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Nanotechnology-Powered Cosmetics: Progress in Hyperpigmentation Treatment

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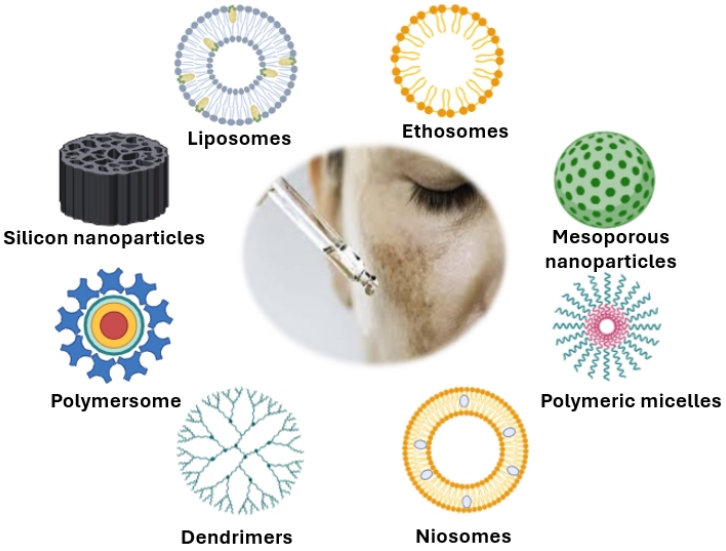
Graphical abstract



Abstract

Hyperpigmentation is a prevalent and notable skin issue affecting individuals across all skin types. Although several depigmentation agents are available to address hyperpigmentation, their effectiveness is limited due to inadequate skin absorption and considerable toxicity, which can lead to side effects like irritative dermatitis, redness, itching, and peeling skin. Nanotechnology is pivotal in advancing cosmetic formulations by enhancing drug solubility, stability, safety, payload efficiency, and skin permeability. This study aims to thoroughly explore how different nanomaterials can improve cosmetic formulations for treating hyperpigmentation. It focuses on how nanotechnology can enhance the effectiveness of common treatments such as hydroquinone, arbutin, kojic acid, azelaic acid, and retinoic acid. Notably, lipidic nanoparticles have become the most popular nanomaterial for treating hyperpigmentation. Despite their benefits, the lack of regulation for nanomaterials calls for thorough safety assessments and stricter guidelines to ensure consumer safety.

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Purpose, Rationale, and Limitations

This study explores the potential of nanotechnology to improve the effectiveness and safety of depigmentation treatments for hyperpigmentation. Despite the availability of various treatments, their efficacy is often limited by poor skin absorption and high toxicity, leading to side effects. Nanotechnology can address these challenges by enhancing the delivery, stability, and skin penetration of active ingredients, offering a promising solution for more effective and safer treatments. Several limitations must be considered, including the lack of standardized regulations and safety assessments for nanomaterials, which raise concerns about their long-term effects. While lipid nanoparticles have shown promise, challenges remain in ensuring consistent formulations and accounting for individual skin differences. These factors highlight the need for further research and stricter guidelines to ensure the safe use of nanotechnology in cosmetic products.

Introduction

Over the past fifty years, nanotechnology has seen remarkable growth and has been integrated into various industrial fields [1]. Its application has notably advanced dermatology and skincare, paving the way for innovative treatments. Nanotechnology involves the creation of nanoparticles or nanomaterials, which can be either naturally occurring or synthetically produced, with sizes from 1 to 200 nm [2]. This technology has significantly impacted medical devices, including imaging investigations, drug delivery systems, and diagnostic biosensors in the pharmaceutical domain. In cosmetics, nanotechnology offers substantial benefits for topical applications. The small size of nanomaterials provides a high surface area to volume ratio, allowing for more efficient delivery of active molecules to the skin's outer layer. Furthermore, nanoparticles can improve skin absorption, enhance blood circulation of entrapped compounds, and target the delivery of active compounds to specific areas [3]. They can also improve the stability of cosmetic compounds, especially those prone to oxidation. Cosmetics have long been used to enhance appearance and attractiveness. As cosmeceuticals and cosmetics play a crucial role in daily routines, advancements in skincare are driven by growing consumer awareness of skin health and aesthetic considerations, along with an increased focus on a healthy lifestyle [4]. Recent advancements in cosmeceuticals have focused on enhancing the effectiveness of active agents, with nanotechnology emerging as a key tool in improving the delivery and absorption of these constituents into the skin [5]. The cosmeceutical production utilizes numerous nanomaterials for skincare applications [6]. Nanoparticles, including nanoemulsions, liposomes, and lipid nanoparticles, are becoming crucial for the controlled delivery of cosmetic agents, particularly in penetrating different skin layers [7]. Many cosmetics now incorporate these nanomaterials in products like cleansers, shampoos, and nail polishes.

Skin hyperpigmentation, characterized by darker patches compared to surrounding skin, encompasses conditions such as hyperpigmentation, ephelides, lentigines, and age spots [8]. Hyperpigmentation treatment options include oral and topical medications, herbal remedies, and cosmetic products. This review examines the role of nanotechnology in treating hyperpigmentation, highlighting its benefits and limitations compared to traditional treatments.

Discussion

Inhibition of tyrosine and enzyme expression

Melanin synthesis initiates with the conditionally nonessential amino acid tyrosine, which can be acquired by diet or synthesized from the essential amino acid phenylalanine. Phenylalanine hydroxylase (PAH) catalyzes the hydroxylation of the aromatic side chain of phenylalanine to yield tyrosine[9]. It's the main pigment responsible for pigmentation in human skin, hair, and eyes and is synthesized by melanocytes through melanogenesis. The atypical loss of

melanin and depigmentation can pose a significant aesthetic and dermatological issue for individuals[10]. Melanogenesis is a complex process involving several enzymatic and chemical processes, with enzymes like tyrosinase and tyrosinase-related proteins (TYRP1 and TYRP2) playing a crucial part in melanin formation [11]. Tyrosinase is a copper-related enzyme that only exists in melanocytes and performs various tasks that play as a rate-limiting enzyme in melanin synthesis [12]. It catalyzes the biotransformation of L-tyrosine into L-DOPA, which is subsequently transformed into dopaquinone and, eventually, dopachrome. Dopachrome polymerizes to produce melanin. Tyrosinase enzyme inhibition lowers melanin formation, which aids in treating hyperpigmented skin. Tyrosinase involved in melanin synthesis has changed their transcriptional expression [13].

