]. Lipid nanocarriers, particularly SLNs and NLCs, were the most extensively investigated systems and frequently exhibited high encapsulation efficiencies, in many cases above 90%, highlighting their strong capacity to incorporate both synthetic and natural depigmenting compounds. In addition, homogenization and ultrasonication-based techniques were among the most frequently employed methods for the preparation of SLNs and NLCs, producing systems with particle sizes ranging from approximately 51 to 435 nm, PDI values between 0.140 and 0.430, and zeta potential values from −39 to −2 mV [13,19,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82]. Overall, the compiled studies demonstrate that both formulation composition and preparation methodology play a critical role in determining the physicochemical characteristics and potential performance of nanotechnology-based depigmenting systems.

As can be seen in Table 2 (Ref. [4,12,13,20,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90]), *in vitro* methodologies employed in the reviewed studies mainly involved release assays, skin permeation and retention studies, cytotoxicity analyses, and tyrosinase inhibition assays.

Among these, permeation and skin retention studies using Franz diffusion cells were some of the most frequently reported approaches, particularly employing porcine ear skin as a biological membrane due to its close structural similarity to human skin. The reviewed studies employed different experimental protocols to evaluate the cutaneous delivery of depigmenting compounds incorporated into nanotechnology-based systems. Overall, the results demonstrated enhanced accumulation of these compounds within the skin, while some studies further stratified the skin layers and showed increased distribution in the stratum corneum, epidermis, and dermis [20,83,84]. Other biological membranes, including human skin, rat skin, mouse skin, goat skin, cadaver skin, and artificial membranes, were also employed to evaluate permeation behavior and controlled-release profiles [13,71,73,75,79,85,86,87]. Cytotoxicity studies were commonly performed using MTT or resazurin assays in cell lines such as B16F10, HaCaT, NIH 3T3, L-929, and HFF-1, with most formulations demonstrating high cell viability and low toxicity at the evaluated concentrations. In addition, tyrosinase inhibition assays represented one of the most frequently explored methodologies to assess the anti-melanogenic potential of the developed formulations. These assays were mainly conducted using mushroom tyrosinase or cellular tyrosinase models in B16F10 melanoma cells, consistently demonstrating significant inhibition of tyrosinase activity and reduction of melanogenesis markers following incorporation of active compounds into nanocarriers.

3.1 Liposomes

Liposomes are nanosized vesicles consisting of an aqueous core enclosed by one or more phospholipid bilayers. Their main advantage in topical drug delivery lies in their structural similarity to skin membranes, which facilitates membrane fluidization and enhances drug permeation. Literature reports indicate that liposome-based formulations achieve promising outcomes, including improved penetration into the deeper skin layers. However, entrapment efficiency and vesicle size remain critical parameters in the design of effective topical liposomal formulations [63,66].

Samadi et al. (2020) [66] developed a vitamin K1 liposome for treating purpura and hyperpigmentation induced by cosmetic and laser products. In this study, the authors concluded that encapsulating vitamin K1 in liposomes resulted in controlled and sustained release, allowing for greater permeation in human skin, as measured by the dialysis method, compared to the vitamin K1 control solution. In 2024, Hatem et al. [63] demonstrated the development of liposomes containing arbutin for targeting melanocytes and treating melasma. The formulation demonstrated good stability, and permeation studies showed that it reached the dermis.

3.2 Nanocrystals

Nanocrystals are crystalline particles formed by pure drugs and can be stabilized by ionic or non-ionic surfactants, with high biodegradability and biocompatibility. As an advantage, it can increase the bioavailability of the encapsulated drug in topical applications by enhancing the solubility of pharmaceutical compounds that are not very soluble in water. However, the disadvantages of nanocrystals include low stability, and depending on the activity, they can crystallize [65].

According to Taheri and Mohammadi (2015) [65], cellulose-derived nanocrystals exhibit favorable conditions for developing cosmetic products that treat the skin, which are non-toxic and biodegradable, helping to maintain skin hydration. Hydroquinone was the drug used and characterized with the nanocrystal, in which it presented an excellent release profile. The test was carried out using the dialysis method. A slower and more sustained release was observed during the experiment.

3.3 Nanoemulsions

Nanoemulsions are dispersions of two immiscible liquids (oil and water) stabilized by a surfactant system and commonly produced using high- and low-energy emulsification methods, including industrially scalable techniques such as high-pressure homogenization. These systems have attracted considerable interest in pharmaceutical and cosmetic applications due to their physicochemical stability and versatility for topical delivery. In addition, the reduced droplet size of nanoemulsions may enhance the penetration

Table 2. Summary of *in vitro* experiments reported in the literature.

System	Pharmaceutical compounds	Assay	Conditions	Results	Ref
Liposomes	Vitamin K1	Release	Dialysis Method	79.2% in 12 hours	[66]
		Permeation	Human Skin, Franz Cell	327.36 ± 22.1 μg/cm^2 after 24 h	
Liposomes	Arbutin	Release	Franz Cell, Cellulose Membranes	100% in 24 hours	[63]
		Permeation	Dorsal Rat Skin, Franz Cell	Epidermis (up to 43.44 %), stratum corneum (up to 26.57%) and dermis (up to 21.92 %)	
Nanocrystals	Hydroquinone	Release	Dialysis Method	80% in 4 hours	[65]
Nanoemulsions	4-n-Butylresorcinol	Permeation	BALB/c Mice and Nude Mouse Skin, Diffusion Cell	Increased permeation	[4]
Nanoemulsions	Kojic Monooleate	Cell Viability	3T3, MTT	IC50 >100 μg/mL	[12]
Nanoemulsions	Kojic Dipalmitate and Rosehip Oil	Permeation	Porcine Ear Skin, Franz Cell	Reached the stratum corneum and epidermis	[83]
		Cell Viability	3T3-L1, MTT	Near 100% cell viability	
		Tyrosinase Inhibition	Amount of Dopachrome Formed	Inhibited tyrosinase by approximately 20%	
Nanoemulsions	Kojic Acid and Kojyl 3-Aminopropylphosphonic Acid	Cell Viability	B16F10, MTT	100%	[88]
		Tyrosinase Inhibition	Cellular Tyrosinase in B16F10	Reduced the melanin content to 84%	
		Permeation	Porcine Ear Skin, Franz Cell	Reached all skin layers	
Nanoemulsions	Azelaic Acid	Cell Viability	BALB/c 3T3, MTT	Did not decrease the cell viability	[84]
		Tyrosinase Inhibition	Mushroom Tyrosinase	IC50 = 13.97 mM	
Nanoemulsions	Quercetin and Olive Oil	Tyrosinase Inhibition	Mushroom Tyrosinase	Inhibited 56.24 ± 3.38% at 5 μg/mL	[67]
Nanosized Ethosomal Gel	Kojic Acid Dipalmitate	Permeation	Albino Rat Skin, Franz Cell	67% at 12 hours, 53 μg/cm^2/h	[86]
Nanosponges	Azelaic acid	Release	Dialysis Method	Up to 29.58% in 8 h and 67.75% in 24 h	[89]
		Cell Viability	HaCaT, MTT	A dose-dependent inhibitory effect was observed	
		Tyrosinase Inhibition	Mushroom Tyrosinase	IC50 = 4.76 mM/mL	
NLCs	MHY908-Loaded	Release	Dialysis Method	60% in 10 hours and 87% in 48 hours	[13]
		Permeation	Skin of C57BL/6 Mice, Franz Cell	57.7% after 48 h, 3.6 ± 0.05 μg/cm^2/h	
		Cell Viability	L-929, MTT	More than 80% viable	
NLCs	N-Acetyl Glucosamine	Release	Franz Cell, Semipermeable Membrane	More than 90% in 6 h	[72]
NLCs	Kojic Acid	Release	Dialysis Method	Up to 0.8% (30 min) and 15.6% (24 h)	[75]
		Permeation	Human Skin, Wistar Rat Skin, Artificial Membrane, Franz Cell	308.0, 351.7 and 45.5 μg/cm^2	
		Cell Viability	HFF-1, MTT	>90%	
		Tyrosinase Inhibition	Mushroom Tyrosinase	IC50 = 5.4 ± 0.1 mg/mL	
NLCs	Ginger Oil and Hexylresorcinol	Release	Franz Cell, Semipermeable Membrane	The results showed a sustained release	[69]
NLCs	Deoxyarbutin	Permeation	Spangler's membrane, Franz Cell	Gel-NLCs (57.97%) and NLCs (47.39%) in 8 h	[70]

Table 2. Continued.

