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REVIEW

Current application of phytocompound-based nanocosmeceuticals for beauty and skin therapy

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Abstract: Phytocompounds have been used in cosmeceuticals for decades and have shown potential for beauty applications, including sunscreen, moisturizing and antiaging, and skin-based therapy. The major concerns in the usage of phyto-based cosmeceuticals are lower penetration and high compound instability of various cosmetic products for sustained and enhanced compound delivery to the beauty-based skin therapy. To overcome these disadvantages, nanosized delivery technologies are currently in use for sustained and enhanced delivery of phyto-derived bioactive compounds in cosmeceutical sectors and products. Nanosizing of phytocompounds enhances the aseptic feel in various cosmeceutical products with sustained delivery and enhanced skin protecting activities. Solid lipid nanoparticles, transfersomes, ethosomes, nanostructured lipid carriers, fullerenes, and carbon nanotubes are some of the emerging nanotechnologies currently in use for their enhanced delivery of phytocompounds in skin care. *Aloe vera*, curcumin, resveratrol, quercetin, vitamins C and E, genistein, and green tea catechins were successfully nanosized using various delivery technologies and incorporated in various gels, lotions, and creams for skin, lip, and hair care for their sustained effects. However, certain delivery agents such as carbon nanotubes need to be studied for their roles in toxicity. This review broadly focuses on the usage of phytocompounds in various cosmeceutical products, nanodelivery technologies used in the delivery of phytocompounds to various cosmeceuticals, and various nanosized phytocompounds used in the development of novel nanocosmeceuticals to enhance skin-based therapy.

Keywords: nanodelivery technologies, skincare, nanophytocompounds, nanophytocosmeceuticals, nanotherapy

Introduction

Cosmeceutical research is a rapid growing area in personal care sectors, which extends from facial products to skin and body products.[1–3] A forecasted report suggested that by 2018, the global market for cosmeceuticals will reach ~42 billion dollars and lead to a great demand in near future.[4] Even though various synthetic compounds are currently available in the world market, human toxicity is increasing with cosmeceutical interference in certain treatments.[5–8] Alternatively, plant-derived natural, bioactive compounds show enhanced beauty roles, along with health benefits against diseases.[9–15] Plant-derived bioactive compounds have been used for centuries in cosmeceuticals for a wide variety of beauty treatments for the skin, face, lips, hair, and nail care with beneficial actions against photoaging, inflammation, hair loss, lip care, psoriasis, and ultraviolet (UV) toxicity.[13–21] Further, UV radiation causes skin tanning and endothelial cell necrosis and suppresses immunological functions. Some natural phytobioactive compounds can prevent these deleterious effects with skin care.[20,22–25]

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Phytobioactive compounds used in cosmeceuticals include catechins, gallic acids, epicatechins, curcumin, hydroxylbenzoic and cinnamic acids, quercetin, ascorbic acids, luteolin, alpha and beta carotene, complex polysaccharides, and fatty acids.[26–31] These compounds, in addition to their cosmetic effects, enhance antibacterial, antifungal, anticarcinogenic, and anti-inflammatory biological actions.[31–37] Even though various macrosized phytobioactive compounds are used in cosmeceutical formulations, their solubility and formulation type have limitations in enhancing the effect of phyto-based cosmeceuticals and therapy.[38–41] The major limitations of phyto-based cosmeceutical therapy include less skin penetration, lower prolongevity, less final quality and lower whitening effects. These qualities depend on the solubility and size of the active phytocompounds.[40,42] This leads us in search of novel, highly promising technologies for enhanced skin health efficiency of cosmeceutical products.

Nanotechnology solves most issues with higher protective and skin health-enhancing efficiency. Various nanotechnology methods are involved in active roles in beauty enhancement, such as nanoemulsions, liposomes, solid lipid nanoparticles, smaller sized nanoparticles, hydrogels, and dendrimers.[4,43,44] Commercially, many synthetic compounds are used in nanocosmeceuticals that cause toxicity and skin health concerns. Natural phytocompounds are in a greater demand.[45–47] Nanoscale phytocompounds used in cosmeceutical products are gradually increasing among products such as sun screens, antiaging, and UV protectants.[47–56] Fewer phyto-based cosmeceutical nanoproducts available in the market are reviewed, namely, vitamin E in acne lotion, tea extracts in nanoshampoo, green tea extracts in the ageless skin care miracle kit, and vitamin E and aloe in UV protection moisture lotion. These phyto-based cosmeceutical nanoproducts contribute to the higher efficacy of the products mentioned for skin-based nanotherapy.[57,58]

Recent studies suggest that phyto-based nanocosmeceuticals will play a greater dual role in the near future for their enhanced protective, beauty, and health benefits.[4,43,44,59] Therefore, the current review focuses on the different types of nanosized cosmeceuticals, current nanotechnology usage in the development of nanosized compounds or carriers for the delivery of phytobioactive compounds, and various nanosized phytobioactive compounds used in cosmeceutical therapy for their enhanced skin therapeutic applications.

Phytoconstituent-based nanocosmeceuticals for skin therapy

Nanoantiaging

Aging is the critical factor that causes skin collagen to lose its physical appearance in many ways such as oil production decrease, dry skin, texture loss, age spots, and loose skin. Aging causes skin thinning, and the end result is wrinkle formation.[60,61] This is not limited to the aged population; younger individuals exposed to various harsh environmental conditions such as infrared and ultraviolet rays, chemical pollution, and other physical stresses can also be affected.[62,63] Currently, various synthetic and natural antiaging creams using nanosize technology are available on the market with enhanced skin protection to moisturize, lift, and whiten skin.[64–68] Recently, Lohani et al[4] reviewed some nanoproducts produced by few companies for enhanced beauty, such as Hydra Zen Cream, Revitalift, and Skin Caviar Ampoules that contain phytocompounds, using various nanotechnologies. Nanosized phytobioactive compounds, such as curcumin and vegetable oils, show enhanced skin appearance by various antioxidative mechanisms. The aforementioned products prevent skin aging due to oxidative stress and premature aging.[69–73] The combination of polyphenols with retinols enhances skin protection. Other than nanosizing, few delivery systems have been used to develop nanoantiaging creams and lotions for the enhanced activity of bioactive compounds to deeper layers of skin. Recently, a nanoemulsion system was constructed using *Eysenhardtia platycarpa* leaf flavanones with 70 nm nanoparticles that enhanced antiaging activity. Polymeric nanoparticles of *E. platycarpa* leaf flavanones with the particle sizes between 156 nm and 202 nm also showed the enhanced antiaging effects.[74] In addition, coencapsulation of resveratrol and curcumin showed enhanced delivery of phytocompounds for disease treatment with their antioxidant activities and thereby delays aging effects.[75,76]