Cho et al. found that isoimperatorin and imperatorin, extracted from the ethanolic extract of Angelica dahurica, restrained tyrosinase synthesis in Bl6 melanoma cells by lowering tyrosinase mRNA levels, promoting skin whitening [14]. Most herbal depigmenting agents inhibit melanin synthesis by suppressing tyrosinase activity [15]. Herbal extracts are rich in natural tyrosinase inhibitors and are regularly used in conventional treatments for pigmentation issues [16]. For example, green tea has been identified as a competitive tyrosinase inhibitor, with its key catechins—such as epicatechin gallate, epigallocatechin gallate, and gallocatechin gallate—responsible for this influence [17]. Aloe vera's compound, aloesin, acts as a non-competitive tyrosinase inhibitor, preventing the conversion of DOPA to melanin [18]. Glycyrrhiza glabra, widely used in skin lightening, also inhibits tyrosinase and reduces pigment formation. Glabridin and isoliquiritigenin, the main components of licorice extract, have shown more effective tyrosinase inhibition than hydroquinone, a common synthetic depigmentation agent [19].

Inhibition of Melanin dispersion

Recent research on the regulatory mechanisms involved in melanosomes. Melanosomes, classified as lysosome-related organelles, are endosome-derived, possess lysosomal characteristics, and exhibit acidity during their initial synthesis phases. Melanosomes exhibit four unique stages of maturation: In stages I and II, they are non-pigmented and initially resemble multivesicular endosomes. Pheomelanosomes retain a spherical morphology, but eumelanosomes have an elliptical morphology due to internal fibril nucleation of the pre-melanosomal protein (PMEL) [20].

Melanogenic enzymes essential for eumelanin synthesis, including tyrosinase and tyrosinase-related proteins (TYRP1/2), are mobilized to stage III melanosomes, where melanin progressively accumulates on PMEL fibrils until melanosomes attain complete pigmentation (stage IV) [21]. Mature melanosomes accumulate at melanocyte dendrites and are then transferred to keratinocytes to exert their photoprotective function in these cells [22]. Several chemicals have been found that alter melanin removal from melanocytes to keratinocytes, potentially providing skin lightening and hyperpigmentation therapies [14]. Goldberg et al. demonstrated that aloe vera extract can induce skin lighting by activating several adrenergic receptors in different melanophore models [23]. Melanin synthesis and dispersion in human skin are crucial for pigmentation. Melanin is generated in mammalian melanocytes and delivered to dendrites via actin filaments and microtubules before being transferred to nearby keratinocytes [24].

Melanin degradation

Certain substances promote the breakdown and elimination of pigment grains from the skin, reducing excess melanin and acting as both cosmetic and medicinal agents [25]. Licorice extracts have several active compounds that may stimulate or suppress melanogenesis. Glabridin, the

main component of the hydrophobic fraction of licorice extract, inhibits tyrosinase activity in cultivated B16 murine melanoma cells at doses ranging from 0.1 to 1.0 mg/ml without impacting DNA synthesis. Additional active chemicals, including glabrene, isoliquiritigenin, licuraside, isoliquiritin, and licochalcone A, derived from licorice extracts, have also been demonstrated to suppress tyrosinase activity [26]. Amer and Metwalli discovered that liquiritin, a compound derived from licorice root extracts, possesses significant skin-lightening properties in melasma patients by increasing keratinocyte turnover, shortening the cell cycle, and facilitating rapid pigment loss. Studies further demonstrate that a 20% liquiritin cream, applied at 1 g per day for four weeks, is therapeutically effective in treating melasma [27].

Accelerated degradation of Microphthalmia-Associated Transcription Factor (MITF)

MITF is a critical regulator of melanogenesis, controlling the transcription of genes such as tyrosinase, TRP-1, TRP-2, Cdc42, and Rab27a [28]. The extracellular signal-regulated kinase (ERK), p38, and c-Jun N-terminal kinase signaling pathways are critical in pigmentation processes [29]. ERK phosphorylation induces MITF degradation, suppressing melanogenic stimulation and serving as a substantial negative response mechanism [30].

Treatment of Skin hyperpigmentation

Oral treatments:

Oral treatments address internal factors such as oxidative stress, inflammation, or hormonal imbalances. Antioxidants such as glutathione and vitamin C inhibit melanin production and reduce pigmentation [31]. Recently, tranexamic acid has been widely used to lighten pigmentation, particularly melasma, by reducing melanin synthesis by inhibiting plasminogen activation [32]. Polypodium leucotomos extract, a fern-derived supplement, offers antioxidant and anti-inflammatory benefits that can help prevent pigmentation from worsening, particularly after sun exposure [33]. Moreover, niacinamide (vitamin B3) has been shown to decrease the transfer of melanin to skin cells, reducing discoloration [34].

Topical treatments

Topical treatments directly target the skin to reduce dark spots. Hydroquinone, alpha-arbutin, and kojic acid inhibit melanin production, but hydroquinone can irritate some individuals, while alpha-arbutin is generally gentler on sensitive skin [35]. Retinoids, including retinol and tretinoin, help to shed pigmented skin cells and stimulate collagen production by promoting cell turnover [36]. Vitamin C topical formulations are widely used as a brightening agent by neutralizing free radicals and preventing melanin formation [37]. Azelaic acid is particularly beneficial for treating post-inflammatory hyperpigmentation [38]. Chemical peels containing exfoliating acids like glycolic or salicylic acid can help remove pigmented skin cells, revealing fresher, more even-toned skin [39].

Furthermore, sunscreen plays a crucial role in any hyperpigmentation treatment regimen. Additionally, treatments such as liquid nitrogen, chemical peels, superficial dermabrasion, chemexfoliation, and laser therapy can be effective alone or in combination with other medications [40]. Table 1 categorizes different depigmenting agents by their mechanisms of action.

