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NANOTECHNOLOGY - ENHANCED HERBAL ANTIOXIDANT CREAMS: BREAKTHROUGH IN SKIN PENETRATION, STABILITY AND EFFICACY

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ABSTRACT

Skin is constantly exposed to environmental stressors such as UV radiation, pollution, and chemicals, which generate reactive oxygen species (ROS) and cause oxidative stress, accelerating aging and various dermatological disorders. Herbal antioxidants, including polyphenols, flavonoids, terpenoids, and alkaloids, can neutralize ROS, modulate antioxidant pathways, and protect structural proteins, supporting skin health. Conventional herbal creams, however, often face limitations such as poor solubility, low stability, limited skin penetration, and reduced bioavailability, limiting their therapeutic effectiveness. Nanotechnology-based delivery systems such as liposomes, nano emulsions, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and polymeric nanogels offer innovative solutions by enhancing solubility, stability, penetration, and controlled release of herbal antioxidants. Mechanisms including nanoscale size, lipid mimicry, follicular targeting, and surface modification contribute to improved dermal delivery and prolonged activity. Future research should focus on safety, biocompatibility, targeted delivery, and clinical validation to realize the full potential of nanotechnology - enhanced herbal antioxidant formulations for dermatological and cosmetic applications.

Keywords: Herbal antioxidants, Nanotechnology, Skin penetration, Liposomes, SLNs, NLCs

INTRODUCTION

The skin, being the largest organ of the human body, is continuously exposed to environmental stressors such as ultraviolet (UV) radiation, pollution, and chemical irritants. These external factors induce the excessive generation of reactive oxygen species (ROS), leading to oxidative stress that accelerates skin aging and contributes to dermatological disorders including hyperpigmentation, photoaging, and inflammatory conditions[1,2]. Antioxidants of natural origin, particularly those derived from medicinal plants rich in polyphenols, flavonoids, and terpenoids, have gained considerable attention in dermatology for their ability to neutralize ROS, chelate pro-oxidant metals, and modulate endogenous antioxidant defense systems[3,4]. At physiological levels, reactive oxygen species (ROS) act as essential signaling molecules and contribute to normal cellular functions, including host defense and regulation of proliferation and differentiation. However, excessive ROS production or a weakened endogenous antioxidant defense system disrupts intracellular redox homeostasis, leading to oxidative stress[1]. Elevated ROS levels can activate various signaling pathways, including mitogen-activated protein kinases (MAPKs), and regulate critical transcription factors such as nuclear factor-κB (NF-κB), nuclear factor erythroid 2–related factor 2 (Nrf2), c-Jun N-terminal kinase (JNK),

and activator protein-1 (AP-1) . Among these, Nrf2 plays a central role in orchestrating the cellular antioxidant response, as its activation leads to the transcription of numerous cytoprotective and detoxifying genes that counteract oxidative damage[3,5].

Antioxidants are molecules that can oxidize themselves before or instead of other molecules. They are compounds or systems that can interact with free radicals and stop a chain reaction before vital molecules are harmed. Antioxidant molecules can be enzymes or low-molecular-weight antioxidants that donate an electron to reactive species, preventing the radical chain reaction, which prevents the formation of reactive oxidants, or behave as metal chelators, oxidative enzyme inhibitors, or enzyme cofactors. Antioxidants can also be used as stabilizers, preventing lipid rancidity. Lipid oxidation occurs not only in cosmetics but also in the human body. Thus, when antioxidants are present in a product, they may serve multiple functions. The number of radicals increases during the initiation phase of lipid oxidation. Molecular oxygen and fatty acid radicals react during the propagation phase, resulting in the formation of hydroperoxide products. Hydroperoxides are unstable and can degrade to produce radicals, which can accelerate the propagation reaction. The termination phase is dominated by radical reactions. Antioxidants can inhibit lipid oxidation by reacting with lipid and peroxy radicals and converting them to more stable, non-radical products. Additionally, antioxidants can deplete molecular oxygen, inactivate singlet oxygen, eliminate peroxidative metal ions, convert hydrogen into other antioxidants, and dissipate UV light[4]. Herbal antioxidants, such as catechins from Camellia sinensis, resveratrol from grapes, quercetin from onions, and curcumin from Curcuma longa, protect the skin by scavenging free radicals and modulating pathways like NF-κB and Nrf2. They also inhibit collagen-degrading enzymes, reduce inflammation, and strengthen the skin barrier, supporting anti-aging and overall skin health[3,4].