Nanomoisturizers

Skin dehydration can be prevented by moisturizers, which support skin beauty and enhance skin flexibility by maintaining moisture.[77] A moisture-preventing barrier on the skin is the stratum corneum, which maintains the skin moisture. Dehydration results in the abundant loss of water from the skin.[78] Moisturizer creates a thin film on the outer surface of the skin maintaining skin moisture and can be effectively achieved by various nanotechnological systems.[79] Currently, nanoemulsions, nanoliposomes, and solid lipid nanocarriers are effectively used in moisturizer formulations with active

phytoingredients and enhance the skin's beauty.[79,80] Further, skin hydration is effectively enhanced with prolonged activity achieved by the solid lipid nanoparticle systems with low viscosity and nongreasy effects.[80] Currently, many phyto-based nanomoisturizing delivery systems are in starting phases of development. Among them, safranol was used in the development of solid lipid nanoparticles with enhanced moisturizing effects, along with UV protecting activity. In this system, the minimum nanoparticle diameter was 100 nm.[80] Similarly, rice bran oil nanoemulsions were also developed with enhanced moisturizing effects to improve various skin diseases, including atopic dermatitis and psoriasis.[69] *Opuntia ficus-indica* (L.) extract mill nanoemulsions were developed with varying particle size from 92 nm to 233 nm and had enhanced moisturizing effects.[79] Currently, various vegetable oil nanoemulsions were studied for their potential use as a moisturizer product. In the future, vegetable oils will be a great alternative for enhanced moisturizing effects for dry skin-related diseases.[69]

Nanoskin cleanser

Skin cleanser plays an active role in maintaining skin health.[81,82] A thin hydrolipid film covers the skin containing cellular debris from the decomposition products of corneocytes and secretions from eccrine, sebaceous, and apocrine glands. Hydrolipid films on the skin surface may attract undesirable microorganisms, which in turn accelerate the odor production with the metabolized products from the sweat glands.[83] Skin cleaning directly promotes the removal of skin surface bacteria, which reduces odor production. Currently, skin cleaning products are available on the market from macro- to nanosize containing both synthetic and natural products.[84,85] Research is being performed on several phyto-based nanocompounds for enhanced skin cleaning. Recently, phyto-based extracts used in cleansers showed enhanced skin cleansing activity by reducing pore size and skin oil content. However, they are only in the budding stage. The effectiveness of using phyto-based compounds in skin cleansing and related to skin disease such as acne[86] is well studied. Similarly, nanosized liposomal lauric acid was constructed in the size range of 113 nm and showed enhanced antimicrobial activity against the acne.[87] Another study, using niosomes by combination of lauric acid and curcumin, showed enhanced antimicrobial activity against acne-caused skin infections.[88] These studies suggest that phyto-based nanotechnologies show enhanced effects on skin cleanser activity on skin disease. Further, phyto-based nanotechnologies will pave the way for the development of skin cleanser products with phytocompounds with enhanced skin cleaning activity.

Nanosunscreens

Sunscreens protect the skin from the harmful sun rays exposure.[89] Commercially, sunscreens available are in the forms of creams and lotions that contain synthetic compounds, which act as a barrier when the harmful rays hit the skin. Sunscreens prevent deep UV ray penetration and inhibit irritation and other consequences. However, synthetic sunscreens have disadvantages, including formation of a chalky layer, greasiness, smelliness, decreased appeal, and toxicity.[90] A few of the mentioned disadvantages are overcome by use of natural phyto-based active ingredients. Recently, Bulla et al[91] studied the usage of phyto-based bioactive compounds derived from *Schinus terebinthifolius Raddi* in sunscreens and found that they enhance antioxidant and sun blocking activities. Similarly, bioactive-rich dried extracts of Brazilian *Lippia* species showed higher photoprotective activity.[92] Even though phytobioactive compounds show increased sunscreen effects, their stability and skin protective effects were greatly enhanced by using nanotechnology delivery systems in the sunscreen cream and lotions.[73,93,94] Recently, saffranol was constructed using solid lipid nanoparticles and had enhanced sun screening activity in the size range of 103–233 nm.[80] Similarly, nanostructured lipid carriers were constructed using rice bran oil and raspberry oil and had enhanced sunscreen activities with higher antioxidant and UV protective activities.[95] In another study, phytoflavanoid-encapsulated poly(lactic-*co*-glycolic) acid nanoparticles were constructed with the particle size of 90–100 nm that had enhanced sunscreen activity along with increased antioxidant activity. In another study, a pomegranate seed oil nanoemulsion was constructed with various nanoparticle sizes and showed increased skin protection against photodamage with enhanced antioxidant activities.[96] The same research group also studied the effect of pomegranate seed oil nanoemulsions on human erythrocytes and found increased photosafety of lipid skin membranes.[97] The earlier research suggests that the development of novel nanosized phytocompounds will enhance sunscreen products with fewer toxic effects.

Nanohair care

Hair care is the most promising cosmeceutical sector. People of all ages are concerned about their hair. Hair loss may occur at any age. Hair loss conditions are associated with scalp

inflammation and growth disorders, which vary with the individual.[98–101] This affects the social status of individuals due to changes in physical appearance of the increased hair loss by vellus follicles transformations.[102] Several plant-derived phytobioactive compounds are extensively used in the hair care products.[103–105] Recently, phytochemicals from rice and artichokes are used to enhance the hair growth, color, and appearance and protect hair from UV-induced degradation.[104] Similarly, pomegranate hydroethanolic extract was used in the reduction of the hair follicle red fading effect and enhanced hair color retention.[103] The mixture of phyto-based bioactive compounds also showed enhanced hair growth in the anagen phase. Along with hair growth, the phyto-based bioactive compound mixture protects from hair loss and breaking. Recently, a nanocosmeceutical-based approach of promoting hair growth was achieved using delivery technologies, such as niosomes and liposomes, to hair follicular cells.[106–113] Curcumin-based liposomes were constructed and had 70% enhanced penetration of the curcumin to the hair growth, irrespective of liposomes type in the size range of 213–320 nm.[114] Similarly, a curcumin-based cyclodextrin complex also showed enhanced follicle penetration and hair growth enhancement.[115] In addition, the combination of polyarginine and oleic acid-modified nanoparticles in size range of 140–143 nm showed enhanced skin penetration of follicular or nonfollicular cell pathways.[116] These studies confirm that higher penetration of bioactive molecules from the plants can be enhanced by nanotechnology to develop better hair growth, disease treatment, and beauty therapies.