Several plants and extracts are used to whiten the skin, including Syzygium aromaticum, Magnolia officinalis, and Holarrhena antidysentrica. Panax ginseng includes ginsenosides and p-coumaric acid, which prevent L-tyrosine oxidation, resulting in skin whitening and protection [44]. Curcuma longa (turmeric) contains chemicals such as curcumin, which effectively inhibits tyrosinase and aids in skin whitening [45, 46].

Crocus sativus (saffron) is recognized for its antioxidant qualities and capacity to diminish melanin pigmentation, making it beneficial in cosmetics [47]. Hemidesmus indicus (Anantmul) inhibits Table 2 outlines various,

Table 1. Classification Based on Mechanism of Action of Depigmenting Agents [41], [42, 43]

Stage of Melanin Synthesis	Deposition	Active Molecules
Before melanin synthesis	Tyrosinase transcription	Tretinoin, c-2 ceramide
	Tyrosinase glycosylation	$PaSSO_3Ca$
	Plasmin inhibition	Tranexamic acid (TA)
Through melanin synthesis	Tyrosinase inhibition	(HQ), mequinol, azelaic acid, (KA), arbutin, deoxyarbutin, licorice extract, rucinol, 2,5-dimethyl-4-hydroxy-3(2H)-furanone, N-acetyl glucosamine, resveratrol, oxyresveratrol, ellagic acid, methyl gentisate, 4-hydroxyanisole
	Inhibition of Peroxidase	Phenolic compounds
	Reactive oxygen species	Ascorbic acid, ascorbic acid palmitate, thiotic acid, hydrocumarins
Later melanin synthesis	Tyrosinase deprivation	Linoleic acid, α-linoleic acid
	Inhibition of melanosome relocation	Niacinamide, serine protease inhibitors, retinoids, lecithins, neoglycoproteins, soybean trypsin inhibitor
	Skin turnover acceleration	Lactic acid, glycolic acid, linoleic acid, retinoic acid
	Directive of melanocyte environment	Corticosteroids, glabiridin
	Interface with copper	(KA), ascorbic acid
	Inhibition of melanosome maturation	Arbutin and deoxyarbutin
	Reserve of protease-activated receptor 2	Soybean trypsin inhibitor

melasma lightening agents and the depigmenting action of natural products. Common skin-lightening agents often cause side effects such as irritative dermatitis redness, itching, and skin flaking, mainly because of poor solubility, limited permeability through the stratum corneum, and high toxicity [73]. Their inadequate skin permeability can lead to excessive accumulation and prolonged retention of active ingredients, increasing the risk of these adverse effects [74]. Research indicates that encapsulating these compounds in nanoparticles can mitigate their negative effects, improve targeted delivery, and enhance stability [75].

Tranexamic acid (TA), a derivative of lysine, reduces melanin synthesis by lowering prostaglandins and inhibiting arachidonic acid, which is necessary for tyrosinase enzyme activation [76] and can be administered through various methods, including oral, topical, intradermal, and micro-needling (Table 3) [77]. In 1979, Nijo Sadako demonstrated that a topical combination of 3% TA and HQ significantly improved hyperpigmentation in patients with melasma, particularly on the cheeks and upper lip [78].

Application of nanotechnology in hyperpigmentation

Solid lipid nanoparticles/ nanostructured lipid carriers

Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) show promise for topical applications because of their capability to establish a skin barrier that improves hydration and medication penetration. They provide high drug entrapment, stability, and enhanced bioavailability [90]. SLNs are useful for regulated or targeted medication release, can accommodate lipophilic and hydrophilic medicines, and are biocompatible because most lipids are biodegradable.

Table 2. Summary of Melasma Lightening Agents and Depigmenting Action of Natural Products

Name	Plant source	Mechanism	Uses	Side effects	Reference
Aloesin	Aloe vera	Tyrosinase inhibition, Reduction of DOPA oxidase	UV radiation hyperpigmentation	Irritation	[48] [49]
Alpha-bisabolol	Chamomile	Inhibits alpha MSH-made melanogenesis by suppressing cAMP	UVA and UVB tanned skin (with solar simulator)	no side effects	[50]
Arbutin	California buckeye, bearberry, cranberry, and blueberry	Prevents DHICA, polymerase, and tyrosinase (Tyrosinase inhibition)	Solar lentigines	Skin sensitivity	[51, 52]
Ellagic acid	Green tea, geranium, strawberry, grapes, walnuts and cherries	Decrease melanocyte production, Copper chelation	Melasma	no side effects	[53]
Liquiritin	Liquorice	Diffusion of Melanin, epidermal deletion	Melasma	Skin sensitivity	[54]
Silymarin	Silybum marianum (standardized extract)	Inhibits l-DOPA oxidation action of tyrosinase	Melasma	Allergic reactions	[55]
Glabridin	Liquorice	Inhibition of tyrosinase	UVB-brought pigmentation	no side effects	[56]
Hesperidin	Citrus fruits	Collagen antioxidant tyrosinase inhibition Prevents melanin synthesis	UV-A-induced oxidative destruction of collagen	no side effects	[57]
Procyanidin	Pinus pinaster	Anti-inflammatory and antioxidant	Melasma	Skin sensitivity	[58]
Green tea	Camellia sinensis	Antioxidant Inhibition of tyrosinase	Melasma	no side effects	[59]
Hydroquinone	Ericales, Lamiales and Asterales	Inhibition of tyrosinase	Treat areas of dyschromia, such as in melasma, chloasma, solar lentigines, freckles, and post-inflammatory hyperpigmentation	Erythema, irritation, exogenous ochronosis	[60]
Azelaic acid	Wheat, rye, and barley	Inhibition of tyrosinase	Mild to moderate acne, melasma and rosacea	Stinging, redness, itching, dryness	[61]