Conventional herbal creams often suffer from poor solubility, instability, and degradation of active phytoconstituents upon exposure to light, oxygen, and heat. Nanotechnology offers an innovative solution to these challenges by enabling the encapsulation of plant-derived antioxidants into nanoscale delivery systems. Liposomes, nano emulsions, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and polymeric nanoparticles have shown the ability to enhance cutaneous penetration, protect labile phytoconstituents from premature degradation, and provide sustained release at the site of action. These nano systems not only increase the therapeutic efficiency of herbal creams but also improve their cosmetic acceptability, stability, and safety profile[5,6].

Conventional herbal creams are often limited by multiple factors that reduce their therapeutic and cosmetic efficacy. Many herbal actives have high molecular weight or hydrophilic properties, which restrict their penetration through the stratum corneum, while others are chemically unstable and prone to degradation when exposed to light, heat, oxygen, or moisture, resulting in diminished potency and shorter shelf life [7]. Only a small fraction of active compounds typically reaches the deeper skin layers, leading to limited bioavailability and the need for higher doses or frequent application. Formulation issues such as poor spread ability, greasiness, phase separation, sedimentation, and variable composition of plant extract further compromise consistency and user acceptability [8]. In addition, lipophilic or poorly soluble actives may not distribute uniformly, and slow or inefficient release can delay therapeutic or cosmetic effects [9]. Without proper stabilization strategies, antioxidants and other sensitive phytoconstituents may lose activity before reaching the skin. Compatibility issues with other ingredients, along with heavy or sticky textures, can also reduce patient adherence, highlighting the need for advanced delivery systems such as nanotechnology to overcome these limitations[10,11].

HERBAL ANTIOXIDANTS

Herbal antioxidants are essential in protecting the skin from oxidative stress, a key factor in skin aging, inflammation, and various dermatological disorders. These compounds can be broadly categorized into several classes, each with distinct mechanisms and benefits. Polyphenols, such as catechins from Camellia sinensis, resveratrol from grapes, and curcumin from Curcuma longa, act by scavenging reactive oxygen species (ROS), chelating pro-oxidant metals, and modulating redox-sensitive transcription factors like NF-κB and Nrf2, thereby protecting cellular components from oxidative damage[12]. Flavonoids, including quercetin, rutin, and apigenin, provide broad-spectrum antioxidant and anti-inflammatory effects, while also inhibiting UV-induced matrix metalloproteinases (MMPs), which are responsible for collagen degradation and loss of skin elasticity[13]. Terpenoids, such as saponins, carotenoids, and triterpenes derived from plants like ginseng and licorice, reduce lipid peroxidation, enhance skin barrier function, and support tissue repair[14]. Lastly, alkaloids and other phytoconstituents, for example berberine and capsaicin, contribute additional antimicrobial, anti-inflammatory, and antioxidant activities, making them valuable for both anti-aging and the management of

various skin conditions[15]. Collectively, these herbal antioxidants not only neutralize ROS but also modulate enzymatic pathways, protect structural proteins, and maintain skin homeostasis, forming the basis for many topical dermatological and cosmetic formulations[16].

Table 1: Herbal Antioxidant Classification

Class	Examples
Flavonoids	Quercetin, Kaempferol, Catechins, Rutin[67 - 69]
Phenolic acids	Caffeic acid, Ferulic acid, Gallic acid[70 - 72]
Tannins	Ellagitannins, Proanthocyanidins[73,74]
Terpenoids	Curcumin, Limonene, Ginsenosides[75 - 77]
Alkaloids	Berberine,Piperine[78,79]
Vitamins	Ascorbic acid (Vitamin C), Tocopherols (Vitamin E)[80,81]

Table 2: List of Herbal Antioxidants

Sl No.	Plant	Botanical Name	Active Antioxidant Constituents	Mechanism of Action
1.		Camellia sinensis (Green Tea)	Catechins (EGCG)	Scavenges ROS, Chelates metals, Modulates NF-κB and Nrf2, Anti-inflammatory[12]
2.		Vitis vinifera (Grape / Grape Seed)	Resveratrol, Proanthocyanidins	Neutralizes free radicals, Inhibits MMPs, Anti-aging, Anti-inflammatory[13]
3.		Punica granatum (Pomegranate)	Ellagic acid, Punicalagin	ROS scavenging, UV protection, Anti-aging, Anti-inflammatory[14]
4.		Curcuma longa (Turmeric)	Curcumin	Scavenges ROS, Inhibits NF-κB, Anti-inflammatory, Photoprotective[1]