Nanonail care

Nanonail care is a promising novel cosmetic and health care sector. Nanonail care particles are developed using synthetic particles and show increased protective effects against nail infections. This treatment increases nail glow and toughness in mammals.[43,44] However, the use of synthetic nanoparticles has a decreased market impact compared to natural products. Therefore, the demand of phyto-based nail care products is gradually increasing. Natural, plant-based pigments mostly consist of phytobioactive compounds and have various therapeutic effects. Bioactive compounds from plants are rich in color such as carotene (orange color), chlorophyll (green), and curcumin (yellow), lycopene (reddish orange), anthocyanin (red/purple), and annatto (yellow/orange). These compounds were used in the traditional practices of mixing colored extracts with honey, ghee, or coconut oil for skin and nail care.[117,118] These bioactive compounds have antibacterial, antifungal, antiviral, and antioxidant health enhancing effects. Even though these compounds are used in foods and cosmetics at the macro- or microlevels, the use of the natural pigments at the nanolevel is limited. Recently, asynthetic nanoemulsion was developed with enhanced antifungal activity against nail infections.[119] Turmeric and henna are rich in phytobioactive compounds, and their role in the nail care is well known. However, the role of nanosized turmeric and henna bioactive compounds remains unstudied. Further, during nanosizing, the colors and their effects may enhance or change, which will give future researchers a broad range of the nanonail care cosmetics to study.

Nanolip care

Nanolip cosmetics are another growing nanosector. Currently, various synthetic and metal particles are used at the nanosize for effective lip protection, enhanced color. These products last longer and have a homogenous distribution.[4] The use of nanometal particles enhances the even distribution of pigments over the lips to increase protection. Since lips are most vulnerable skin-type, caution is necessary when using synthetic and metallic nanoparticles. Generally, phytoconstituents are used in the lip care at the macro- and microlevels such as coconut oil, curcumin, and other bioactive compounds that have increased protective activity.[120,121] Recently, plant betalains, a novel dietary-colored indole-derived pigments, were efficiently used in the lip care products and the extraction of those compounds and their encapsulation enhances storage stability[122–124] and applications. *Bixa orellana* was used as a colorant for lip jelly and was found to have higher organoleptic lipstick properties. Similarly, propolis was also used in the development of a novel lipstick. However, the use of nanotechnology in phyto-based lipstick development is still in the budding stage.

Phytoconstituent-based nanodelivery systems in cosmeceuticals for beauty and health care

Limitations of synthetic bioactive ingredients used in cosmeceuticals increase the demand of nanosized phyto-based bioactive ingredients that can be applied by nanodelivery systems.[64,69,80,93] Nanodelivery systems enhance the solubility of the active phytobioactive compounds and penetrate through the skin. Penetration enhancement of active phyto-based ingredients was achieved through suitable nanodelivery techniques that led to increased cosmeceutical effectiveness.[50,51,96,110,125,126] In addition, phyto-based bioactive ingredients solve most skin diseases, and thereby, nanotechnology enhances the therapeutic value of dual role

cosmeceuticals. Further, nanoparticle formulation increases retention of the product on the outer skin layer. Various nanodelivery techniques used in the formulation of cosmeceuticals are of solid lipid nanoparticles, nanostructured lipid carriers, liposomes, phytosomes, nanoemulsions, nanoniosomes, nanocapsules, and nanolipospheres.[4,57,70] Solid lipid nanoparticle-loaded resveratrol showed enhanced permeation in the porcine skin.[127] Similarly, colloidal silica emulsion loaded with quercetin also showed enhanced human skin permeation owing to the nanosizing of the compounds.[128] Even though various nanotechnology systems enhanced deeper penetration of phytocompounds that are currently available in cosmeceuticals, technology usage depends upon the type of bioactive ingredients, such as hydrophilic or hydrophobic, gel or emulsion, size, degradability, and toxicity. In this section, we discuss the type of nanotechnology delivery techniques used for the development of phytobioactive compound-based nanocosmeceuticals.

Solid lipid nanoparticles

Solid lipid nanoparticles are among the nanotechnologies extensively used in both pharmaceuticals and cosmeceuticals.[45,48,49] Commercially, many cosmeceutical companies produce cosmeceuticals using this technology to enhance beauty and therapy. This nanoparticle system developed from microemulsion systems using solid lipids such as stearic acid, cetyl, and palmitic acid along with plant-derived phytocompounds such as flavonoids, phenolic acids, and other active compounds. Solid lipid nanoparticles have advantages in stability, higher production, and long-term storage compared to other conventional and nanodelivery techniques.[44,50,80,110] Solid lipid nanoparticles also boost the cosmeceutical efficiency by enhancing properties that includes hydration, lower uptake of the systemic circulations, therapeutic values, prolonged, and sustained release in the skin and hair. Recently, sesamol-loaded solid lipid nanoparticle was constructed with the particle size of 127 nm for usage in skin cream, which increased the apoptotic nature of the skin.[129] Vitamin A-loaded solid lipid nanoparticles were constructed with the particle size of 200 nm and increased skin moisture retention and skin occlusive effects in porcine skin.[130,131] Similarly, curcumin, another bioactive compound, was constructed using solid lipid nanoparticles with the particle size of 210 nm. This packaging of curcumin showed enhanced activity in hydrogels prepared for inflammation treatment of porcine skin.[132] However, some solid lipid nanoparticles showed a higher particle size with the addition of quercetin, an average of 574 nm. This size can be reduced with the addition of silica, decreasing the average size to 483 nm causing enhanced skin penetration of quercetin with higher photostability and skin protection.[128,133] In another study, caffeine-loaded solid lipid nanoparticles were constructed, with a particle size of 182 nm and enhanced skin permeation of the bioactive compound with higher skin protection.[134] Similarly, resveratrol-loaded solid lipid nanoparticles with a particle size of 180 nm showed higher skin permeation with enhanced protection.[135,136] Lutein-loaded solid lipid nanoparticles with the various nanosizes showed increased skin protection from the UV light and antioxidant activity retention, thereby prolonging skin health.[137] From the earlier research studies, solid lipid nanoparticles made with plant-based bioactive compounds suggest that cosmeceutical efficiency and health benefits are increased. Solid lipid nanoparticles may promote this sector with further development of phyto-based solid lipid nanoparticle formulations with multiple applications in therapy-based nanocosmeceuticals.