Name (cont)	Plant source	Mechanism	Uses	Side effects	Reference
Kojic acid	Aspergillus oryzae, Aspergillus parasiticus, and Aspergillus candidus	Inhibition of tyrosinase	Skin lightening	Irritation, contact dermatitis	[62]
Ascorbic acid	Oranges and lemons · tomatoes and tomato juice · potatoes · green and red peppers	Inhibition of reactive oxygen species	Skin regeneration	No significant adverse events	[63]
Retinoids	Sea buckthorn (Hippophae Rhamnoides)	Downregulation of tyrosinase	Reducing inflammation and regulating the growth of cells on the skin's surface	Irritant reaction, dehydration, hyperpigmentation	[64]
Corticosteroid treatments	-	Anti-inflammatory and nonselective inhibition of melanogenesis	Management of inflammatory and autoimmune skin diseases	Telangiectasias, epidermal atrophy, steroid-induced acne, striae, hypopigmentation	[65]
Niacinamide	Whole grains and mushrooms	Inhibition of melanosome transfer	Melasma	Irritation	[66]
Licorice	Glycyrrhiza glabra	Melanin dispersion, tyrosinase inhibition	Melasma	No significant adverse events	[67]
Undecylenoyl phenylalanine	-	An antagonist of the α-melanocyte-stimulating hormone, β-adrenergic, stem cell receptors	Hyperpigmentation	No significant adverse events	[68]
4-N-butylresorcinol	-	Tyrosinase inhibition, antioxidant, anti-inflammatory	Hyperpigmentation	Mild erythema and itching	[69]
Soybean	Glycine max is a species of legume	Inhibits melanosome transfer to keratinocytes	Melasma	No significant adverse events	[70]
Glucosamine	Seed of palmyrah	Inhibition of tyrosinase activation	Melasma	Skin rash	[71]
Mequinol	-	Tyrosinase inhibition	Melasma	Skin irritation, soreness, peeling	[72]

DHICA = 5,6-dihydroxyindole-2-carboxylic acid; UV = ultraviolet.

Table 3. Latest Oral/Topical Photoprotection Treatments

Type	Agent	Mechanism of Action	Reference
Topical	Iron oxide sunscreens	Blocks of blue visible light	[79, 80]
Oral	Polypodium leucotomos	↑ p53 suppressor gene expression, modulation of inflammatory cytokines, ↑ endogenous antioxidant systems, blockade of UV radiation-induced COX-2 expression	[81]
Oral & Topical	Tranexamic acid	Blocks conversion of plasminogen to plasmin, blocks required of plasminogen to keratinocytes, ↓ arachidonic acid release, prostaglandin synthesis and FGF, ↓ melanin synthesis, ↓ mast cells, ↓ angiogenesis	[82]
	Melatonin	Potent antioxidant/free radical scavenger, ↑ superoxide dismutase, (GSH) reductase, (GSH) peroxidase, ↓ α-MSH receptors	[83]
	Reduced glutathation (GSH)	Losses tyrosinase, skews conversion of eumelanin to pheomelanin	[84]
Topical	Cysteamine	Radioprotector (via direct scavenging effects of hydroxyl radicals), tyrosinase peroxidase inhibition	[85]
	Pigment-correcting Serum	Melanocyte activation, melanosome increase, melanin synthesis, melanosome transfer, keratinocyte differentiation, and desquamation	[86]
	Methimazole	Potent peroxidase inhibitor blocks melanin synthesis	[87] [88]
	Flutamide	Blocks action of endogenous/exogenous testosterone by necessary to androgen receptor	[89]

They employ water-based technology, which avoids organic solvents and is cheaper than polymeric or surfactant-based nanocarriers. Furthermore, SLNs are scalable, sterilizable, and efficient [91].

Vitro studies indicate that hydroquinone-loaded SLNs exhibit lower systemic absorption than hydroquinone hydrogels. Furthermore, hydroquinone encapsulated in NLCs has demonstrated improved skin penetration and enhanced protection against ultraviolet (UV)A/UVB radiation. Artificial skin permeation studies also confirm hydroquinone in NLCs provides superior percutaneous penetration. Another study found that NLC loaded with azelaic acid enhanced melanocyte targeting due to their small size and improved skin penetration. A combination of sustained release and rapid onset of action is advantageous for topical applications, as it provides localized drug effects while minimizing side effects compared to azelaic acid gel and water-based solutions [92] .

Khezri et al. revealed that kojic acid-SLN dispersion improved dermal delivery, providing higher concentrations, more controlled release, and greater tyrosinase inhibition than free kojic acid. Furthermore, the formulation of kojic acid in NLCs demonstrated enhanced release profiles, stronger tyrosinase inhibition, and greater antioxidant activity than pure kojic acid [93]. Raza et al. demonstrated that using SLNs, NLCs, and liposomes enhanced the delivery of retinoic acid. These nanoparticulate carriers improved its photostability, skin penetration, and anti-psoriatic effects, making it more effective and biocompatible than existing products. In another study, Shah et al. found that SLNs enhanced retinoic acid's physical stability and skin tolerance [94, 95].

Encapsulating kojic acid in SLNs significantly improves their skin delivery. These SLNs demonstrated higher drug concentrations in the skin, more controlled release, and enhanced tyrosinase inhibition compared to conventional formulations. Furthermore, azelaic acid-loaded NLCs offer superior occlusive properties, improved skin penetration, and targeted delivery to melanocytes, resulting in better clinical outcomes. The sustained release of azelaic acid from NLCs provides long-lasting therapeutic effects on the skin [96].

Liposomes and nanosomes

Liposomes/nanosomes, well-known in dermatology, particularly for hyperpigmentation therapy, have a wide range of uses. They excel at targeted delivery by encapsulating skin-lightening chemicals such as kojic acid, arbutin, vitamin C, TA, and linoleic acid (LA), increasing efficacy while reducing adverse effects. These medicines' ability to penetrate the skin's outer layer easily allows them to reach melanocytes, which improves therapy outcomes. Furthermore, encapsulation improves stability and shelf life, which is critical for preserving efficacy. The lipid bilayers also prevent direct skin contact, which reduces discomfort caused by some lightening chemicals. Furthermore, these formulations allow for combination therapy, which combines various substances with complementary activities to provide synergistic effects, offering improved clinical outcomes in hyperpigmentation treatment. Topical tranexamic acid hyaluronic acid-loaded liposome naogels, named HA/TA-LP, were created to treat hyperpigmentation by minimizing epidermal diffusion and combining the benefits of liposome and HA [97]. LA exhibits a depigmenting effect on hyperpigmented skin and is encapsulated in liposomes for topical application due to its limited solubility in aqueous solutions[98]. In an in vitro study, arbutin liposomes exhibited slower skin permeation and greater skin deposition than an arbutin solution. This means that the liposome formulation allowed the arbutin to remain in the skin for longer and in higher amounts, leading to less systemic absorption of the drug. As a result, the drug's localized effects are enhanced while minimizing the amount absorbed into the bloodstream, which could potentially reduce the risk of side effects associated with systemic exposure.[99]. Niosomes can serve as delivery systems for the treatment and management of hyperpigmentation, exemplified by arbutin-loaded niosomes (termed "arbusomes") [100]. An ultrasonic method, known as the green method, was employed to manufacture kojic acid niosomes (kojisomes) to enhance cutaneous delivery and anti-melanogenesis characteristics [101].