System	Pharmaceutical compounds	Assay	Conditions	Results	Ref
NLCs	Auraptene	Permeation	Mouse Abdominal Skin (BALB/c), Franz Cell	14.85% in 24 hours	[80]
		Cell Viability	B16F10, Resazurin	More than 90% viable	
		Tyrosinase Inhibition	Cellular Tyrosinase in B16F10	Significant inhibition at 125 and 250 µM	
		Release	Dialysis Method	35% in 48 hours	
NLCs	Glycyrrhiza Glabra Extract	Cell Viability	B16F10, MTT	100%	[81]
		Tyrosinase Inhibition	Spectrophotometric Method, DOPA rate	Significantly reduce the activity of tyrosinase	
		Release	Dialysis Method	49% at 48 h	
NLCs	Dihydrooxyresveratrol	Permeation	Skin-Like Hydrophobic Membrane, Franz Cell	Enhance permeation	[82]
Nanovesicles	Curcumin	Cell Viability	B16F10 and HaCaT, MTT	B16F10 (>2 µg/mL) and HaCaT (>500 µg/mL)	[90]
		Tyrosinase Inhibition	Cellular Tyrosinase in B16F10	Tyrosinase activity decreased significantly	
		Release	Dialysis Method	72.26 ± 2.9% after 6 hours	
		Permeation	Dermatomized Skin of Sprague-Dawley Rats, Franz Cell	Increased permeation	
Nanovesicles	Hydroquinone	Release	Franz Cell, Dialysis Membrane	54.39 ± 1.92% to 76.05 ± 1.18% up to 24 hours	[87]
		Permeation	Wistar Rat Skin, Franz Cell	4589 ± 1.06 ug/cm^2 in 24 hours and 60.89 ± 0.13 µg/cm^2/h	
Niosomes	Arbutin	Cell Viability	L-929, MTT	Cytotoxicity is directly linked to the concentration	[64]
		Tyrosinase Inhibition	Mushroom Tyrosinase	% Tyrosinase inhibition activity = 94.56 ± 0.96	
		Permeation	Abdomen Wistar rats skin	602.1 ± 25.48 µg/cm^2	
		Cell Viability	HFF, MTT	About 86%	
Polymeric nanoparticles	Vitamin C	Release	Dialysis Method	25 to 102% after 8 hours	[85]
		Permeation	Freshly Excised Goat Skin Membrane, Franz Cell	40% drug up to 8 h	
SLNs	Trans-Resveratrol-Loaded	Cell Viability	NIH 3T3, MTT	Treated cells were 80–100% viable	[20]
		Permeation	Porcine Ear Skin, Franz Cell	45% after 24 hours	
		Cell Viability	HaCaT, MTT	85%	
		Tyrosinase Inhibition	Mushroom Tyrosinase	Greater inhibition	
SLNs	MHY498-Loaded	Release	Dialysis Method	70% in 6 hours and 90% over 48 hours	[71]
		Permeation	Dorsal Skin from Male C57BL/6 Mice, Franz Cell	5.7 µg/cm^2 after 12 hours, 4.1 µg/cm^2 after 24 hours, 3.3 µg/cm^2 after 48 hours	
SLNs	N-Acetyl-D-Glucosamine	Cell Viability	L-929, MTT	90%	[73]
		Release	Franz Cell, Hydrophilic Polysulfone Membrane	4.4 to 64% after 4 hours	
		Permeation	Human Skin, Franz Cell	13.2 to 23.4% after 24 hours	

Table 2. Continued.

System	Pharmaceutical compounds	Assay	Conditions	Results	Ref
SLNs	Curcumin	Permeation	Human Cadaver Skin, Franz Cell	9.43 ± 0.34% in 24 hours	[68]
		Tyrosinase Inhibition	Mushroom Tyrosinase	% Tyrosinase inhibition activity = 94.30 ± 0.30	
SLNs	Kojic Acid	Release	Paddle Method (type II)	3.947% ± 0.307 in 30 minutes	[74]
		Tyrosinase Inhibition	Mushroom Tyrosinase	IC50 = 3.84 ± 0.122 µg/mL	
SLNs	Ethanol Leaves Extract of *Prunus persica* (L.)	Cell Viability	Human Keratinocytes Cell Line, MTT	90% in 24 h	[76]
		Tyrosinase Inhibition	Mushroom Tyrosinase	% Inhibition = 78.12 ± 1.50, IC_{50} = 303.03 ± 4.15 µg/mL	
SLNs	Hydroquinone	Release	Differential Pulse Voltammetry	Continuous prolonged release	[77]
SLNs	Azelaic Acid	Release	Franz Cell, Dialysis Membrane	93.9% in 24 hours	[78]
		Cell Viability	B16F10, MTT	99.05%	
		Tyrosinase Inhibition	Mushroom Tyrosinase	% Tyrosinase inhibition activity = 60.06%	
SLNs	Hydroquinone	Permeation	Wistar Rat Skin, Franz Cell	Deposition of 46.5 ± 2.6 %	[79]
SLNs	Ginger Oil and Hexylresorcinol	Release	Franz Cell, Semipermeable Membrane	Sustained release	[69]

of compounds into the skin, an effect that can also be influenced by the composition of the oil phase and the surfactants employed in the formulation [12,92].

Kojic acid (KA) and its derivatives have been widely investigated as depigmenting agents for the treatment of skin hyperpigmentation. In this context, Kojic Monooleate (KMO) was incorporated into nanoemulsions, aiming to inhibit the tyrosinase process and thus treat hyperpigmentation in the skin. Overall results indicate that the optimized nanoemulsion enriched with KMO is an ideal treatment for hyperpigmentation due to its physicochemical properties. Moreover, results of *in vitro* cytotoxicity assays of the nanoemulsion, carried out with mouse embryonic fibroblast cells (3T3), indicated safety and efficacy for cosmetic application [12].

Zilles et al. (2023) [83] described the production of a nanoemulsion containing Kojic Dipalmitate (KPD) and Rosehip Oil. Permeation studies with formulations containing 1 and 2 mg/mL revealed similar results, with approximately 1.2 µg/cm^2 of KPD detected in the epidermis for both treatments. In cell viability tests, no decrease was observed at different formulation concentrations in 3T3-L1 mouse embryonic fibroblast cells. The nanoemulsion showed the same tyrosinase inhibition as ascorbic acid. The study demonstrated that the free drug showed greater inhibition compared to the nanoemulsion. This may have occurred, according to the authors, due to the presence of the nanostructure, which is disrupted during skin permeation, thereby promoting the release of the drug. More recently, in studies carried out by Chang and collaborators in 2025 [88], KA and kojyl 3-aminopropylphosphonic acid were carried in a nanoemulsion to develop a skin lightening formulation, which proved to be stable and demonstrated its ability to reduce melanin content.

Azelaic acid (AzA) has also been explored in nanoemulsion-based formulations for the treatment of hyperpigmentation disorders. In a study conducted by Jacobus Berlitz and co-workers (2019) [84], nanoemulsions containing AzA and hyaluronic acid (HA) were developed aiming to enhance skin retention and tyrosinase inhibition activity. *In vitro* permeation studies using porcine ear skin demonstrated that the formulations were able to reach deeper skin layers, while also improving tyrosinase inhibition when compared to the free compound. In addition, the formulations did not reduce cell viability in BALB/c 3T3 cells, highlighting their potential as a promising and safe strategy for the treatment of hyperpigmentation and melasma.

Quercetin, a polyphenolic compound with antioxidant and depigmenting properties, has also been investigated as a potential agent for the treatment of skin hyperpigmentation. In a 2022 study, Silva and colleagues [67] evaluated the tyrosinase inhibitory activity of a quercetin–olive oil nanoemulsion, comparing its performance with that of free quercetin and other cosmetic market candidates. The developed formulation demonstrated notable potential in suppressing melanin formation, highlighting the applicability of nanoemulsion-based systems for the topical delivery of depigmenting compounds.