Nanostructured lipid carriers

Nanostructured lipid carriers are another important delivery technology used in cosmeceuticals to deliver natural and synthetic bioactive ingredients with increased efficiency.[138–140] This technology has more advantages than other nanotechnologies in bulk production, increased stability of the carriers, and is different from solid lipid nanocarriers with the use of liquid lipids such as oleic acid. In addition, nanostructured lipid carrier has different structures such as imperfect type with different lipid structures, formless type with lipid preventing crystallization, and multiple type with the lipid oil containing bioactive compounds thereby limit the expulsion of bioactive compounds, which is a major drawback in solid lipid nanoparticles. Several phytobioactive compounds are highly used in the preparation of nanostructured lipid carriers with high efficiency in the topical applications, thereby protecting the skin and enhancing beauty. Okonogi and Riangjanapatee[141] recently developed a nanostructured lipid carrier for topical delivery of lycopene with particle size ranging from 150 nm to 160 nm. Similarly, a lutein-nanostructured lipid carrier with particle size of 166–350 nm was constructed and tested for UV protection in the pig ear skin studies. These studies confirm that the lutein nanoparticle formation and their skin protective effects vary with nanocarrier type. Solid lipid nanocarriers showed higher lutein photostability followed by nanostructured lipid carrier and nanoemulsion. Moreover, the stability of all three types of nanocarriers showed better photoprotection of the skin.[137]

In another study, a quercetin-loaded nanostructured lipid carrier was constructed with the particle size of 282 nm and showed enhanced topical delivery of bioactive compounds with higher antioxidant activity. This quercetin product enhances the beauty of the skin from preventing oxidative stress.[138] Similarly, nanostructured lipid carrier was constructed using phenylethyl resorcinol with a particle size of 218 nm and showed enhanced photostability and water stability, which may be applied as a whitening agent in the near future.[142,143] Resveratrol was also constructed using nanostructured lipid carrier systems in the size range of 110 nm and showed enhanced skin protection with higher antioxidant activity, than solid lipid nanoparticle-loaded resveratrol.[144] Further E-resveratrol greatly protects skin through the lipid-based nanoparticle system, under UV radiation.[145] In certain studies, some bioactive compounds, such as squalene, promote drug absorption to the hair follicles, for example, a squalene-enriched nanostructured lipid carrier with a particle size of 208–265 nm is used to treat hair follicles of individuals suffering from alopecia areata.[146] From these recent research studies, we confirm that nanostructured lipid carrier systems will open a gateway for phytobioactive compounds to enhance beauty and personal care.

Nanosingle or multiemulsions

Single or multiple nanoemulsions are currently used in various cosmetic products for their specific application using sizes between 10 nm and 300 nm with enhanced activity.[69,147,148] The major advantages of using nanoemulsions in cosmetics are their unique size, which can enhance the bioactive activity of both hydrophilic and lipophilic types. However, this method has limitations in cosmeceutical production due to instability of emulsions during storage.[149–158] Further, the emulsion core compounds direct whether a single or multiple nanoemulsions can be formed based on their number of core compounds in the nanosized emulsions.[159,160] Multiple emulsions have advantages over single emulsions, due to their wider applications in cosmeceuticals, which can further reduce cosmeceutical cost. Several plant-derived bioactive compounds are used in nanoemulsions, such as flavonoids and polyphenols. Their bioactive role enhances cosmeceutical value with lower toxicity.[161–164] Recently, quercetin-rich nanoemulsions, in the size range of 200–300 nm, were prepared from the ethanolic extract of *Achyrocline satureioides* and showed increased skin retention of bioactive compounds with enhanced antioxidant activities in porcine skin studies.[164] In another study, genistein, a soy bioactive compound, coloaded with tocomin, acts as multiple nanoemulsions with the particle size of 173–208 nm and showed enhanced skin protection from UV damage. This treatment will be useful in the sunscreen lotion production.[165] Similarly, retinyl palmitate was used in the production of nanoemulsions in the size range of <275 nm and showed enhanced skin penetration with increased inner skin protection.[166] Similarly curcumin nanoemulsions were developed using a self-nanoemulsifying method with the mean particle size of 85 nm and showed enhanced transdermal availability with high permeability and without degradation.[71] This might be useful in the skin care sectors for developing novel skin cream emulsions. In another study, lutein was successfully encapsulated into nanoemulsions in the size range of 150–350 nm and increased the release of the active compound compared to other lipid carriers. It showed comparatively better protection than corn oil suspended lutein.[137] Nanoemulsions are highly used in skin-based beauty therapy. *Achyrocline* extract nanoemulsions show enhanced protection against herpes virus infections.[161] Even though these phytocompound-rich single or multiple nanoemulsions showed better protective effects in various cosmeceuticals compared to commercial macroformulations, the stability of nanoemulsions is a big issue in the production and commercialization of these delivery technologies in the cosmeceutical sectors.

Lipid-based nanocapsules

Lipid-based nanocapsules show promising effects in biomedical applications along with cosmeceuticals.[59,167–169] These delivery systems have enhanced effects in the delivery of phytobioactive compounds in oral therapy, which boosts the cosmeceutical sectors for the development of cosmeceuticals with enhanced activity by topical application. However, synthetic compounds are extensively developed using this technique,[170] and phytocompounds used for cosmeceuticals are limited. Recently, resveratrol and curcumin were constructed using lipid core nanocapsules at 201 nm with an increased retention of polyphenols in the skin and increased skin protection.[59] This confirms that coencapsulation enhances the bioavailability compounds in the skin and promotes skin protection against physiological environments. This technology will be potentially useful in the near future of the cosmeceuticals sectors. Similarly, an individual phytocompound of resveratrol was constructed using lipid-derived nanocapsules at 207 nm that enhanced skin protection with higher bioavailability of those bioactive compounds under UV radiation.[145] Chitosan hydrogels combine nanocapsules with the active compounds of capsaicinoids and enhance skin protection by the control release of those compounds.[171–173] The same research group studied the effects of capsaicinoids

in nanocapsules and found greater skin care with sustained release.[172] These studies confirm that phyto-derived bioactive compounds can be used for the construction of nanocapsules to apply in cosmeceutical sectors and beauty therapies.