Shigeta et al. found that loading linoleic acid into liposomes enhanced its solubility and improved its ability to reduce pigmentation compared to non-liposomal forms. Linoleic acid inhibits tyrosinase, an enzyme involved in skin pigmentation [102]. Another study revealed that liposomal anthocyanin, a flavonoid with antioxidant and tyrosinase-blocking properties, was more effective than the plain drug. Encapsulating aloe vera extract into liposomes increased its bioavailability and enhanced its skin-lightening effects compared to the pure extract. Huh et al. observed that liposomal 4-n-butyl resorcinol exhibited improved stability and skin absorption, boosting its ability to inhibit melanogenesis. Other liposomal formulations containing various extracts enhanced skin penetration and tyrosinase inhibition, resulting in better skin whitening [103].

Nano/microemulsions

Nanoemulsions and microemulsions, consisting of an aqueous phase and an oil phase stabilized by surfactants, are advanced vehicles for treating hyperpigmentation, offering effective solutions for skin pigmentation disorders [104, 105]. Their small droplet sizes enhance skin penetration, enabling targeted delivery of melanin regulators to melanocytes. These formulations maintain ingredient stability, ensuring prolonged efficacy and minimizing degradation, which is crucial for sensitive components. They provide uniform distribution for consistent applications, reduce skin irritation, and are suitable for sensitive skin types. Like liposomes and nanosystems, nano and microemulsions support combination therapies by integrating multiple active ingredients with complementary effects, improving treatment outcomes for various hyperpigmentation issues. Table 4 represents a summary of nano/microemulsions involved in hyperpigmentation treatments. Nanoemulsions incorporating arbutin with coumaric acid enhance their stability and delivery. Encapsulated arbutin demonstrated

Table 4. Nano/Microemulsions Involved in Hyperpigmentation Treatments

Type	Drug	Observations	Reference
Microemulsion	Genistein isoflavone	Enhances bioavailability 10-fold	[110]
	Hydroquinone	A promising alternative for the treatment of melasma disease	[111]
	Punica Granatum extract	Decreased skin melanin contents	[112]
	Hesperetin	Showed a significant topical whitening effect	[113]
	Resveratrol	Higher drug penetration and skin retention than in the Suspension Group	[114]
	Pouteria macrophylla Fruit extract (EXT)	Decreased intracellular melanin production and secretion	[115]
	DeoxyArbutin	May allow the use of deoxyArbutin instead of hydroquinone	[116]
Nanoemulsion	Azelaic acid / hyaluronic acid	Reached the deeper layers of the skin while Improving in vitro tyrosinase inhibition	[117]
	Kojic Acid and Tetrahydro Curcumin	Excellent diffusion results	[118]
	Quercetin-loaded olive oil	Inhibited 56% of tyrosinase activity, indicating its Potential for free radical scavenging and Reducing skin hyperpigmentation	[119]
	Development of kojic monooleate (kmo)	KMO formulation was less toxic and can be applied for cosmeceutical applications	[120]
	Kojic Dipalmitate and Rosehip Oil	Antioxidant and depigmenting activities	[121]
	Tetrahydrocurcumin / lecthin	Antimelanogenic /enhance the topical delivery efficacy	[122]

high stability and efficient encapsulation when formulated in a hydrocolloid medium. The gelatin hydrocolloid facilitated sustained release, compared to only release from free arbutin [106].

Also, combining azelaic acid and hyaluronic acid in nanoemulsion has demonstrated improved drug retention and enhanced inhibition of tyrosinase activity. Hyaluronic acid aids in reducing melanin production by promoting interaction with melanocytes. This nanoemulsion successfully delivered azelaic acid through the skin without inducing cytotoxic effects [107].

Chlorogenic acid-containing nanoemulsions were prepared using an ultrasonic homogenization technique. Chlorogenic acid -NE formulation was evaluated in terms of its impact on tyrosinase activity and melanogenesis. The findings suggest that nanoformulation may be a promising option for skin-lightening in cosmetic products [108].

Punica granatum extract microemulsion was prepared using a spontaneous emulsification technique, which showed good skin compatibility and reduced melanin content in healthy male volunteers. Also, Ascorbic acid-loaded microemulsion demonstrated effective skin penetration and potential for skin whitening [103].

Arbutin incorporated into w/o/w nanoemulsions with coumaric acid demonstrated improved encapsulation, stability, sustained release, and skin delivery compared to the free drug. Arbutin was combined with lactic acid and niacinamide in microemulsions to enhance stability, skin penetration, and whitening effects. Another study on azelaic acid and hyaluronic acid-loaded nanoemulsions showed better

drug deposition in the skin, improved tyrosinase inhibition, and reduced cytotoxicity. Adding hyaluronic acid to the azelaic acid nanoemulsions improved interactions, leading to decreased melanin synthesis [96].

Hydroquinone 4% microemulsions exhibited enhanced drug release and stability, causing less skin irritation than conventional creams. Encapsulation in microemulsions improved skin permeability and photostability. Kojic dipalmitate also showed better stability in nanoemulsions. Adding ascorbic acid to microemulsions improved skin penetration and protection. Co-encapsulation of kojic acid and arbutin in microemulsions offered better photostability against UVB radiation than their aqueous solutions [96, 109].