Shao et al. (2024) [4] highlighted that, although 4-n-butylresorcinol (4-nBR) is highly effective in treating hyperpigmentation, its clinical use is restricted by low solubility, instability, and skin irritation. The development of nanoemulsion-based formulations addressed these limitations by enhancing solubility and stability, reducing irritation, and improving percutaneous absorption. Moreover, the study successfully produced nanoemulsions with adjustable viscosity and low surfactant content, broadening their potential applicability in topical therapies.

3.4 Polymeric Nanoparticles

Nanoparticles have emerged as an important strategy for enhancing the topical delivery of bioactive compounds by improving skin permeation, retention, and controlled release at the target site. In this context, Duarah et al. (2017) [85] developed polymeric nanoparticles (NPs) encapsulating vitamin C and incorporated them into a polymeric gel intended for the treatment of skin hyperpigmentation. The developed nanoencapsulated formulation showed promising potential for topical application in hyperpigmentation disorders. Drug release studies performed using the dialysis bag technique demonstrated an initial rapid release followed by a sustained release profile over time. *In vitro* permeation studies using Franz diffusion cells indicated slow permeation during the first 2 hours, followed by a linear permeability profile. In addition, cytotoxicity evaluation through the MTT assay using murine embryonic fibroblast cells demonstrated that the formulation was non-toxic, even at the highest tested concentrations.

3.5 Nanosponges

Nanosponges are a type of nanoparticle, characterized as polymeric, cross-linked, and porous structures, that have been extensively studied as a promising drug delivery platform for dermatological applications. This nanostructure can enhance stability, solubility, permeability, encapsulation, safety, and other drug delivery characteristics. An important feature of these sponges is their aqueous solubility [89,93].

In a study by Kumar and Rao (2021) [89], cyclodextrin nanosponges for encapsulating azelaic acid were proposed and developed using the melt method, employing β-cyclodextrin (β-CD) as the polymer and diphenyl carbonate (DPC) as the cross-linker. Overall results revealed that azelaic acid encapsulation in nanosponges enhanced drug efficacy in terms of solubility, release, and safety, with adequate antimicrobial, antioxidant, and antityrosinase activities. The dialysis method was employed for release studies, and nanosponges facilitated a controlled and precise release of the drug. The cytotoxicity of the free drug

and nanosponges was evaluated using HACaT cell lines by the MTT assay. The results showed that the nanosponges exhibited slightly lower cytotoxicity compared to the free drug. For the tyrosinase inhibition assay, KA was used as a positive control. The nanosponges demonstrated a similar result to that presented by the positive control, inhibiting tyrosinase.

3.6 Niosomes

Niosomes are vesicles composed of non-ionic surfactants, which are biodegradable, non-toxic, stable, and more cost-effective. Recently, a study by Radmard et al. (2021) [64] established arbutin-loaded niosomes via an ultrasonic method as a green preparation for a cosmetic product (arbusome gel). Overall results indicated that the presence of cholesterol in the formulation increased the arbusome's vesicle size, and that the zeta potential and the size of vesicles can be modulated by the modifications in the ratio of cholesterol:surfactant. In addition, the rat skin permeation results showed superior quantities in the skin layers and the receptor chamber for the arbusome gel compared to the arbutin simple gel. Therefore, no chemical interactions with the components of the niosome formulation were observed, and the formulation did not exhibit any significant irritancy, cytotoxicity, or immunogenicity. Finally, the authors suggested that the niosomes could be utilized as a possible nano-vehicle for arbutin topical delivery and emerge as a new approach for the treatment of skin hyperpigmentation.

As early as 2023, Inal and collaborators [91] dedicated their efforts to the development and physicochemical characterization of lipid-based niosomes encapsulating the glutathione tripeptide, a molecule of considerable interest for dermatological applications. The research group successfully obtained the system using the microfluidization technique, producing a stable formulation that demonstrated properties highly suitable for topical administration, especially in terms of favorable texture, appropriate viscosity, and overall consistency, which together contribute to improved applicability and potential therapeutic performance.

3.7 Nanostructured Lipid Carriers (NLCs) and Solid Lipid Nanoparticles (SLNs)

Nanostructured lipid carriers (NLCs) and solid lipid nanoparticles (SLNs) are among the most widely investigated nanocarriers for the topical delivery of depigmenting agents. These lipid-based systems have attracted considerable interest due to their ability to enhance the penetration and retention of active compounds within the skin, promote controlled and sustained release, improve chemical stability, and increase drug accumulation in the epidermis and dermis. In addition, their occlusive properties and strong interaction with the stratum corneum contribute to improved dermal delivery of both lipophilic and hydrophilic compounds [18,94].

Hydroquinone, one of the most commonly used depigmenting agents, has been associated with lipid nanocarriers in different studies. Ghanbarzadeh et al. (2015) [79] developed hydroquinone-loaded SLNs with good physicochemical stability and high resistance to oxidation. The formulation promoted nearly three-fold higher skin accumulation through excised rat skin compared with hydroquinone incorporated into a Carbopol hydrogel, while also favoring increased cutaneous penetration and lower systemic permeation, highlighting the potential of SLNs for topical treatment of hyperpigmentation. Later, Talele et al. (2022) [77] developed hydroquinone-loaded SLNs stabilized with different emulsifiers (CTAB and SLS). Release studies based on differential pulse voltammetry (DPV) demonstrated that the CTAB formulation promoted a more continuous and prolonged release profile, whereas the SLS-based formulation exhibited faster release.

Al-Amin et al. (2016) [71] investigated SLNs containing MHY498, a newly synthesized tyrosinase inhibitor. The formulation exhibited prolonged release, enhanced *in vitro* skin permeation, and pronounced inhibition of UV-induced melanogenesis *in vivo*, demonstrating promising potential for hyperpigmentation treatment. More recently, Banna et al. (2018) [13] developed NLCs loaded with a newly synthesized tyrosinase inhibitor (MHY908). Regarding the results, the authors demonstrated higher *ex vivo* mouse skin permeation, a significant occlusive effect (both *in vitro* and *ex vivo*), and improved anti-melanogenesis activity against UV-B-induced hyperpigmentation *in vivo* from MHY908/NLCs compared to the MHY908 solution. Additionally, non-toxicity *in vitro* was observed in MHY908/NLCs, suggesting it is a promising topical delivery system for treating hyperpigmentation.

Plant-derived extracts have also been explored in SLN and NLC systems for depigmenting applications. Mostafa et al. (2021) [76] produced SLNs containing *Prunus persica* leaf extract, which showed higher anti-collagenase and anti-tyrosinase activities compared with EDTA and KA, together with prolonged release and low cytotoxicity in human keratinocytes. Yet, the association of ginger oil and 4-hexylresorcinol in NLCs was produced by high-shear homogenization using Precirol ATO 5 as the solid lipid. These formulations were optimized regarding particle size, stability, and rheological properties and compared with SLNs. Clinical evaluation in women with hyperpigmentation demonstrated that both systems, particularly NLCs, effectively reduced skin spots, reinforcing the growing interest in lipid nanocarriers as platforms for natural and multifunctional depigmenting agents [69]. Hoseinsalari et al. (2024) [81] reported NLCs containing *Glycyrrhiza glabra* extract with favorable permeation behavior, biphasic release, and pronounced tyrosinase inhibition.

Natural compounds-loaded with SLN and NLC were also investigated as depigmenting agents. Rigon et al. (2016) [20] developed trans-resveratrol-loaded SLNs and

demonstrated that the SLN-based gel potentiated the tyrosinase inhibitory activity of trans-resveratrol, with activity comparable or superior to KA and without evidence of cytotoxicity. Mikled et al. [82] developed NLCs loaded with dihydroxyresveratrol, demonstrating enhanced permeation and reduced melanogenesis in B16F10 cells. Shrotriya et al. (2018) [68] reported curcumin-loaded SLNs incorporated into a carbopol gel. The formulation provided controlled release for up to 24 h, enhanced skin deposition, effective tyrosinase inhibition, suppression of ear swelling, and reduction of skin water content *in vivo*.