Nanophytosomes

Phytosomes are another novel technology, particularly for plant polyphenolics, which enhance bioavailability of phyto-bioactive compounds to the skin[5] and in other therapeutic applications[174–177] for skin beauty and health care. The greater advantage of these techniques involves chemical bonding between the polyphenolics and the lipid bilayer and thereby enhances the physical stability of bioactive compounds, which prolong the compound's effectiveness.[178,179] Phytosomes are extensively used in cosmeceutical sectors for their beauty and therapeutic applications with the phyto-derived crude extracts or with the individual bioactive compounds.[179,180] Recently, extracts from the *Citrus auranticum* and *Glycyrrhiza glabra* were used for the construction of phytosomes and for the skin aging studies. The researchers confirmed that phytosomes enhance the bioavailability of those compounds in cream and thereby protect skin from aging.[181] Further, nanosizing of those phytosomes increases the bioavailability of those compounds for beauty and health care applications.[182,183] Gold nanoparticle-bound phytosomes containing phytoextracts rich in quercetin were constructed and had enhanced quercetin efficiency at a particle size of 100 nm.[184] Similarly, rutin-based phytosomes were developed with enhanced compound bioavailability and antioxidant activity.[185]

Nanoliposomes

Liposomes are effective in carrying phytobioactive compounds in cosmeceuticals. Products containing liposomes increase skin protection and beauty qualities.[43,186–189] Generally, nanoliposomes are spherical, have a uni- or multilamellar structures, and are a few nanometers in size. Liposomes have high efficiency in phyto-based compounds delivery to the dermal layer. Nanoliposomes are used in cosmeceutical products such as antiaging cream, sun block cream, hair cream, and skin moisturizer, which contain synthetic as well as phytobioactive compounds.[43,187–189] The major advantages of nanoliposomes are their unique size, they can encapsulate hydrophilic and hydrophobic bioactive compounds, UV absorbing lipids can protect the skin and the bioactive compounds without further degradation.[43,187] Figure 1 shows the possible nanoliposome mechanism in reducing skin wrinkles. Among nanoliposomes that contain phytobioactive compounds, curcumin was studied with enhanced stability and prolonged activity of transdermal application.[190] Recently, curcumin-loaded 80 nm nanoliposomes were constructed and showed skin protection.[191]

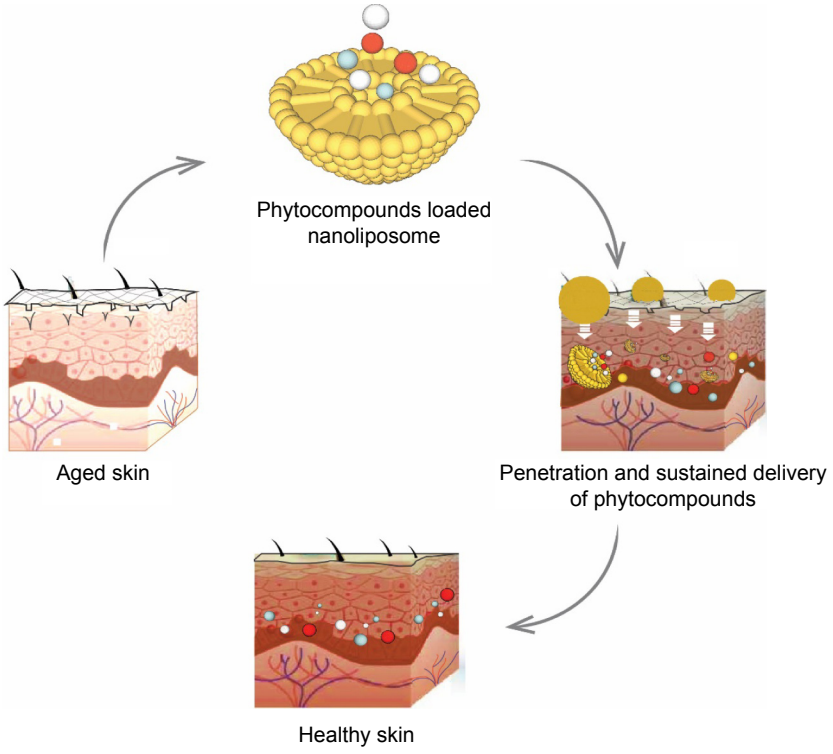

Figure 1 Nanoliposome-based delivery of antioxidants for skin wrinkles in antiaging treatment.

The same research group focused on 110 nm nanoliposome development with long circulating nanoliposomes for skin care and disease treatment.[192] The combination of curcumin with hyaluronic acid enhances the bioavailability of curcumin in the skin and body, which leads to many novel nanoapproaches for the skin-based nanotherapautics and beauty.[193] Even though several phytocompound-encapsulated liposome technologies are used in cosmeceuticals and therapy, the nanosize of liposomes is still in the budding stages with the active phyto-derived compounds. Phytocompound-encapsulated liposomes will be an innovative technology in the near future for application in therapy-based beauty.

Nanoniosomes

Niosomes are extensively used in cosmeceutical sectors since it has multiple advantages over liposomes such as higher stability, enhanced skin penetration, low toxicity, and higher protection of the bioactive compounds.[194–196] Niosome sizes vary from nanometer to micrometer, the lower the size greater the efficiency. Nanoniosomes are smaller, unilamellar structures in the size range of 10–100 nm.[197–200] Niosomes are extensively used to deliver antioxidants such as ascorbic acid, resveratrol, and ellagic acid through skin and are used orally to treat diseases.[196,201–207] Even though commercially many cosmeceutical creams and lotions contain niosomes with synthetic compounds, phyto-derived bioactive compound usage is a new sector in the development of nanoniosomes. Recently, Tavano et al[202] produced a slightly larger niosome in the size range of 471–565 nm containing phyto-derived antioxidants such as resveratrol, alpha-tocopherol, and curcumin. This product showed enhanced antioxidant activity to the skin with increased skin permeation activity for cosmeceutical applications. This study confirmed that phyto-derived compounds can be effectively used in noisome formulation for cosmeceutical applications without change in bioactivity and enhanced skin protection. However, the size is a big factor, and reduction to nanosize with alteration in production methods may enhance their activity with a broad range of applications in cosmeceutical sectors. Recently, individual phytocompounds, such as curcumin, were developed using nanoniosome methods in the size range of 91 nm and showed enhanced skin protective activity.[208–215] From the earlier studies, phytocompound-containing nanoniosomes may be useful for both cosmeceuticals and pharmaceutical sectors.

Nanoethosomes, glycerosomes, and hyalurosomes

Ethosome, glycerosomes, and hyalurosomes are modified liposomes, named based on their compounds used in the phospholipids, such as ethanol, glycerol, or sodium hyaluronate. They are modified for the enhanced delivery of the active ingredients to the skin and exclusively used in cosmeceutical sectors for their therapy and beauty treatments.[216,217] Further, nanosizing of vesicles with incorporation of phytocompounds showed enhanced protective and beauty activity.[218–221] Recently, quercetin glycerosomes were developed in the size range of 80–110 nm with a unilamellar structure and showed enhanced skin protective activity.[222] This may be used in the future for the production of antioxidant skin cream. Ethosomes nanovesicles in the size range of 128 nm were prepared with polyphenolic extracts of *Fraxinus angustifolia* leaf and bark and showed enhanced wound healing and skin protection activity.[223] Similar to the ethosomes, nanosized hyalurosomes of liquorice extract were prepared in the size range of 100 nm and enhanced skin beauty.[224] The same research group also developed curcumin-based nanohyalurosomes with a minimal particle size of 112 nm and showed enhanced skin beauty-based therapy.[193] From these studies, extracts can be used to develop nanovesicles, which could be efficiently used in the cosmeceutical sector, and it will give a broader scope of research and development for cosmeceutical products with multiple efficiencies.