5.		Ginkgo biloba	Flavonoids, Terpenoids	Scavenges ROS, Improves microcirculation, Anti-aging[16]
6.		Rosmarinus officinalis (Rosemary)	Rosmarinic acid, Carnosic acid	Antioxidant, Anti-inflammatory, Lipid peroxidation prevention[17]
7.		Silybum marianum (Milk Thistle)	Silymarin	Protects against lipid peroxidation, Antioxidant, Anti-inflammatory[18]
8.		Camellia japonica	Polyphenols, Flavonoids	ROS scavenging, Anti-aging, Skin barrier protection[19]
9.		Clerodendrum infortunatum	Flavonoids, Phenolic compounds	Scavenges free radicals, Antioxidant, Anti-inflammatory[20]
10.		Withaniasomnifera (Ashwagandha)	Withanolides	Reduces oxidative stress, Anti-inflammatory, Cytoprotective[21]
11.		Glycyrrhiza glabra (Licorice)	Glycyrrhizin, Glabridin	Scavenges free radicals, Increases endogenous antioxidant enzyme activities[82 - 84]

12.		Crocus sativus (Saffron)	Crocin, Crocetin	Inhibits ROS formation, Enhances glutathione activity, Reduces lipid peroxidation[85,86]
13.		Bacopa monnieri (Brahmi)	Bacosides, Flavonoids, Saponins	Enhances SOD, CAT, and GPx activity, Reduces lipid peroxidation, Protects neuronal cells[87,88]
14.		Azadirachta indica (Neem)	Azadirachtin, Nimbin, Quercetin	Prevents oxidative DNA damage, Enhances cellular antioxidant defense system[89,90]
15.		Centella asiatica (Gotu Kola)	Asiaticoside, Madecassoside, Triterpenoids,Quercetin	Scavenges hydroxyl radicals, Increases SOD, CAT, and GPx activities[91,92]

NANOTECHNOLOGYBASED DELIVERY SYSTEMS FOR HERBAL ANTIOXIDANTS

In pharmaceutical sciences, nanotechnology refers to the design and use of nanosized carriers such as liposomes, nano emulsions, solid lipid nanoparticles, nanostructured lipid carriers, and polymeric nanoparticles to enhance the solubility, stability, penetration, bioavailability, and targeted delivery of drugs or bioactive compounds[22].Nanotechnology has emerged as a transformative approach in dermatology and cosmetology by addressing the limitations of conventional herbal creams[23 - 25].The major nanocarrier systems:

- Liposomes**:** Liposomes are nanosized spherical vesicles composed of phospholipid bilayers that can encapsulate both hydrophilic and lipophilic herbal antioxidants[26]. They enhance the solubility, stability, and penetration of sensitive compounds like curcumin and quercetin through the stratum corneum by interacting with skin lipids[27]. Liposomes also provide controlled and sustained release, prolonging the therapeutic action of encapsulated antioxidants[28]. However, they face limitations such as aggregation, fusion, and phospholipid oxidation during storage, as well as higher production costs[29]. Newer modifications, including transferosomes and ethosomes, have been developed to improve stability and skin penetration compared to conventional liposomes[30].
- Nanoemulsions**:** Nanoemulsions are colloidal dispersions of oil and water stabilized by surfactants, with droplet sizes typically ranging from 20 to 200 nm[31]. They enhance the solubility of poorly water-soluble herbal antioxidants such as resveratrol and carotenoids, improving their bioavailability in skin applications[32]. The small droplet size increases surface area, facilitating faster absorption through skin appendages and lipid channels, while providing good spread ability and a non-greasy, consumer-friendly feel[33]. However, nano emulsions require relatively high surfactant concentrations, which may cause skin irritation if not carefully optimized, and they can be prone to phase separation under stress conditions like temperature fluctuations or freeze–thaw cycles[34]. Studies have shown that

resveratrol nano emulsions exhibit superior antioxidant activity and higher skin retention compared to conventional cream formulations[35].