Aliasgharlou and collaborators (2016) [72] developed N-acetylglucosamine (NAGA)-loaded NLCs. For this purpose, a stable derivative was used; it is a monosaccharide derived from glucose, chemically produced by the linkage of glucosamine and acetic acid. Regarding the results, NAGA-loaded NLCs were considered suitable for dermal delivery, exhibited sustained release, and led to a decline in melanin distribution. Furthermore, Marto et al. (2017) [73] developed N-Acetyl-D-Glucosamine (NAG)-loaded SLNs, which resulted in higher NAG permeation through human skin's stratum corneum compared to the control. They also observed a sustained and prolonged release in Franz-type diffusion cells.

In the study reported by Khezri et al. (2020) [74], SLNs loaded with KA presented tyrosinase inhibition potency and improved percutaneous delivery of KA compared to pure KA. Furthermore, the release profile demonstrated a sustained and prolonged release, emerging as a new potential topical preparation for skin hyperpigmentation. Later, in 2021, Khezri and collaborators [75] conducted experiments with KA-loaded NLCs. Release studies were evaluated using the dialysis membrane method, and the NLCs demonstrated sustained and controlled release. The test showed that the toxicity of NLCs in HFF-1 cells is concentration-dependent, as well as the inhibition of tyrosinase.

Meanwhile, in 2023, Nautiyal and Wairkar [78] produced and characterized azelaic acid-loaded SLNs for treating hyperpigmentation. Release studies were carried out in a Franz-type diffusion cell. SLNs demonstrated rapid release in the first few hours, followed by prolonged release. Different concentrations of SLNs were applied to B16F10 melanoma cell cultures. The assay demonstrated that SLNs reduced cellular cytotoxicity and increased viability. Tyrosinase inhibition was also determined at different concentrations of SLNs, and the results revealed a significant reduction in tyrosinase activity.

Tofani et al. (2016) [70] developed NLCs-loaded deoxyarbutin (dArb), and the results showed improved *in vitro* penetration of dArb through NLCs compared to nanoemulsions and conventional emulsions across Spangler's membrane. In 2022, Daneshmand et al. [80] developed NLCs containing auraptene. The experiments demonstrated a biphasic release pattern, characterized by an initial burst followed by sustained release. The formulation did not exhibit significant cytotoxic effects on the B16F10 melanoma cell line, and its effects on cellular tyrosinase activity indicated significant inhibition.

3.8 Nanovesicular Carrier Systems

In recent years, nanovesicular carrier systems have been developed to enhance drug delivery through the skin. This category includes nanovesicles and ethosomes. Nanovesicles have a concentric bilayer, and their physicochemical properties are affected by their composition. Encapsulating drugs in nanovesicles can improve solubility and stability, increase permeation, and reduce adverse effects [95]. Ethosomes are considered an improved form of liposomes and are composed of phospholipids, ethanol, and water, a composition that facilitates better permeability in the skin [86].

In 2022, Farooqui and collaborators [90] developed curcumin nanovesicles for treating hyperpigmentation. The release was assessed using the dialysis membrane diffusion tube method, which showed that the nanovesicles effectively transport the drug across the membrane. Additionally, permeation studies indicated increased drug permeation. In the same year, Jamadar et al. [87] formulated and optimized hydroquinone nanovesicles. Release and permeation tests were conducted in Franz diffusion cells. The formulation showed an initial burst release followed by controlled and sustained release, along with good permeation into the skin. The inhibition of the tyrosinase enzyme was measured for both the simple gel and the gel containing nanovesicles and KA. The studies demonstrated that the gel with nanovesicles exhibited greater inhibition compared to the other tested products.

Also in 2022, Tanveer et al. [86] developed a nanosized ethosome gel loaded with kojic acid dipalmitate for the treatment of hyperpigmentation. The permeation assay was conducted using Franz-type diffusion cells with albino rat skin. The formulation showed a better profile compared to the control, as it penetrated more deeply into the skin and demonstrated sustained action.

4. Concluding Remarks

This review provides a comprehensive overview of skin hyperpigmentation and recent advances in nanotechnology-based delivery systems explored for its management. Growing evidence highlights the potential of nanostructured systems, including liposomes, nanocrystals, nanoemulsions, polymeric nanoparticles, nanosponges, niosomes, NLCs, SLNs, and nanovesicular carrier systems, to improve the topical delivery of depigmenting compounds by enhancing skin permeation and retention, promoting controlled release, and, in some cases, providing superior performance compared with conventional formulations or free compounds. In addition to the reformulation of already established depigmenting agents, recent studies

have also explored the incorporation of novel synthetic molecules and natural bioactive compounds, including plant-derived extracts, reinforcing nanotechnology strategies as a promising and innovative approach for the future management of cutaneous hyperpigmentation.

Overall, the reviewed nanotechnology-based systems present distinct physicochemical and technological characteristics, differing in terms of stability, drug-loading capacity, skin interaction, and manufacturing complexity. Although most nanocarriers demonstrated favorable *in vitro* performance, their advantages and limitations are strongly dependent on formulation composition and the physicochemical properties of the incorporated compounds. In this context, lipid-based nanosystems clearly predominate in the literature, likely due to their versatility, biocompatibility, and ability to improve the cutaneous delivery of a broad range of depigmenting agents. Furthermore, many of these systems are produced using scalable and well-established industrial techniques, which may facilitate their future translation into pharmaceutical and cosmetic products.

Finally, it is important to emphasize that the currently available studies do not allow a direct comparison capable of establishing one nanocarrier as superior to another, since comparative investigations employing the same depigmenting compound across different nanosystems remain scarce. Nevertheless, solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) stand out as the most frequently investigated systems for topical depigmenting therapies. Their prominence is probably associated with advantageous characteristics such as high loading capacity, improved physicochemical stability, controlled release behavior, and occlusive properties capable of enhancing skin hydration and drug retention. In addition, SLNs and NLCs have demonstrated industrial feasibility and scalability, with lipid nanoparticle-based systems already being incorporated into commercial cosmetic and dermatological formulations, further supporting their potential applicability in topical treatments for skin hyperpigmentation.

5. Translational Challenges, Future Directions and Limitations

Although nanotechnology-based systems have shown considerable potential for the treatment of skin hyperpigmentation and topical drug delivery, their clinical translation still faces important technical and regulatory challenges. Concerns related to long-term safety, including irritation, sensitization, and possible nanoparticle accumulation, have stimulated the development of safer and more biocompatible formulations [96,97]. At the same time, advances in formulation design and manufacturing technologies have improved nanocarrier stability, reducing aggregation, fusion, precipitation, and degradation during storage, while supporting formulation reproducibility and large-scale production [96,97,98]. In parallel, the establishment of more specific regulatory guidelines has provided greater clarity for the evaluation and approval of nanotechnology-based products [98]. Although additional studies are still necessary to confirm long-term safety and efficacy, current evidence supports the growing translational potential of these systems for improving hyperpigmentation therapies.

Recent studies indicate that nanostructured depigmenting formulations are progressively advancing toward cosmetic and clinical applications, demonstrating improved skin retention, controlled release, reduced irritation, and enhanced anti-melanogenic activity [64,68,69,72,76,84,86,90]. Formulation stability remains a critical factor, particularly for unstable or poorly soluble compounds, reinforcing the importance of controlling physicochemical properties to ensure safety and efficacy [4,12,64,72,74,75,79,83,84]. In addition, several studies already incorporate optimization strategies and scalable production approaches, including factorial designs and industrially compatible preparation methods, bringing academic development closer to the requirements for reproducibility and large-scale manufacturing [12,63,69,83,87]. The growing number of patents involving nanocarriers for skin-lightening applications further highlights the increasing industrial and technological interest in this field [99,100,101,102,103,104,105,106].

Future investigations should focus on expanding the current evidence through long-term safety studies, well-designed clinical trials, and the development of multifunctional nanosystems combining antioxidant, anti-inflammatory, and melanogenesis-modulating properties. Personalized approaches considering different skin phototypes, together with advances in regulatory standardization and production scalability, may further strengthen the clinical applicability of these systems. Finally, this review presents some limitations related to the heterogeneity of the nanocarriers, active compounds, and experimental methodologies included, which restricts direct comparisons among formulations. In addition, the evaluated studies ranged from *in vitro* assays to *in vivo* and early clinical investigations, contributing to variability in the reported outcomes.