Fullerene

Fullerene is yet another novel technology made of carbon atoms of 1 nm size, consisting of even numbers known as C60, which is used in the cosmeceutical sectors to carry phytocompounds. Fullerene itself acts as an antioxidant and prevents premature skin aging.[225–229] Fullerene delivers vitamins to effectively enhance the skin. Recently, some researchers developed a fullerene nanocapsule with ascorbic acid and vitamin E. It showed enhanced skin protective activity against premature aging by its antioxidant activities.[230,231] Further, skin protection was also enhanced by the fullerenes with some modifications.[232–234] Fullerene-based photodynamic therapy was used for skin-based disease treatment with the bioactive compounds, such as curcumin.[235,236] However, further study on the application of various phyto-derived bioactive compounds with fullerenes in cosmeceutical-based skin therapy has yet to be carried out. This will give way for the development of the new cosmeceutical products with better protective activity by the carrier and bioactive compounds.

Carbon nanotubes

Carbon nanotubes are a novel technology currently used in the cosmeceutical sectors particularly for the skin care. Similar to fullerene, carbon nanotubes alone act as an antioxidant at 100 nm in size.[237,238] In addition to their uses in

cosmeceutical sectors, they are effective in delivery systems for phytocompounds in biomedical applications.[226,239,240] Recently, curcumin was conjugated to a single wall carbon nanotube for the effective delivery.[241] The role of hyaluronic acids in the delivery of drugs using carbon nanotubes was reviewed recently,[242] and further clinical trials are needed to assess their biosafety. However, a study on the application of carbon nanotubes with phytocompounds in skin care and cosmeceuticals is yet to be done.

Phytoconstituents in nanosize cosmeceuticals and skin therapy

Nanosize phytoconstituents are gaining popularity among the active ingredients in the cosmeceuticals, as they enhance beauty and have therapeutic roles in diseases such as antiaging, UV protection, and prevention of skin-related diseases.[190,243–246] Increased skin protective activity of bioactive compounds is related to polyphenol content along with their reduced size. Compounds vary from macro to nano and with skin penetration using different delivery techniques.[193,247–251] Recently, resveratrol encapsulated in the solid lipid nanoparticle showed enhanced skin uptake with increased protection and antioxidant activity.[144] Solid lipid nanoparticles were compared nanostructured lipid carrier systems and found similar efficiencies with increased retention in the skin. Nanodelivery technologies also enhance the compound bioavailability not only to the skin but also to the brain to treat disorders such as Parkinson's disease.[252] Further modification of bioactive compounds along with the nanodelivery technologies can enhance skin bioavailability to increase protection.[145] Similarly, quercetin encapsulated into a solid lipid nanoparticle system showed increased skin retention of quercetin with greater antioxidant activity.[138,253,254] Genistein-loaded nanoemulsions were incorporated into hydrogels in the size range of 250 nm and enhanced delivery of the bioactive compound to the skin for a beauty-based therapy. In addition, coencapsulation of resveratrol and curcumin with lipid core nanocapsules increased delivery of the resveratrol to the skin.[59] Further, several other phytobioactive compounds were efficiently encapsulated into various nanodelivery systems to enhance beauty and therapy applications. Specific compounds, their skin protecting activity, and beauty applications are discussed in the following sections. Some of the nanophytobioactive compounds and its role in beauty and skin therapy are listed in Table 1.

Nano Aloe vera

Aloe vera consists of several active constituents such as proteins, minerals, carbohydrates, and vitamins from the inner portions of the leaf, which are widely used in the skin care and the medicine.[255–259] Aloe gel greatly enhances moisturizing activity and antiaging by enhancing the synthesis of collagen and elastin fibers. In addition, it also helps in the wound healing.[257–263] The higher moisture, bioactive compound, and mineral content of aloe gel enhance the moisturizing effects and skin protection. Therefore, aloe is often used in cosmetic products such as creams, lotions, and gels.[189,264,265] However, for their enhanced bioactivity of the aloe compounds, nanodelivery techniques are recently used in the cosmeceutical sections. Further, the use of nanosize *A. vera* in the preparation of cosmeceutical products is now in early stages. Few nanotechniques enhanced skin care activities. *A. vera* gel extract liposomes were constructed, with the particle size of 200 nm, that enhanced skin collagen synthesis and growth of skin cell lines, which confirm that it may be used to enhance skin care products.[189] Similarly, some researchers patented nanoemulsion technology varying the nanosize containing *A. vera* extract. The resulting product caused skin rejuvenation and had antiwrinkle activity. In addition, coencapsulation of *A. vera* with curcumin enhances phytocompound delivery to the skin and protects antioxidant activity.[266] From the earlier studies, nanosizing bioactive compounds from *A. vera* enhances beauty applications. Further development of various nanodelivery techniques is a good research opportunity.

Nanocurcumin

Curcumin is the active compound in turmeric, which is native to India and other Asian countries. Turmeric is widely used in cooking, medicine, beauty, and health products.[267–273] Turmeric as a crude extract or tuber powder normally used for skin care among South Indian women in their daily routine owing to its multibeneficial activities such as antiaging, moisture retention, antioxidant activity, and natural beauty products with yellow pigments.[274–281] Although turmeric has multiple beneficial activities, its bright yellow color and instability under certain environmental conditions make researchers look for alternative delivery technologies for skin care and beauty applications. Nanodelivery techniques such as solid lipid nanocarriers, nanoliposomes, nanoniosomes, and nanoemulsions solve most of their difficulties with turmeric and enhance the bioavailability of its polyphenolic compounds in cosmeceutical product.[4,43,44] Curcumin nanotransfersomes, nanoethosomes, and nanoliposomes were prepared and studied for the skin hydration and UV protection activity. Three nanodelivery technologies enhanced the delivery of curcumin to the skin with greater hydration and UV protective in cream containing the nanoformulations.