Nanospheres

Nanospheres are divided into biodegradable (gelatin and albumin) and non-biodegradable (polylactic acid). Nanospheres are utilized in cosmetics to deliver active substances deep into the skin. They have shown potential in dermatology, particularly for reducing hyperpigmentation. Nanospheres improve therapeutic effectiveness, decrease adverse effects, and ensure sustained release by encapsulating hydroquinone, kojic acid, and arbutin. Their tiny size enhances melanocyte penetration, enhancing therapy efficacy and reducing skin irritation. Nanospheres also aid in combination therapy, which targets various pigmentation processes for improved effects [123]. For example, the sequential release of salidroside and paeonol from a nanosphere-hydrogel considerably improved the anti-melanogenesis actions of both compounds [124].

Nanocrystals

Nanocrystals are another type of polymeric nanoparticle used to deliver insoluble active compounds [125]. Nanocrystals are clusters of atoms organized individually or in polycrystalline structures. When distributed in water, they create topical formulations or nanosuspensions [126]. The particle diameters range from 100 to 400 nanometers. They are extremely water soluble and biodegradable [127]. Nanocrystals are mostly employed for substances with poor water solubility.

Nanocrystals (NCs) represent a promising approach to improving the solubility of phloretin (PHL), a potent agent that reduces melanin, lightens the skin, and promotes bioavailability. Niacinamide (NIC) functions as a melanin transfer inhibitor, suppressing melanin formation. Therefore, PHL-NIC-NCs developed [128]. Hydroquinone could inhibit melanin production and eliminate skin discoloration; hence, a hydroquinone-cellulose nanocrystal complex was prepared by incubating hydroquinone solution in cellulose nanocrystal suspension[129].

Tomic and colleagues encapsulated azelaic acid in nanocrystals using Pluronic® F127 and hyaluronic acid, improving both solubility and dissolution rate. Their results showed that when incorporated into PHA hydrogel, these nanocrystals exhibited significantly better skin bioavailability than standard commercial azelaic acid products [130].

Carbon nanotubes

Carbon nanotubes (CNTs) can be defined as rolled graphene with SP2 hybridization. CNTs are usually self-assembled into “ropes” by pi-stacking. The diameter ranges from 0.75 to 60 nm with lengths in the range of tens of microns [131].

CNTs have various biomedical applications, including dermatology and the treatment of hyperpigmentation. While research in this area is still in its early stages, some potential applications of carbon nanotubes in hyperpigmentation present potential in drug delivery for hyperpigmentation treatment by loading them with active ingredients like skin-lightening agents or antioxidants [131]. Their high surface area and unique structure could effectively enhance ingredient penetration and efficacy, targeting melanocytes. Moreover, CNTs possess photothermal properties, potentially enabling selective destruction of melanocytes through light-based therapies, offering a minimally invasive treatment option. Also, their anti-inflammatory effects could mitigate conditions like post-inflammatory hyperpigmentation (PIH) by reducing skin inflammation. Furthermore, CNTs may improve the skin barrier function, preventing factors like UV radiation from triggering hyperpigmentation and enhancing the penetration of topical treatments. However, concerns exist regarding their safety, including toxicity and biocompatibility issues, necessitating further research for safe and effective clinical applications. Additionally, the use of CNTs for analy-

sis is detailed, specifically employing a microcolumn packed with multiwalled carbon nanotubes (MWCNTs) for the preconcentration of certain heavy metals in skin whitening cosmetics before measuring them via inductively coupled plasma atomic emission spectrometry [132].

Cubosomes

Cubosomes are advanced nanostructured particles with a cubic or bicontinuous cubic phase formed by the self-assembly of lipid and surfactant systems in water. These submicron liquid crystal particles have distinct features that make them interesting for biological applications. Cubosomes have various benefits in the treatment of hyperpigmentation. Their organized internal matrix enables the effective encapsulation of hydrophilic and hydrophobic components, increasing solubility and stability. They increase deeper skin penetration by successfully targeting melanocytes. Cubosomes, which are engineered for continuous release, give longer-lasting therapeutic benefits while reducing the need for repeated administration. Surface modification provides focused distribution to specific cells, reducing off-target effects while increasing effectiveness. Their biocompatible lipid composition allows the stability and preservation of active substances, establishing cubosomes as novel therapies for hyperpigmentation [133]. Lyotropic liquid crystal nanoparticles (LLCNPs), specifically GMO-based cubosomes, were synthesized by altering the ionic strength of mixed lipids comprising sodium dodecyl and tetradecyl glycoside sulfate (APGS-Na) to encapsulate α-arbutin as the medication delivery barrier.

Zinc oxide nanoparticles

Zinc oxide nanoparticles (ZnO NPs), found in wurtzite and zinc blende crystalline forms, with optical refractive indices of 2.0 to 2.3 in the 375–900 nm range, indicating a less dramatic whitening impact than titanium dioxide (TiO_2). In dermatology, ZnO nanoparticles are prized for their multifunctional qualities, which include UV protection, anti-inflammatory actions, and possible skin-lightening properties. They operate as physical UV filters in sunscreens, inhibiting UVA and UVB rays to prevent and treat hyperpigmentation. ZnO nanoparticles also provide photoprotection by absorbing and scattering UV radiation, lowering oxidative stress and inflammation linked to hyperpigmentation. Furthermore, they may inhibit melanin synthesis, facilitate wound healing, and function as transporters for active substances in hyperpigmentation treatments, thereby increasing efficacy and delivery. Amiodarone, a benzofuran derivative, was initially introduced 17 years ago as a vasodilatory antianginal medication [134]. The adverse effects of amiodarone frequently affect the endocrine, respiratory, ophthalmic, and neurological systems, as well as the skin [135]. Cutaneous reactions encompass photosensitivity, which has been documented to impact up to 50% of patients undergoing treatment. Preparations containing zinc oxide demonstrated the most efficacy in diminishing cutaneous photosensitivity [136]. Thus, melanin treatment may be delivered via zinc ascorbic acid vacuole (ZAA_vac), which has a superior depigmenting effect compared to the wild-type vacuole or ascorbic acid, achieving a reduction of 75% in melanin pigmentation. ZnAA_Vac was determined to be non-toxic and did not induce cytotoxicity in the cells. ZnAA_Vac is a potent, safe, and efficacious skin-whitening agent [137].