Author Contributions

GFLF, GFO, DCCD, APH, CLD, LSK, FNSF, HFT contributed to the study conception and design. Material preparation, data collection, and analysis were performed by GFLF and GFO. The first draft of the manuscript was written by GFLF, and GFLF, GFO, FNSF and HFT commented on previous versions of the manuscript. DCCD, APH, CLD, and LSK participated in reviewing and revising the manuscript. All authors read and approved the final manuscript. All authors contributed to editorial changes in the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This work was supported by the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq, Brazil) (Award number 420025/2021-9) and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES, Brazil) (Finance Code 001).

Conflicts of Interest

The authors declare no conflicts of interest.

References

[1] Lotfollahi Z. The anatomy, physiology and function of all skin layers and the impact of ageing on the skin. Wound Practice and Research. 2024; 32: 6–10. https://doi.org/10.33235/wpr.32.1.6-10

[2] Aida Maranduca M, Liliana Hurjui L, Constantin Branisteanu D, Nicolae Serban D, Elena Branisteanu D, Dima N, et al. Skin - a vast organ with immunological function (Review). Experimental and Therapeutic Medicine. 2020; 20: 18–23. https://doi.org/10.3892/etm.2020.8619

[3] Lipsker D, Lenormand C. Hyperpigmentation. Annales De Dermatologie et De Venereologie. 2019; 146: 666–682. https://doi.org/10.1016/j.annder.2019.05.005

[4] Shao W, Ren H, Yin M, Li X, Zhang F, Wang X, et al. Enhanced stability and reduced irritation of 4-n-butylresorcinol via nanoemulsion formulation: Implications for skin pigmentation treatment. European Journal of Medicinal Chemistry. 2024; 279: 116867. https://doi.org/10.1016/j.ejmech.2024.116867

[5] Martel JL, Miao JH, Badri T, Fakoya AO. Anatomy, Hair Follicle. 2024. Available at: https://www.ncbi.nlm.nih.gov/books/NBK470321/ (Accessed: 13 June 2026).

[6] Bento-Lopes L, Cabaço LC, Charneca J, Neto MV, Seabra MC, Barral DC. Melanin's Journey from Melanocytes to Keratinocytes: Uncovering the Molecular Mechanisms of Melanin Transfer and Processing. International Journal of Molecular Sciences. 2023; 24: 11289. https://doi.org/10.3390/ijms241411289

[7] Pawlina W, Ross MH. A Text and Atlas: With Correlated Cell and Molecular Biology. Morphologia. 2019; 13: 76–89. https://doi.org/10.26641/1997-9665.2019.4.76-89

[8] Kapoor R, Dhatwalia SK, Kumar R, Rani S, Parsad D. Emerging role of dermal compartment in skin pigmentation: comprehensive review. Journal of the European Academy of Dermatology and Venereology: JEADV. 2020; 34: 2757–2765. https://doi.org/10.1111/jdv.16404

[9] Won YK, Loy CJ, Randhawa M, Southall MD. Clinical efficacy and safety of 4-hexyl-1,3-phenylenediol for improving skin hyperpigmentation. Archives of Dermatological Research. 2014; 306: 455–465. https://doi.org/10.1007/s00403-014-1439-9

[10] Nieuweboer-Krobotova L. Hyperpigmentation: types, diagnostics and targeted treatment options. Journal of the European Academy of Dermatology and Venereology: JEADV. 2013; 27 Suppl 1: 2–4. https://doi.org/10.1111/jdv.12048

[11] Zolghadri S, Beygi M, Mohammad TF, Alijanianzadeh M, Pillaiyar T, Garcia-Molina P, et al. Targeting tyrosinase in hyperpigmentation: Current status, limitations and future promises. Biochemical Pharmacology. 2023; 212: 115574. https://doi.org/10.1016/j.bcp.2023.115574

[12] Syed Azhar SNA, Ashari SE, Salim N. Development of a kojic monooleate-enriched oil-in-water nanoemulsion as a potential carrier for hyperpigmentation treatment. International Journal of Nanomedicine. 2018; 13: 6465–6479. https://doi.org/10.2147/IJN.S171532

[13] Banna H, Hasan N, Lee J, Kim J, Cao J, Lee EH, et al. In vitro and in vivo evaluation of MHY908-loaded nanostructured lipid carriers for the topical treatment of hyperpigmentation. Journal of Drug Delivery Science and Technology. 2018; 48: 457–465. https://doi.org/10.1016/j.jddst.2018.10.032

[14] Carazo E, Borrego-Sánchez A, García-Villén F, Sánchez-Espejo R, Cerezo P, Aguzzi C, et al. Advanced Inorganic Nanosystems for Skin Drug Delivery. Chemical Record (New York, N.Y.). 2018; 18: 891–899. https://doi.org/10.1002/tcr.201700061

[15] Marafon P, Fachel FNS, Dal Prá M, Bassani VL, Koester LS, Henriques AT, et al. Development, physico-chemical characterization and in-vitro studies of hydrogels containing rosmarinic acid-loaded nanoemulsion for topical application. The Journal of Pharmacy and Pharmacology. 2019; 71: 1199–1208. https://doi.org/10.1111/jphp.13102

[16] Tangau MJ, Chong YK, Yeong KY. Advances in cosmeceutical nanotechnology for hyperpigmentation treatment. Journal of Nanoparticle Research. 2022; 24: 155. https://doi.org/10.1007/s11051-022-05534-z

[17] Hatem S, El Hoffy NM, Elezaby RS, Nasr M, Kamel AO, Elkheshen SA. Background and different treatment modalities for melasma: Conventional and nanotechnology-based approaches. Journal of Drug Delivery Science and Technology. 2020; 60: 101984. https://doi.org/10.1016/j.jddst.2020.101984

[18] Mishra V, Bansal KK, Verma A, Yadav N, Thakur S, Sudhakar K, et al. Solid Lipid Nanoparticles: Emerging Colloidal Nano Drug Delivery Systems. Pharmaceutics. 2018; 10: 191. https://doi.org/10.3390/pharmaceutics10040191

[19] Daudt RM, Emanuelli J, Külkamp-Guerreiro IC, Pohlmann AR, Guterres SS. Nanotechnology as a strategy for the development of cosmetics. Ciência e Cultura. 2013; 65: 28–31. (In Portuguese)

[20] Rigon RB, Fachinetti N, Severino P, Santana MHA, Chorilli M. Skin Delivery and in Vitro Biological Evaluation of Trans-Resveratrol-Loaded Solid Lipid Nanoparticles for Skin Disorder Therapies. Molecules (Basel, Switzerland). 2016; 21: E116. https://doi.org/10.3390/molecules21010116

[21] Fireman S, Toledano O, Neimann K, Loboda N, Dayan N. A look at emerging delivery systems for topical drug products. Dermatologic Therapy. 2011; 24: 477–488. https://doi.org/10.1111/j.1529-8019.2012.01464.x

[22] Psotova J, Svobodova A, Kolarova H, Walterova D. Photoprotective properties of Prunella vulgaris and rosmarinic acid on human keratinocytes. Journal of Photochemistry and Photobiology. B, Biology. 2006; 84: 167–174. https://doi.org/10.1016/j.jphotobiol.2006.02.012

[23] Zaidi Z. Skin of colour: Characteristics and disease. JPMA. the Journal of the Pakistan Medical Association. 2017; 67: 292–299.