Table 1 Nanosized phytocompounds used in cosmeceuticals

S no	Phytocompounds	Nanodelivery methods	Size (nm)	Applications	References
1	Rice bran oil	Nanoemulsion	69	Moisturizers Antiaging Skin care Skin care	Bernardi et al[69]
2	Rice bran and raspberry seed oil	Lipid nanocarriers		Sunscreens	Niculae et al[95]
3	Lavender extracts	Polymeric poly(lactic-*co*-glycolic) acid (PLGA) nanoparticle	301–303	Antiaging Antioxidant	Pereira et al[350]
4	Rosemary extracts	Solid lipid nanocarriers Nanostructured lipid carriers	57 68	Antioxidant (skin) Antioxidant	Lacatusu et al[351]
5	*Aloe vera* extract	Nanoliposome	200	Skin care	Takahashi et al[189]
6	Saflower extracts	Nanostructured lipid carriers	100	Hair care	Kumar et al[352]
7	Lutein	Nanostructured lipid carriers and nanoemulsion	150–350	Skin care	Mitri et al[137]
8	Quercetin	Nanostructured lipid carriers	215	Skin care	Guo et al[353]
9	Ganoderma triterpenoids	Nanostructured lipid carriers – gel	179	Skin enhancement	Shen et al[354]
10	Hinokitiol	Poly(epsilon-caprolacton) nanocapsules	223	Hair care	Hwang and Kim[355]
11	Hinokital	Bilayer vesicles		Hair growth	Yang et al[356]
12	Curcumin	Nanoencapsulation	190 and 276	Skin care	Suwannateep et al[357]
13	Tocopherol	Nanostructured lipid carriers (NLCs) and nanoemulsion (NE)	67 and 576	Skin care	Abla and Banga[358]
14	Resveratrol	Solid lipid nanoparticles versus nanostructured lipid carriers	287.2 and 110.5	Skin care	Gokce et al[144]
15	Resveratrol	Niosomes	299	Skin care	Pando et al[196]
16	Resveratrol and curcumin	Lipid care nanocapsules	202–209	Skin care	Friedrich et al[59]
17	Resveratrol, alpha-tocopherol, and curcumin	Niosomes	471–565	Skin care	Tavano et al[204]
18	D-Limonene	Nanoemulsions	54	Skin care	Lu et al[359]
19	Aqueous propolis and lycopene	Nanoemulsions	NA	Skin care	Butnariu and Giuchici[360]
20	Lycopene	Transfersomes Ethosomes	124 154	Skin care Skin care	Ascenso et al[208] Ascenso et al[208]

Abbreviation: NA, not available.

Greater efficiency among the nanodelivery techniques was observed in the order of nanotransfersomes having the most efficiency, nanoethosomes and nanoliposomes having the least. They also varied in size from 167 nm to 262 nm.[219] In another study, curcumin nanoethosomes were prepared with particle sizes of 216 nm and enhanced antiwrinkle properties. Further, skin permeation of the curcumin-loaded nanoliposome with particle sizes of 82–92 nm showed higher skin protection.[191] Similarly, nanohyaluronosomes with particle sizes of 112–220 nm enhanced curcumin bioavailability to the skin and will potentially be used for beauty-based therapies in near future.[193] Similarly, curcumin-loaded niosomes were prepared with enhanced bioavailability in the skin.[282] In addition to the individual compounds, coadministration of curcumin with resveratrol in the lipid core nanocapsules increased delivery of the phytocompounds to the skin with better antioxidant potential and skin care.[59] Likewise, codelivery of curcumin with resveratrol in the nanosized niosomal formulations enhanced skin beauty with increased antioxidant activity.[202]

Nanovitamin E

Vitamin E is heat stable fat soluble compound most commonly used in cosmeceuticals for skin protection properties such as antiwrinkle, enhanced skin moisturizing, and prevention of skin disease.[283] Since most cosmeceutical products contain the precursor of active tocopherol and its cleavage products in the skin is minimal, which leads to a decrease in skin protection. Even though vitamin E is naturally present in human skin, most of it is not active due to prolonged solar irradiation. Nanodelivery techniques solve issues with sufficient delivery along with prolonged and sustained release of vitamin E associated with enhanced beauty. Vitamin E nanoemulsion was prepared using nanoemulsion techniques and enhanced bioavailability of the vitamin compared to microsized emulsions.[284] Vitamin E was also prepared using

solid lipid nanoparticle delivery systems with size equivalent to 292 nm and enhanced skin protection activity. Further, solid lipid nanoparticle vitamin E preparation enhanced vitamin E delivery for cosmeceutical-based skin therapy.[285–290] Teo et al[291] reported that vitamin E-enriched palm oil nanoemulsions with particle sizes of 94 nm enhanced product stability and may be useful for their novel nanosized cosmeceuticals. In near future, vitamin E will be delivered with suitable nanodelivery technologies in therapy-based cosmeceuticals for enhanced activity, stability, and beauty care.

Nanovitamin C

Vitamin C is a vitamin abundant in plants and has multiple roles in the beauty and health care, involving collagen synthesis.[292,293] Vitamin C readily undergoes degradation when exposed to harsh environments and UV radiation. A continuous supply of vitamin C compounds enhances the skin's beauty. Nanodelivery techniques help sustain vitamin C supplementation without changes in its biological activity after applying to the skin. Recently, several nanotechnological approaches have been published using vitamin C for skin health and beauty, such as solid lipid nanoparticles and nanostructured lipid carriers.[294] Vitamin C-encapsulated solid lipid nanoparticle was prepared with a particle size of 200–225 nm. Solid lipid nanoparticle enhanced the carrier of the vitamin against apoptotic effects.[295] Similarly, nanoliposomes were constructed using vitamin C that enhanced skin permeation activities with different particle sizes, ranging from 66 nm to 130 nm.[296] In addition, vitamin C nanoliposomes had enhanced stability and higher antioxidant activity compared to ordinary liposomes after 60 days of storage.[297] In another study, a vitamin C and gold-loaded nanofiber mask were prepared for the effective delivery of vitamins to the face. The liposomal preparation delivery of vitamins through mask enhanced facial beauty.[298] Therefore, vitamin C can be delivered to the skin using nanodelivery technologies for enhanced skin beauty-based therapies.

Nanoresveratrol

Resveratrol is another polyphenolic compound with multiple beneficial roles in quenching free radicals and protecting skin against harmful environmental conditions.[299] Polyphenolic compounds inhibit oxidative mechanisms and UV-induced radiation. They are widely used in functional foods for skin care and health.[56,300–304] In comparison to other antioxidants, resveratrol shows higher efficiency of skin protection against UV-B radiation.[305,306] However, resveratrol stability and beauty effects are limited due to compound degradation under harsh environmental conditions. To overcome this, nanodelivery techniques such as solid lipid nanoparticles, nanoemulsions, and transfersomes showed enhanced resveratrol stability and delivery to the skin.[136,307,308] Recently, microemulsions were constructed using resveratrol with particle sizes of 66–68 nm that enhanced resveratrol bioavailability to the skin to protect against UV radiation.[309] Recently, three different nanodelivery techniques, such as solid lipid nanocarrier, nanostructured lipid carrier, and nanoemulsions, were studied for resveratrol delivery efficiency to the skin. Among them, the solid lipid nanocarrier preparation has the most enhanced resveratrol delivery to the skin.[310] Analyzing resveratrol nanodelivery studies, we conclude resveratrol may be highly protective through nanodelivery techniques and may be used in the preparation of natural nanocosmeceutical products to enhance beauty.