- Solid Lipid Nanoparticles**:** Solid Lipid Nanoparticles (SLNs) are submicron carriers composed of lipids that remain solid at both room and body temperature, stabilized by surfactants[36]. Their solid lipid core provides a crystalline matrix that allows encapsulation of lipophilic herbal antioxidants, such as catechins and curcumin, protecting them from chemical degradation, oxidation, and photolysis[37]. SLNs improve skin barrier function by increasing occlusivity, which reduces transepidermal water loss (TEWL) and enhances hydration[38]. They also enable controlled release of the encapsulated actives, prolonging their residence time on the skin and maintaining sustained antioxidant activity[39]. However, SLNs have limitations, including limited drug-loading capacity due to the tightly packed crystalline structure of lipids and the risk of polymorphic transitions that can lead to drug expulsion during storage[40].
- Nanostructured Lipid Carriers (NLCs)**:** Nanostructured Lipid Carriers (NLCs) are advanced, second-generation lipid nanoparticles made from a mixture of solid and liquid lipids[41]. This less - ordered lipid matrix creates imperfections that allow higher loading of herbal antioxidants compared to conventional Solid Lipid Nanoparticles (SLNs), improving both stability and efficacy[42]. NLCs protect bioactive compounds such as polyphenols and flavonoids from chemical degradation while enhancing penetration through both intercellular and transappendageal pathways of the skin[43]. They also reduce drug expulsion during storage, offering better long-term stability and sustained release of the encapsulated actives[44]. However, NLCs require a more complex formulation process than SLNs and careful selection of lipid blends to prevent phase separation[45]. For example, NLCs containing rutin and apigenin have demonstrated improved anti-aging effects by reducing matrix metalloproteinase (MMP) activity and promoting collagen synthesis, making them highly effective for topical applications[46].
- Polymeric Nanoparticles and Nanogels**:** Polymeric nanocarriers are nanoscale systems or hydrophilic nanogels prepared from natural polymers such as chitosan and alginate, or synthetic polymers like PLGA and PEG[47]. They can effectively encapsulate herbal antioxidants, protecting them from degradation while enabling controlled, sustained, or stimuli-responsive release, for example, triggered by pH or enzymes in the skin[48]. These carriers increase the residence time of actives on the skin surface and enhance penetration into deeper dermal layers[49]. Polymeric nanoparticles and nanogels also offer versatility in surface modifications, allowing targeted or localized delivery of antioxidants to specific skin sites[50]. However, they involve higher production costs, complex formulation processes, and potential biocompatibility or regulatory challenges depending on the polymer used[51]. For instance, chitosan - based nanogels encapsulating quercetin have shown improved antioxidant activity, anti-inflammatory effects, and enhanced skin hydration compared to free quercetin formulations[52].

MECHANISM OF ENHANCED SKIN PENETRATION AND STABILITY

Nanotechnology-based delivery systems significantly improve the dermal delivery and stability of herbal antioxidants by manipulating particle size, surface characteristics, and carrier composition. Their nanoscale dimensions (10–200 nm) allow close contact with the stratum corneum and facilitate penetration through intercellular lipid channels, follicular routes, or via transient disruptions of the skin barrier. Lipid-based carriers such as liposomes, nano emulsions, SLNs, and NLCs mimic the skin's natural lipid matrix, enhancing compatibility and promoting diffusion of actives. Encapsulation protects sensitive phytoconstituents from environmental degradation (light, heat, oxygen) and enzymatic metabolism, ensuring prolonged antioxidant activity. Moreover, polymeric nanocarriers and nanogels provide sustained or stimuli-responsive release, maintaining therapeutic levels for extended periods and minimizing irritation or dose-related toxicity[53].

- Reduced Particle Size and Enhanced Surface Area**:** Nanocarriers possess nanoscale dimensions that allow them to interact intimately with the skin surface. Their small size facilitates closer contact with the stratum corneum, improving passive diffusion through intercellular lipid channels. The increased surface area enhances the dissolution rate of poorly soluble phytoconstituents such as curcumin and resveratrol, leading to higher concentration gradients that drive permeation. This physical effect is particularly beneficial for herbal antioxidants that are otherwise limited by low aqueous solubility or large molecular size[54].