[24] Visscher MO. Skin Color and Pigmentation in Ethnic Skin. Facial Plastic Surgery Clinics of North America. 2017; 25: 119–125. https://doi.org/10.1016/j.fsc.2016.08.011

[25] Li S, Arvisais-Anhalt S, Vandergriff T, Le LQ. Ashy dermatosis-like hyperpigmentation in a patient taking hydroxyurea. JAAD Case Reports. 2020; 6: 797–800. https://doi.org/10.1016/j.jdcr.2020.06.030

[26] Sepehri N, Iraji A, Yavari A, Asgari MS, Zamani S, Hosseini S, et al. The natural-based optimization of kojic acid conjugated to different thio-quinazolinones as potential anti-melanogenesis agents with tyrosinase inhibitory activity. Bioorganic & Medic-

inal Chemistry. 2021; 36: 116044. https://doi.org/10.1016/j.bmc.2021.116044
[27] Cichorek M, Wachulska M, Stasiewicz A, Tymińska A. Skin melanocytes: biology and development. Postepy Dermatologii i Alergologii. 2013; 30: 30–41. https://doi.org/10.5114/pdia.2013.33376
[28] Gillbro JM, Olsson MJ. The melanogenesis and mechanisms of skin-lightening agents–existing and new approaches. International Journal of Cosmetic Science. 2011; 33: 210–221. https://doi.org/10.1111/j.1468-2494.2010.00616.x
[29] Kim YJ, Uyama H. Tyrosinase inhibitors from natural and synthetic sources: structure, inhibition mechanism and perspective for the future. Cellular and Molecular Life Sciences: CMLS. 2005; 62: 1707–1723. https://doi.org/10.1007/s00018-005-5054-y
[30] Bae-Harboe YSC, Park HY. Tyrosinase: a central regulatory protein for cutaneous pigmentation. The Journal of Investigative Dermatology. 2012; 132: 2678–2680. https://doi.org/10.1038/jid.2012.324
[31] Tang HC, Chen YC. Identification of tyrosinase inhibitors from traditional Chinese medicines for the management of hyperpigmentation. SpringerPlus. 2015; 4: 184. https://doi.org/10.1186/s40064-015-0956-0
[32] Homma T, Kageyama S, Nishikawa A, Nagata K. Antimelanogenic activity of salacinol by inhibition of tyrosinase oligosaccharide processing. Journal of Biochemistry. 2020; 167: 503–511. https://doi.org/10.1093/jb/mvz115
[33] Bastonini E, Kovacs D, Picardo M. Skin Pigmentation and Pigmentary Disorders: Focus on Epidermal/Dermal Cross-Talk. Annals of Dermatology. 2016; 28: 279–289. https://doi.org/10.5021/ad.2016.28.3.279
[34] Slominski A, Wortsman J, Plonka PM, Schallreuter KU, Paus R, Tobin DJ. Hair follicle pigmentation. The Journal of Investigative Dermatology. 2005; 124: 13–21. https://doi.org/10.1111/j.0022-202X.2004.23528.x
[35] Lin JY, Fisher DE. Melanocyte biology and skin pigmentation. Nature. 2007; 445: 843–850. https://doi.org/10.1038/nature05660
[36] Murase D, Hachiya A, Takano K, Hicks R, Visscher MO, Kitahara T, et al. Autophagy has a significant role in determining skin color by regulating melanosome degradation in keratinocytes. The Journal of Investigative Dermatology. 2013; 133: 2416–2424. https://doi.org/10.1038/jid.2013.165
[37] Xing X, Dan Y, Xu Z, Xiang L. Implications of Oxidative Stress in the Pathogenesis and Treatment of Hyperpigmentation Disorders. Oxidative Medicine and Cellular Longevity. 2022; 2022: 7881717. https://doi.org/10.1155/2022/7881717
[38] Wang F, Ma W, Fan D, Hu J, An X, Wang Z. The biochemistry of melanogenesis: an insight into the function and mechanism of melanogenesis-related proteins. Frontiers in Molecular Biosciences. 2024; 11: 1440187. https://doi.org/10.3389/fmolb.2024.1440187
[39] Moolla S, Miller-Monthrope Y. Dermatology: how to manage facial hyperpigmentation in skin of colour. Drugs in Context. 2022; 11: 1–14. https://doi.org/10.7573/dic.2021-11-2
[40] Nomakhosi M, Heidi A. Natural options for management of melasma, a review. Journal of Cosmetic and Laser Therapy: Official Publication of the European Society for Laser Dermatology. 2018; 20: 470–481. https://doi.org/10.1080/14764172.2018.1427874
[41] Ortonne JP, Bissett DL. Latest insights into skin hyperpigmentation. The Journal of Investigative Dermatology. Symposium Proceedings. 2008; 13: 10–14. https://doi.org/10.1038/jidsymp.2008.7
[42] Dai NT, Chang HI, Wang YW, Fu KY, Huang TC, Huang NC, et al. Restoration of skin pigmentation after deep partial or full-thickness burn injury. Advanced Drug Delivery Reviews. 2018; 123: 155–164. https://doi.org/10.1016/j.addr.2017.10.010
[43] Ke MS, Soriano T, Lask GP. Optimal treatments for hyperpigmentation. Journal of Cosmetic and Laser Therapy: Official Publication of the European Society for Laser Dermatology. 2006; 8: 7–13. https://doi.org/10.1080/14764170600620668
[44] Grayson C, Heath CR. Dupilumab Improves Atopic Dermatitis and Post-Inflammatory Hyperpigmentation in Patient With Skin of Color. Journal of Drugs in Dermatology: JDD. 2020; 19: 776–778. https://doi.org/10.36849/JDD.2020.4937
[45] Sarkar R, Parmar NV, Kapoor S. Treatment of Postinflammatory Hyperpigmentation With a Combination of Glycolic Acid Peels and a Topical Regimen in Dark-Skinned Patients: A Comparative Study. Dermatologic Surgery: Official Publication for American Society for Dermatologic Surgery [et Al.]. 2017; 43: 566–573. https://doi.org/10.1097/DSS.0000000000001007
[46] Camayo TV, Lee VR, Zhou XA. Drug-Induced Pigmentation. 2026. Available at: https://www.ncbi.nlm.nih.gov/books/NBK542253/ (Acessed: 19 November 2024)
[47] Afrin A, Cohen PR. Doxycycline-Associated Hyperpigmentation: A Case Report and Literature Review. Cureus. 2022; 14: e23754. https://doi.org/10.7759/cureus.23754
[48] Miot LDB, Miot HA, Silva MGD, Marques MEA. Physiopathology of melasma. Anais Brasileiros De Dermatologia. 2009; 84: 623–635. https://doi.org/10.1590/s0365-05962009000600008
[49] Puri N, Gill SK, Kumar S, Brar BK, Chahal A. A study of dermoscopy in patients of melasma in a tertiary care centre in North India. Pigment International. 2022; 9: 176–181.
[50] Han HJ, Kim JC, Park YJ, Kang HY. Targeting the dermis for melasma maintenance treatment. Scientific Reports. 2024; 14: 949. https://doi.org/10.1038/s41598-023-51133-w
[51] Duval C, Bourreau E, Warrick E, Bastien P, Nouveau S, Bernerd F. A chronic pro-inflammatory environment contributes to the physiopathology of actinic lentigines. Scientific Reports. 2024; 14: 5256. https://doi.org/10.1038/s41598-024-53990-5
[52] Jung JM, Yang H, Lee WJ, Won CH, Lee MW, Choi JH, et al. Inflammatory features and rete ridge patterns of facial solar lentigo may guide laser treatment. Dermatologic Therapy. 2020; 33: e13464. https://doi.org/10.1111/dth.13464
[53] Rendon M, Horwitz S. Topical treatment of hyperpigmentation disorders. Annales De Dermatologie et De Venereologie. 2012; 139 Suppl 4: S153–S158. https://doi.org/10.1016/S0151-9638(12)70128-X
[54] Davis EC, Callender VD. Postinflammatory hyperpigmentation: a review of the epidemiology, clinical features, and treatment options in skin of color. The Journal of Clinical and Aesthetic Dermatology. 2010; 3: 20–31.
[55] Kanlayavattanakul M, Chongnativisit W, Chaikul P, Lourith N. Phenolic-rich Pomegranate Peel Extract: In Vitro, Cellular, and In Vivo Activities for Skin Hyperpigmentation Treatment. Planta Medica. 2020; 86: 749–759. https://doi.org/10.1055/a-1170-7785
[56] Zaidi KU, Ali SA, Ali A, Naaz I. Natural Tyrosinase Inhibitors: Role of Herbals in the Treatment of Hyperpigmentary Disorders. Mini Reviews in Medicinal Chemistry. 2019; 19: 796–808. https://doi.org/10.2174/1389557519666190116101039
[57] Ha SK, Koketsu M, Lee K, Choi SY, Park JH, Ishihara H, et al. Inhibition of tyrosinase activity by N,N-unsubstituted selenourea derivatives. Biological & Pharmaceutical Bulletin. 2005; 28: 838–840. https://doi.org/10.1248/bpb.28.838
[58] Shivaram K, Edwards K, Mohammad TF. An update on the safety of hydroquinone. Archives of Dermatological Research. 2024; 316: 378. https://doi.org/10.1007/s00403-024-02990-6
[59] Zilles JC, Dos Santos FL, Kulkamp-Guerreiro IC, Contri RV. Biological activities and safety data of kojic acid and its derivatives: A review. Experimental Dermatology. 2022; 31: 1500–