Nanoquercetin

Quercetin is another phytoactive flavonoid compound having efficiency in multiple aspects such as skin care and beauty through antioxidant activities; thereby, it enhances skin beauty and personal care.[311–314] In comparison to other flavonoids, quercetin showed higher skin protecting efficiency and enhanced beauty due to its abundance of OH groups. This leads many researchers to analyze the multiple efficiencies of quercetin in cosmetics. However, the major drawback of quercetin applications is its stability and penetrating efficiency, which is solved by nanodelivery techniques. Solid lipid nanoparticle and nanostructured lipid carrier nanodelivery systems were compared for the effective delivery of the quercetin to the skin. The nanostructured lipid carrier showed higher quercetin retention in the skin membrane with a particle size of ~282 nm.[138] The same research group also suggests that quercetin in the solid lipid nanoparticle preparation has increased skin protection against UV radiation of human skin.[253] Nanoglycerosomes were also prepared with particle sizes between 80 nm and 110 nm that enhanced skin delivery of quercetin along with its photoprotective effects against oxidative damage.[222] Similarly, quercetin-rich nanoemulsions and *A. satureioides* nanoemulsions were prepared with nanoparticles ranging from 200 nm to 300 nm. This preparation had higher skin retention of the phytocompounds with increased skin protecting activity.[164] In another study, quercetin-loaded nanocapsules were constructed with a particle size of 228 nm for sustained delivery of quercetin to the skin to increase antioxidant activity.[315] From these studies, we conclude that quercetin may be used in the preparation of various nanosized cosmeceuticals products with increased

stability, prolonged beautifying effects, and without harmful side effects.

Nanogreen tea

Natural green tea extract is rich source of bioactive compounds, such as catechin, epigallectocatechin, epicatechin, and epigallecto-3-catechin, which are powerful antioxidants widely used in skin care and beauty treatments.[316–320] The individual potential of these compounds also varies in usage for development of cosmeceutical products. Green tea components have multiple skin care roles such as antiaging and prevention of UV-induced photoaging.[316,320–323] The bioactive compounds readily undergo functional group loss during the exposure to environmental conditions and decrease the stability of the compounds, which limits the application of these compounds in cosmeceutical products. Nanodelivery techniques enhance the bioavailability of these compounds in cosmeceutical products, thereby enhancing their usage in the novel development of green tea-based cosmeceuticals. Recently, Montenegro[324] listed group of phytocompounds usage in commercial products. Among them, green tea catechins were used in antiaging cream preparation with fullerene as the delivery agent. Fang et al[325] also prepared green tea catechin liposomes with nanoparticle sizes of 130–268 nm that enhanced antioxidant activity in the skin. In another study, green tea liposomes, with a reduced particle size of ~138 nm, enhanced green tea catechins by ethanol incorporation into the liposomes for enhanced transdermal delivery.[326] Similarly, green tea polyphenol nanoliposomes were developed using milk fat globule membranes and soy lipids to enhance antioxidant activity in the cell model.[327] These studies suggest that green tea polyphenols can be sufficiently nanodelivered to various skin care products for their sustained beautifying effects.

Nanogenistein

Genistein is one of the major isoflavones found in many cereal plants and has skin protecting activities, including antioxidant, collagen synthesis, UV protection, and antiaging benefits.[328–333] Even though genistein has skin protecting activity and enhances beauty, its sustained effect is still limited due to lower stability in cosmeceutical products. In order to enhance stability and prolong activity, nanosized delivery technologies have greater impact in cosmeceutical sectors. Genistein-loaded nanoemulsions were prepared with 250 nm sized nanoparticles and enhanced delivery of isoflavones to the skin with higher skin protecting activity.[334] In another study, nanosized liposome-encapsulated genistein in nanoparticles the size of 84 nm was tested on rat skin, with or without hair.[335] In addition to the nanosized liposomes, the hairs on the skin also affect the delivery of the genistein compound to the skin.

Nanolycopene

Lycopene is another natural phytobioactive compound with multiple applications in skin care, including antiaging and antioxidant activity.[336–345] Owing to its lipophilic nature and decreased delivery to the skin, lycopene is of limited usage in skin care products. In addition to its lipophilic nature, lycopene readily undergoes degradation during light and air exposure, which further limits its usage in cosmeceuticals. However, nanosizing lycopene solves most of these problems and enhances its bioavailability.[141,346,347] Recently, lycopene ethosomes and transfersomes were constructed in the nanosize of 153 nm and 124 nm, respectively, which enhance the bioavailability lycopene to the skin with potential antioxidant activity. Further, it enhances the penetration of lycopene to the inner cell and nucleus, which could be useful in skin protection and care.[348] Research focusing on nanodelivery in cosmeceutical products containing lycopene is still limited.

Nanotoxicity

The major concern of using nanocosmeceuticals is toxicity owing to the small size, allowing the particles to cross the membrane easily and interact with other proteins and cells. This may lead to the other effects by their subsequent metabolic products.[349] Before applying the products, extensive clinical screening must be done, even though many reports suggest that polymers in cosmeceuticals have no deleterious effects. Further, natural products have no side effects. Extensive use of these compounds may also lead to side effects. Further clinical support is needed before nanotechnology proceeds to commercialization and product development.

Conclusion

The greater demand of the nanosized phyto-based bioactive compound usage in the development of nanocosmeceuticals for skincare-based therapy such as moisturizing, sun block, anti-aging, whitening effects along with skin health leads many researchers in search of novel nanocosemecutical-based therapy. Nanosized cosmeceuticals with phyto-based bioactive compounds retain higher amounts of bioactive compounds in the skin, are more stable, and enhance skin appeal with prolong time. Nanosized compounds range in size. Increasing the nanosize limits the penetration ability of

bioactive compounds to the skin, which limits beautifying and therapeutic activities. The solubility types and the cosmeceutical application of phyto-based bioactive compounds determine the delivery technology for nanocosmeceutical development. Further research of their mechanisms is necessary to target site release from the delivery agents. This further boosts nanosized phytobioactive compound-based cosmeceutical research and skin health.

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Disclosure

The authors report no conflicts of interest in this work.

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