Silicon dioxide nanoparticles

Silicon dioxide nanoparticles (SiO_2NPs) are commonly used in cosmetics and medicine delivery because of their hydrophilic nature, cost-effectiveness, and biocompatibility. They are, on average, 100 nm in size and made up of alternating silicon and oxygen. In dermatology, SiO_2NPs may help manage hyperpigmentation. They can scatter light to balance out skin tone, hide pigmentation flaws, and produce a matte finish by absorbing excess oil. As transporters, they may improve the penetration of active molecules into the skin, allowing them to target melanocytes better. SiO_2NPs have antioxidant capabilities, preventing UV-induced oxidative stress and free radical damage. Furthermore, their anti-inflammatory effect and possible function in wound healing may help cure pigmentation problems and reduce pigmentation alterations. Dermatological diseases extensively use ZnO NPs; however, they incorporate silicon dioxide as a protective cage due to their potential toxicity. Magnesium ascorbyl phosphate (MAP) is a powerful antioxidant that significantly impacts the skin; therefore, a formulation combining silica-coated ZnO nanoparti-

cles and MAP nanovesicles may serve as an effective cosmetic solution for protecting the skin against photodamage manifestations, including hyperpigmentation, roughness, and wrinkles [138].

Silver nanoparticles

Silver nanoparticles (AgNPs) are widely used in cosmetics, representing approximately 12% of all nanoparticles utilized in these products [139]. They are recognized for their antimicrobial, anti-inflammatory, and wound-healing properties. Although research specifically targeting hyperpigmentation is limited, AgNPs may offer several benefits. Their antimicrobial activity can reduce inflammation and prevent pigmentation changes associated with infections or inflammatory conditions like acne or dermatitis. Additionally, AgNPs support wound healing through enhanced cell proliferation and collagen synthesis, potentially lessening pigmentation issues caused by wounds. Their anti-inflammatory and antioxidant potential help protect against UV-induced damage and oxidative stress. AgNPs also improve the delivery of active molecules in hyperpigmentation treatments. However, their safety, including potential cytotoxicity and allergic reactions, requires careful consideration. Homeopathic mother tincture Curcuma longa was utilized to manufacture silver nanoparticles. Curcuma longa serves as a significant tyrosinase inhibitor, and this study expands its efficacy and applicability in cosmetological and dermatological conditions such as pigmented patches, melasma, freckles, ephelides, senile lentigines, PIH, hyperpigmented scars, and acne [140]. The antioxidant, antibacterial, antityrosinase, and anti-melanogenesis activities of green-synthesized silver nanoparticles were examined. Researchers developed a multifunctional silver nanoparticle that serves as a skin-lightening agent, synthesized through the reduction facilitated by the aqueous extract of Cocos nucifera leaf sheath scales [141].

Gold nanoparticles

Gold nanoparticles (AuNPs) such as nanocubes, nanospheres, nanorods, and nanosheets [142] are used for wound healing, antimicrobial effects, drug delivery, and skin regeneration [143]. Although research on AuNPs specifically for hyperpigmentation is limited, they offer several potential benefits. As drug carriers, AuNPs enhance the delivery of active ingredients to melanocytes, potentially improving treatment efficacy. Their wound-healing properties support cell proliferation and tissue regeneration, which may reduce pigmentation issues from wounds or inflammation. Additionally, AuNPs' optical properties enable photothermal therapy to target pigment cells and can be used in imaging techniques like optical coherence tomography for diagnosing pigmentation disorders. However, safety concerns must be addressed, including cytotoxicity and allergic reactions. AuNPs mediated by P. ginseng leaves are innovative materials with enhanced properties, demonstrating moisture retention capabilities and effectively inhibiting mushroom tyrosinase. PgAuNPs exhibited no toxicity to human dermal fibroblasts and B16 cells; furthermore, they significantly diminished melanin content, tyrosinase activity, and the mRNA expression of melanogenesis-associated transcription factors and tyrosinase in B16 cells [144]. Arbutin, a D-glucopyranoside derivative of hydroquinone, is extracted from pear, cranberry, and bearberry plants [145]. Arbutin is a recognized competitive inhibitor of human tyrosinase activity and is frequently utilized as a skin-lightening agent [146]. It is an ideal bioactive ingredient for preparing gold nanoparticles (GNPs) [147]. A research study investigated the effects of Panax ginseng leaf extract-based AuNPs on tyrosinase activity and melanin levels in murine melanoma B16BL6 cell lines. The findings demonstrated that AuNPs could decrease tyrosinase activity and its transcription, making them practical for skin whitening and reducing melanin content [103]. Arbutin and gold nanoparticles were mixed to fabricate a nanocomplex with higher skin-lightening potential. The results of this study indicated that the prepared arbutin nanocomplex was accompanied by lower intracellular and extracellular melanin production, higher anti-inflammatory effects, and reduced toxicity potential compared to the free drug [96].

Copper nanoparticles

Copper nanoparticles (CuNPs) are prized in cosmetics for their anti-aging, wound healing, and hair care properties [148]. They also have antibacterial, antioxidant, and anticancer effects. CuNPs have shown potential in dermatology for treating hyperpigmentation. They inhibit tyrosinase, which decreases melanin formation and lightens hyperpigmented skin.

Their antioxidant qualities shield against UV-induced damage and oxidative stress, while their anti-inflammatory activities aid in treating disorders such as PIH. CuNPs also increase collagen formation, which improves skin texture and tone. Their capacity to penetrate the epidermal barrier enables the efficient delivery of active substances to melanocytes. However, their safety must be thoroughly assessed.

Aluminum oxide nanoparticles

Aluminum oxide nanoparticles (Al_2O_3) are commonly utilized as coating agents in formulations, including TiO_2 and ZnO, where they aid in reducing oxidative stress caused by photocatalytic activity. Al_2O_3 nanoparticles have potential benefits in hyperpigmentation therapy because they inhibit tyrosinase and reduce melanin formation. When used in exfoliating products, they increase cell turnover, resulting in more skin tone. Sunscreens contain Al_2O_3 nanoparticles, which provide broad-spectrum UV protection and prevent sun-induced pigmentation. Their improved penetration enhances the administration and activity of other active substances. However, their safety for topical usage must be thoroughly evaluated.