1521. https://doi.org/10.1111/exd.14662
[60] Mann T, Gerwat W, Batzer J, Eggers K, Scherner C, Wenck H, et al. Inhibition of Human Tyrosinase Requires Molecular Motifs Distinctively Different from Mushroom Tyrosinase. The Journal of Investigative Dermatology. 2018; 138: 1601–1608. https://doi.org/10.1016/j.jid.2018.01.019
[61] Medeiros-Neves B, Nemitz MC, Silveira Fachel FN, Teixeira HF. Recent Patents Concerning the use of Nanotechnology-based Delivery Systems as Skin Penetration Enhancers. Recent Patents on Drug Delivery & Formulation. 2019; 13: 192–202. https://doi.org/10.2174/1872211313666191024112137
[62] Ghasemiyeh P, Mohammadi-Samani S. Potential of Nanoparticles as Permeation Enhancers and Targeted Delivery Options for Skin: Advantages and Disadvantages. Drug Design, Development and Therapy. 2020; 14: 3271–3289. https://doi.org/10.2147/DDDT.S264648
[63] Hatem S, Kamel AO, Elkheshen SA, Nasr M, Moftah NH, Ragai MH, et al. Nano-vesicular systems for melanocytes targeting and melasma treatment: In-vitro characterization, ex-vivo skin retention, and preliminary clinical appraisal. International Journal of Pharmaceutics. 2024; 665: 124731. https://doi.org/10.1016/j.ijpharm.2024.124731
[64] Radmard A, Saeedi M, Morteza-Semnani K, Hashemi SMH, Nokhodchi A. An eco-friendly and green formulation in lipid nanotechnology for delivery of a hydrophilic agent to the skin in the treatment and management of hyperpigmentation complaints: Arbutin niosome (Arbusome). Colloids and Surfaces. B, Biointerfaces. 2021; 201: 111616. https://doi.org/10.1016/j.colsurfb.2021.111616
[65] Taheri A, Mohammadi M. The Use of Cellulose Nanocrystals for Potential Application in Topical Delivery of Hydroquinone. Chemical Biology & Drug Design. 2015; 86: 102–106. https://doi.org/10.1111/cbdd.12466
[66] Samadi N, Aberoomand Azar P, Waqif Husain S, Maibach HI, Nafisi S. Experimental design in formulation optimization of vitamin K_1 oxide-loaded nanoliposomes for skin delivery. International Journal of Pharmaceutics. 2020; 579: 119136. https://doi.org/10.1016/j.ijpharm.2020.119136
[67] Silva CC, Benati RB, Massaro TNC, Pereira KC, Gaspar LR, Marcato PD. Antioxidant and anti-tyrosinase activities of quercetin-loaded olive oil nanoemulsion as potential formulation for skin hyperpigmentation. Journal of Dispersion Science and Technology. 2023; 44: 2628–2638. https://doi.org/10.1080/01932691.2022.2116715
[68] Shrotriya S, Ranpise N, Satpute P, Vidhate B. Skin targeting of curcumin solid lipid nanoparticles-engrossed topical gel for the treatment of pigmentation and irritant contact dermatitis. Artificial Cells, Nanomedicine, and Biotechnology. 2018; 46: 1471–1482. https://doi.org/10.1080/21691401.2017.1373659
[69] Aceto G, Di Muzio L, Di Lorenzo R, Laneri S, Cairone F, Cesa S, et al. Dual delivery of ginger oil and hexylresorcinol with lipid nanoparticles for the effective treatment of cutaneous hyperpigmentation. Journal of Drug Delivery Science and Technology. 2023; 87: 104790. https://doi.org/10.1016/j.jddst.2023.104790
[70] Tofani RP, Sumirtapura YC, Darijanto ST. Formulation, Characterisation, and in Vitro Skin Diffusion of Nanostructured Lipid Carriers for Deoxyarbutin Compared to a Nanoemulsion and Conventional Cream. Scientia Pharmaceutica. 2016; 84: 634–645. https://doi.org/10.3390/scipharm84040634
[71] Al-Amin M, Cao J, Naeem M, Banna H, Kim MS, Jung Y, et al. Increased therapeutic efficacy of a newly synthesized tyrosinase inhibitor by solid lipid nanoparticles in the topical treatment of hyperpigmentation. Drug Design, Development and Therapy. 2016; 10: 3947–3957. https://doi.org/10.2147/DDDT.S123759
[72] Aliasgharlou L, Ghanbarzadeh S, Azimi H, Zarrintan MH, Hamishehkar H. Nanostructured Lipid Carrier for Topical Application of N-Acetyl Glucosamine. Advanced Pharmaceutical Bulletin. 2016; 6: 581–587. https://doi.org/10.15171/apb.2016.072
[73] Marto J, Sangalli C, Capra P, Perugini P, Ascenso A, Gonçalves L, et al. Development and characterization of new and scalable topical formulations containing N-acetyl-d-glucosamine-loaded solid lipid nanoparticles. Drug Development and Industrial Pharmacy. 2017; 43: 1792–1800. https://doi.org/10.1080/03639045.2017.1339083
[74] Khezri K, Saeedi M, Morteza-Semnani K, Akbari J, Rostamkalaei SS. An emerging technology in lipid research for targeting hydrophilic drugs to the skin in the treatment of hyperpigmentation disorders: kojic acid-solid lipid nanoparticles. Artificial Cells, Nanomedicine, and Biotechnology. 2020; 48: 841–853. https://doi.org/10.1080/21691401.2020.1770271
[75] Khezri K, Saeedi M, Morteza-Semnani K, Akbari J, Hedayatizadeh-Omran A. A promising and effective platform for delivering hydrophilic depigmenting agents in the treatment of cutaneous hyperpigmentation: kojic acid nanostructured lipid carrier. Artificial Cells, Nanomedicine, and Biotechnology. 2021; 49: 38–47. https://doi.org/10.1080/21691401.2020.1865993
[76] Mostafa ES, Maher A, Mostafa DA, Gad SS, Nawwar MAM, Swilam N. A Unique Acylated Flavonol Glycoside from *Prunus persica* (L.) var. Florida Prince: A New Solid Lipid Nanoparticle Cosmeceutical Formulation for Skincare. Antioxidants (Basel, Switzerland). 2021; 10: 436. https://doi.org/10.3390/antiox10030436
[77] Talele P, Jadhav A, Tayade S, Sahu S, Sharma KK, Shimpi N. Hydroquinone loaded solid lipid nanoparticles comprised of stearic acid and ionic emulsifiers: Physicochemical characterization and in vitro release study. Journal of Molecular Liquids. 2022; 368: 120590. https://doi.org/10.1016/j.molliq.2022.120590
[78] Nautiyal A, Wairkar S. A reduced dose of Azelaic acid-loaded solid lipid nanoparticles for treatment of hyperpigmentation: In vitro characterization and cell line studies. Journal of Drug Delivery Science and Technology. 2023; 80: 104158. https://doi.org/10.1016/j.jddst.2023.104158
[79] Ghanbarzadeh S, Hariri R, Kouhsoltani M, Shokri J, Javadzadeh Y, Hamishehkar H. Enhanced stability and dermal delivery of hydroquinone using solid lipid nanoparticles. Colloids and Surfaces. B, Biointerfaces. 2015; 136: 1004–1010. https://doi.org/10.1016/j.colsurfb.2015.10.041
[80] Daneshmand S, Yazdian-Robati R, Jaafari MR, Movafagh J, Malaekeh-Nikouei B, Iranshahi M, et al. Evaluation of the anti-melanogenic activity of nanostructured lipid carriers containing auraptene: A natural anti-oxidant agent. Nanomedicine Journal. 2022; 9: 57–66. https://doi.org/10.22038/nmj.2022.62354.1645
[81] Hoseinsalari A, Atapour-Mashhad H, Asili J, Tayarani-Najaran Z, Mohtashami L, Khanavi M, et al. Preparation and Characterization of Nanostructured Lipid Carriers (NLCs) Containing *Glycyrrhiza glabra* Extract for the Treatment of Skin Hyperpigmentation. Current Pharmaceutical Design. 2024; 30: 3213–3232. https://doi.org/10.2174/0113816128327512240730102545
[82] Mikled P, Chavasiri W, Khongkow M. Development of dihydrooxyresveratrol-loaded nanostructured lipid carriers for safe and effective treatment of hyperpigmentation. Scientific Reports. 2024; 14: 29211. https://doi.org/10.1038/s41598-024-80671-0
[83] Zilles JC, Duarte LP, Ruaro TC, Zimmer AR, Kulkamp-Guerreiro IC, Contri RV. Nanoemulsion Containing Kojic Dipalmitate and Rosehip Oil: A Promising Formulation to Treat Melasma. Pharmaceutics. 2023; 15: 468. https://doi.org/10.3390/pharmaceutics15020468
[84] Jacobus Berlitz S, De Villa D, Maschmann Inácio LA, Davies