- Lipid Mimicry and Barrier Interaction**:** Lipid-based nanocarriers, including liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs), structurally resemble the lipid bilayers of the stratum corneum. This similarity allows them to integrate with or fluidize the skin lipids, transiently disrupting the barrier and enhancing penetration. The lipid components (e.g., phospholipids, triglycerides, fatty acids) also contribute to restoring or maintaining the skin's natural barrier function, reducing transepidermal water loss (TEWL) and improving hydration—an effect that further facilitates active diffusion[55].
- Follicular and Transappendageal Pathways**:** Nanocarriers can exploit skin appendages such as hair follicles and sebaceous glands as alternative routes for penetration. Due to their small size and deformable nature, nanoparticles can accumulate within follicular openings, acting as reservoirs for sustained release of antioxidants directly into deeper skin layers. This mechanism is particularly advantageous for long-term antioxidant protection and for treating localized conditions such as acne, pigmentation, or photoaging[56].
- Occlusive and Hydration Effects**:** Lipid nanoparticles, when applied to the skin, form an occlusive film that decreases water evaporation and enhances hydration of the stratum corneum. Increased hydration leads to swelling and loosening of corneocyte packing, reducing the barrier resistance and promoting diffusion of encapsulated compounds. This occlusive property not only enhances the penetration of herbal antioxidants but also provides a protective and moisturizing effect beneficial for maintaining skin health[57].
- Encapsulation and Protection Against Degradation**:** Many herbal antioxidants such as polyphenols, flavonoids, and terpenoids are chemically unstable and prone to degradation upon exposure to light, oxygen, or heat. Nanocarrier encapsulation provides a protective microenvironment that shields these compounds from environmental and enzymatic degradation. The lipid or polymeric matrix prevents direct contact with external oxidants and moisture, thereby extending the shelf life and maintaining the bioactivity of compounds like quercetin, catechins, and curcumin[58].
- Controlled and Sustained Release Mechanisms**:** Nanocarriers offer the advantage of controlled or sustained release, ensuring a continuous supply of antioxidants over an extended period. Polymeric nanoparticles and nanogels can be designed to respond to environmental stimuli such as pH, temperature, or enzymatic activity, releasing the encapsulated actives only under specific conditions. This minimizes the burst release effect, enhances bioavailability, and maintains therapeutic levels within the skin while reducing irritation and the need for frequent application[59].
- Surface Modification and Targeting**:** Surface functionalization of nanocarriers with polymers (e.g., chitosan, PEG) or ligands (e.g., peptides, antibodies) enhances adhesion to skin cells and provides site-specific targeting. For example, chitosan imparts a positive charge that increases electrostatic interaction with negatively charged skin components, facilitating closer contact and enhanced penetration. Such modifications also improve biocompatibility and reduce potential irritation from surfactants or synthetic excipients[60].

FUTURE PERSPECTIVE

Several innovative strategies have been developed to enhance the benefits of antioxidant therapy for topical skin applications. Among these, nanotechnology-based delivery systems have shown significant promise. These systems improve the delivery of antioxidants to the skin, minimize irritation, and protect sensitive compounds from environmental degradation. Different types of nanocarriers such as liposomes, nano emulsions, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and polymeric nanogels—have been explored, each with unique advantages and limitations. The choice of a suitable nanocarrier depends on the physicochemical properties of the antioxidant compound. For instance, lipid-based systems are ideal for lipophilic antioxidants, while polymeric or hybrid systems can accommodate both hydrophilic and lipophilic molecules. Understanding these differences helps achieve optimal penetration and therapeutic effectiveness[61].

While nanotechnology offers clear advantages, safety concerns must be carefully evaluated. Due to their small size, nanoparticles can penetrate deeper skin layers and potentially enter systemic circulation, causing unintended effects. These may include off-target interactions, formation of reactive metabolites, or disturbances in redox balance sometimes leading to reductive stress, a condition opposite to oxidative stress, which can impair normal cellular function. Controlling particle size and incorporating targeting ligands can help direct antioxidants precisely to their intended skin sites, reducing such risks. Moreover, the possibility of immune responses to nanoparticles remains a challenge. Therefore, future developments should prioritize biocompatible and biodegradable materials and minimize the use of toxic organic solvents during formulation. When solvents are necessary, ensuring that their residues remain within safe limits is critical for product safety[62,63].

Nanotechnology also offers exciting opportunities for targeted therapy. By attaching specific ligands to nanoparticles, it is possible to target particular skin regions or even cellular organelles. Mitochondria, being the main source of reactive oxygen species (ROS), present a particularly attractive target for antioxidant delivery, potentially opening new pathways for managing oxidative skin damage[64].Despite the promising laboratory results, challenges such as formulation stability, regulatory approval, production scalability, and limited clinical data remain significant obstacles. Although nanocarriers have consistently shown superior penetration and sustained release compared to traditional formulations, there is still a lack of comprehensive clinical trials, especially for chronic conditions such as melasma and dermatitis. Recent data show that while over 250 studies have explored antioxidants in skin therapy, only a small fraction focus on nano formulations, highlighting the need for further research in this field[65,66].

CONCLUSION

Nanotechnology offers a promising way to improve the delivery and effectiveness of herbal antioxidants in topical treatments. It helps overcome problems of poor solubility, stability, and limited skin penetration seen in conventional creams. Nanocarriers such as nano emulsions, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and polymeric nanogels provide better protection, controlled release, and deeper skin absorption of antioxidants. However, the safety of these systems must be carefully evaluated, as nanoparticles can sometimes penetrate too deeply or cause unwanted reactions. Using safe, biocompatible, and biodegradable materials can help reduce these risks. Future research should focus on improving the stability, large-scale production, and clinical testing of nanocarrier-based herbal antioxidant creams. With further development, these systems could provide safer and more effective treatments for various skin disorders.

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