Evaluation methods for pigmentation treatment

There is no universal standard for assessing the efficacy of whitening and spot-lightening products. Clinical research often evaluates changes in skin pigmentation before and after pharmacological intervention; however, the subjective nature of these assessments may compromise their reliability. To investigate the inhibitory effects of treatments on hyperpigmentation, various in vitro (tyrosinase activity, antioxidant capacity, cell model testing) while in vivo models such as the Mouse Model and the Zebrafish Model have been developed. In vitro studies primarily examine the impact of tyrosinase inhibitors and antioxidants on melanin reduction. More advanced experimental models utilize cultured melanocytes, fibroblasts, and keratinocyte cell lines to assess how pharmacological agents influence melanin synthesis, transfer, and other cellular processes [149].

Clinical Trials

Clinical trials on topical molecules for hyperpigmentation aim to assess the efficacy and safety of various active components in decreasing skin discoloration and uneven pigmentation. These studies frequently investigate chemicals such as hydroquinone, retinoids, vitamin C, arbutin, niacinamide, and newer drugs, including TA and licorice extract (Table 5) [150]. Researchers investigate how these compounds function, such as suppressing melanin synthesis, controlling inflammatory pathways, and enhancing skin barrier. Clinical studies usually include both in vivo and in vitro research to establish the best concentration, frequency of use, and any adverse effects. The objective is to find safe, effective therapies that enhance skin tone while reducing risks such as irritation or long-term side effects, especially for people with sensitive skin or darker skin tones [151].

Numerous clinical studies have assessed the effectiveness of various topical nanoformulations for hyperpigmentation. Topical liposomal TA was developed to minimize skin irritation and enhance whitening effects. Studies indicated that around 80% of participants showed positive results after 8 weeks of treatment [159]. However, another study conducted in 2012 in Thailand found no additional benefits from liposomal TA compared to conventional formulations, possibly due to its small sample size. Despite this, results demonstrated that topical TA significantly reduced average MASI scores after 12 weeks, with effects lasting for a month post-treatment [160].

A clinical trial compared liposomal hydroquinone 4% with conventional hydroquinone 4% for melasma management. Both formulations significantly reduced MASI scores, but neither was clearly superior [161]. The effectiveness of a liposomal serum containing azelaic acid, 4-n-butyl resorcinol, and retinol was evaluated in melasma patients. Improvements in MSS, MASI scores, and overall quality of life were observed, indicating the potential of this formulation [162]. Additionally, a double-blind trial found that liposomal aloe vera gel improved MASI scores by 32%, compared to only a 10% improvement with conventional aloe vera gel, suggesting that liposomal formulations might provide superior results for melasma treatment [163].

Table 5. Clinical Experiments on Topical Molecules for Hyperpigmentation

	Study Group	Study Type	Outcome/s	Refs
Hydroquinone (4%)	30 melasma patients with skin types III-V	Double-blind, randomized, prospective study	Enhancement in hyperpigmentation in 76.9% of patients treated with 4% topical (HQ) as related to placebo, adverse effects such as itching and eruptions reported in 25% of patients	[152]
Arbutin (3%)	50 Caucasian and dark-skinned patients with solar lentigines	Paired comparison, vehicle-controlled, double-blind study	Effective in treating solar lentigines in patients with lighter skin but failed to display therapeutic response in darker-skinned individuals	[153]
Tretinoin (0.1%)	40 Caucasian patients	Randomized, double-blind, vehicle-controlled study	Additional effective against photoaging-related hyperpigmentation in dark-skinned patients as compared to vehicle but stated retinoid dermatitis as a side effect	[154]
Azelaic Acid (20%)	155 patients of Indo-Malay and Hispanic origin	Randomized double-blind study	20% azelaic acid cream was found to be more effective than 2% (HQ) cream besides hyperpigmentation	[155]
Azelaic Acid (20%)	329 female patients	Randomized double-blind study	20% azelaic acid cream was found to be as effective as 4% (HQ) cream against hyperpigmentation	[156]
Niacinamide (5%)	18 Japanese women with multiple types of brown pigmentation	Randomized split-face double-blind balancing design study	Important decrease in facial hyperpigmentation spots in the patients as compared to vehicle	[157]
Fluocinolone acetonide (0.01%), Hydroquinone (4%), Tretinoin (0.05%)	228 patients with facial melasma	Long-term, multicenter, open-label, 12-month study	Melasma either totally or mostly cleared in more than 90% of patients, with no prominent safety concerns	[158]

A clinical study comparing a topical vitamin C nanosome with iontophoresis to a 70% glycolic acid peel showed that the vitamin C treatment provided better results in managing hyperpigmentation while causing fewer side effects such as skin burning, irritation, and dryness. [164] A clinical trial involving a liposomal cream containing 4-n-butyl resorcinol and resveratrol showed promising results in treating melasma. After two weeks, the treatment significantly reduced the melanin index in melasma lesions, with no notable changes observed in normal skin [165]. Over two months, another study compared arbutin-loaded chitosan nanoparticle hydrogel with regular arbutin gels in melasma patients. The findings showed that the chitosan nanoparticles were more effective in improving melasma, reducing the Melasma Area and Severity Index (MASI) score and the size of melanin particles in the skin [166]. A study of niacinamide-loaded flexible liposomes examined their skin-whitening effects in melasma patients. Results showed significant improvements in melanin levels after four and eight weeks of treatment and better visual and subjective assessments of skin

whiteness [167]. A study comparing a 20% topical liposomal azelaic acid cream with a 4% hydroquinone cream in patients with hyperpigmentation showed that the azelaic acid produced more significant improvement and was better tolerated than the hydroquinone cream [168].

Conclusions

Nanotechnology has revolutionized the cosmetic industry, introducing advanced delivery systems to enhance the efficacy of cosmeceuticals. Over the past decade, these innovations have significantly improved formulations for skin whitening and hyperpigmentation. Current nanotechnology improves active ingredient solubility, stability, and dermal penetration while minimizing toxicity through controlled release. Lipid nanoparticles, particularly popular for their skin permeability and biodegradability, are extensively used for treating hyperpigmentation. Despite their benefits, the lack of regulation for nanomaterials calls for thorough safety assessments and stricter guidelines to ensure consumer safety. As nanotechnology advances, its integration into daily cosmetic routines is becoming increasingly widespread and accepted.

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