S, Zatta KC, Guterres SS, et al. Azelaic acid-loaded nanoemulsion with hyaluronic acid - a new strategy to treat hyperpigmentary skin disorders. Drug Development and Industrial Pharmacy. 2019; 45: 642–650. https://doi.org/10.1080/03639045.2019.1569032

[85] Duarah S, Durai RD, Narayanan VB. Nanoparticle-in-gel system for delivery of vitamin C for topical application. Drug Delivery and Translational Research. 2017; 7: 750–760. https://doi.org/10.1007/s13346-017-0398-z

[86] Tanveer N, Khan HMS, Akhtar N. Whitening effect of kojic acid dipalmitate loaded nanosized ethosomal gel for the treatment of hyperpigmentation: In vitro and in vivo characterization. Journal of Cosmetic Dermatology. 2022; 21: 6850–6862. https://doi.org/10.1111/jocd.15408

[87] Jamadar AT, Peram MR, Chandrasekhar N, Kanshide A, Kumbar VM, Diwan PV. Formulation, Optimization, and Evaluation of Ultradeformable Nanovesicles for Effective Topical Delivery of Hydroquinone. Journal of Pharmaceutical Innovation. 2023; 18: 506–524. https://doi.org/10.1007/s12247-022-09657-7

[88] Chang NF, Wu PS, Yang HJ, Zheng YM, Lin CC. Preparation and Evaluation of Nanoemulsion Formulation Containing Kojic Acid and Kojyl 3-aminopropylphosphonic Acid. Current Pharmaceutical Biotechnology. 2025; 26: 608–616. https://doi.org/10.2174/0113892010310230240615112928

[89] Kumar A, Rao R. Enhancing efficacy and safety of azelaic acid via encapsulation in cyclodextrin nanosponges: development, characterization and evaluation. Polymer Bulletin. 2021; 78: 5275–5302. https://doi.org/10.1007/s00289-020-03366-2

[90] Farooqui RK, Kaurav M, Kumar M, Sudheesh MS, Pandey RS. Permeation enhancer nanovesicles mediated topical delivery of curcumin for the treatment of hyperpigmentation. Journal of Liposome Research. 2022; 32: 332–339. https://doi.org/10.1080/08982104.2021.2024567

[91] Inal O, Amasya G, Sezgin Bayindir Z, Yuksel N. Development and quality assessment of glutathione tripeptide loaded niosome containing carbopol emulgels as nanocosmeceutical formulations. International Journal of Biological Macromolecules. 2023; 241: 124651. https://doi.org/10.1016/j.ijbiomac.2023.124651

[92] Souto EB, Cano A, Martins-Gomes C, Coutinho TE, Zielińska A, Silva AM. Microemulsions and Nanoemulsions in Skin Drug Delivery. Bioengineering (Basel, Switzerland). 2022; 9: 158. https://doi.org/10.3390/bioengineering9040158

[93] Shah AA, Kehinde EO, Patel J. An Emerging Era for Targeted Drug Delivery: Nanosponges. Journal of Pharmaceutical Research International. 2021; 33: 153–160. https://doi.org/10.9734/jpri/2021/v33i31B31703

[94] Queiroz MD, Muehlmann LA. Characteristics and Preparation of Solid Lipid Nanoparticles and Nanostructured Lipid Carriers. Journal of Nanotheranostics. 2024; 5: 188–211. https://doi.org/10.3390/jnt5040012

[95] Touitou E, Natsheh H. The Evolution of Emerging Nanovesicle Technologies for Enhanced Delivery of Molecules into and across the Skin. Pharmaceutics. 2024; 16: 267. https://doi.org/10.3390/pharmaceutics16020267

[96] Choudhury A, Kirti A, Lenka SS, Naser SS, Sinha A, Kumari S, et al. Strategic advances in liposomes technology: translational paradigm in transdermal delivery for skin dermatosis. Journal of Nanobiotechnology. 2025; 23: 576. https://doi.org/10.1186/s12951-025-03660-z

[97] Sguizzato M, Esposito E, Cortesi R. Lipid-Based Nanosystems as a Tool to Overcome Skin Barrier. International Journal of Molecular Sciences. 2021; 22: 8319. https://doi.org/10.3390/ijms22158319

[98] Joyce P, Allen CJ, Alonso MJ, Ashford M, Bradbury MS, Germain M, et al. A translational framework to DELIVER nanomedicines to the clinic. Nature Nanotechnology. 2024; 19: 1597–1611. https://doi.org/10.1038/s41565-024-01754-7

[99] Yong KN, Youngjae K, Changsoo K, Yejn P, inventor; NUMAIS CO LTD, assignee. Composition For Skin Whitening Comprising Nanovesicles. South Korea KR20220155224 (A). November. 22 November 2022.

[100] Paithankar D, inventor; SEBACIA INC, assignee. Methods Of Treating Skin Conditions Using Plasmonic Nanoparticles. China CN108430431 (A). August. 21 August 2018.

[101] Zheng Q, Cao Y, Zhang Z, inventor; Zhang Z, assignee. Nano preparation for treating pigmentation diseases and preparation method of nano preparation. China CN112107600 (A). December. 22 December 2020.

[102] Yen RCK, inventor; Yen RCK, PTLNV LLC SERIES FOUR 4, assignee. Nanoparticles for the therapeutic treatment of radiation-induced skin ulcers. United States of America US2019328844 (A1). October. 31 October 2019.

[103] Zhou Y, inventor; FOSHAN CITY CHANCHENG DISTR RELA SPACE BIOTECHNOLOGY CO LTD, assignee. Preparation method of plant compound skin-whitening agent nano particles. China CN108714131 (A). October. 30 October 2018.

[104] Park SC, J BK, Lee TH, Ko YT, Moh SH, Baek SH, et al., inventor; UNIV GACHON IND ACAD COOP FOUND, REPUBLIC KOREA MAN RURAL DEV, assignee. Composition For Skin-Whitening Comprising Nanoparticle Of Callus Derived From Resveratrol-Enriched Rice. South Korea KR20160029979 (A). March. 16 March 2016.

[105] Li Z, inventor; LVEN ZEYA GROUP CO LTD, assignee. Whitening nano-composition targeting fibroblasts and melanocytes as well as preparation method and application of whitening nano-composition. China CN116531271 (A). August. 4 August 2023.

[106] Lee S K, Urabe T, Choi CH, Chae YS, Woo JW, Lee JS, inventor; Choi CH, JE MA YU CO LTD, KIMIWA CO LTD, assignee. Skin Bleaching Composition Including Nanopolisome Involving Horse Oil And Horse Placenta Extract, And Method For Producing Water- Soluble Nanoliposome. Japan JP2010215605 (A). September. 30 September 2010.