The role of bioactive phytoconstituents-loaded nanoemulsions for skin improvement: a review

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ABSTRACT
As the largest organ in the human body, the skin should be protected from various harmful chemicals and pollutants from the surrounding environment and ultraviolet (UVA/UVB) radiation emitted from sunlight. This has prompted formulation scientists to embark on new technology to formulate cosmetics free of synthetic chemicals using natural plant-based extracts as the replacement. Natural phytoanti-oxidants, viz. catechin, quercetin and gallic acid, are polyphenols whose therapeutic values (antioxidative, antityrosinase, antiviral and antimicrobial) are underutilized. Plant-based nanoemulsions offer an efficient and safe topical delivery system for improving the skin and regenerative treatment. The bioavailability of the phytoanti-oxidants for molecular-level skin repair is enhanced by better permeation of the nanoemulsions’ nano-sized particles through the stratum corneum. This review highlights several phytoconstituent-containing nanoemulsions and their bioactivities for cosmetic applications. The mechanisms of skin improvement for anti-aging skin are also presented in detail. In short, nanoemulsion technology is a powerful tool for an effective topical delivery system of potent skin-protecting and rejuvenating plant-based extracts. With increasing demand from consumers worldwide for nano-formulated phytohormones or phytoextractives, nanoemulsions will see a new dimension with better future prospects.

Introduction
The skin is the largest organ of the human body whose proper function is to protect against external factors, for instance, invading microorganisms, temperature, ultra-violet (UV) rays, and preventing our body from water and electrolyte loss. This organ contributes to approximately 16% of the total human body weight, which is the equivalent of 9 kg and covers a surface area of 1.8 m\textsuperscript{2} \cite{1–3}. The outermost layer of the skin structure is the stratum corneum, a crucial and formidable barrier to be overcome by any topical or transdermal applications due to the complicated physiology of the human skin. The densely packed lipid mortar and protein bricks in the stratum corneum acts as the primary barrier limiting the permeability of active ingredients or drugs \cite{4}. The human skin undergoes several changes when exposed to the sun, including the formation of wrinkles, alongside the physiological and appearance of skin layers associated with skin aging \cite{5,6}. Therefore, any damage to the skin barrier function is manifested by a change in the stratum corneum integrity followed by an increase in transepidermal water loss and decreased skin hydration \cite{7,8}. The stratum corneum of the human skin is illustrated in Figure 1.

The human skin has three layers, viz. epidermis, dermis and hypodermis (Figure 1), with each layer differing in 1.5 mm thickness. The epidermis comprises the stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum and stratum basale. Keratinocytes and melanocytes are largely produced in this outer layer, responsible for protecting skin against UV rays, microorganisms, air and chemical pollutants. While collagens, elastic fibers, sweat glands, hair follicles, connective tissues, touch receptors, blood capillaries exist in the dermis. The hypodermis is the last layer of skin structure, primarily constructed of areolar and adipose tissues and large blood vessels \cite{9,10}. Noteworthily, skin pigmentation/hyperpigmentation is one of the aging processes occurring at the epidermis layer caused by UV-induced radiation. Excessive melanin is produced by melanocytes in melanosomes during melanogenesis in response to UV
exposure. The melanosomes are then transported to the keratinocytes around the melanocytes. Likewise, elastin and collagen degradation in the dermis cause wrinkles and skin elasticity loss [11]. Hence, sun protection, skin repair treatment, and rejuvenation are carried out at the skin's epidermis layer to avoid this circumstance [12].

There are treatments by which the human skin can be regenerated, and the current trend in cosmeceutical products has seen nano-sized emulsions playing a larger role in this industry. Nanotechnology is a science that manipulates and reduces materials to the nanometer scale (1–100 nm), bringing about new properties that can regulate the different aspects that control the diffusion of ingredients through the skin [13]. The colloidal dispersion system in a nanoemulsion consists of oil, water, and surfactant. The >500 nm mean droplet size of the particles can augment the dermal and transdermal effectiveness of the incorporated bioactive ingredients [14,15]. Two categories of nanoemulsions exist: the ‘water-based’ (O/W) and the oil-based (W/O). The former has water as the continuous phase and oil as the dispersed phase, whereas the phases are inverted in the latter’s colloidal dispersion system [16]. Figure 2 represents the basic structures of (a) water-in-oil (W/O) and (b) oil-in-water (O/W) nanoemulsions,
comprising of oil, water and surfactant as the major compositions. The water-in-oil depicts the formation of nano-sized water droplets in which the hydrophilic head of the surfactant orientates towards the water, and the hydrophobic tail faces the oil. Contrariwise, the o/w system arranges the hydrophobic tail towards the oil droplets and the hydrophilic head to water [17]. More complex dispersion systems include double nanoemulsion systems (oil-water-oil or water-oil-water) [18]. The above-said colloid systems exist by emulsification with a specific hydrophilic-lipophilic balance (HLB) value. In this respect, surfactants are prudently selected to avert physical instability in these nano-systems. Surfactants and sometimes co-surfactants used during the nano emulsification step are mostly non-ionic. The rule of thumb, surfactants of a final HLB value between 4–6 are ideal for preparing W/O nanoemulsions, whereas a higher HLB value (8-16) is suitable for oil-in-water systems.

Colloidal nano-formulations can be prepared via low energy and high energy methods where the latter requires significant energy input to break the larger particles into nano-sized droplets [20]. Examples of the high energy methods viz. ultrasonication, microfluidization, and high-pressure homogenization depend on mechanical devices such as ultrasoundators, microfluidizer, and high-pressure homogenizers for disruptive forces to obtain the smallest particles size in the system. High energy is also required to initiate the stress level to exceed the Laplace pressure with pressures between 10–100 atm to transform microemulsions to nanoemulsions. This outcome is achieved by rupturing the droplets [21]. Conversely, low energy nano-emulsification methods through spontaneous emulsification, phase inversion composition and phase inversion do not involve mechanical forces to break down the droplets [22]. Pertinently, transforming the microemulsion system to nano ones greatly improves the bioavailability of active ingredients to the targeted cells and facilitates their diffusion through the skin [23,24]. This is due to the uniform deposition of the active ingredients and their better permeability or penetration through the skin surface [25]. Nanoemulsions are also described to be exceptionally stable against colloidal destabilizing factors, for instance, sedimentation, flocculation, coalescence or creaming [26,27].

Plant extracts from seeds, flowers, leaves, roots, and fruits were popular beauty ingredients in China and Egypt during ancient times [28]. The use of plant-based bioactive compounds in topical skincare products is considered far more efficient, safe and cost-effective than synthetic ones [29]. Plants are rich in valuable secondary metabolites, namely, phenolic acids, flavonoids, polyphenols, terpenoids and amino acids, all of which are well-known UV blockers or UV filters skincare products [30]. Conversely, synthetic chemicals, such as preservatives and fragrances, may be detrimental to human health, possibly triggering severe side effects, including cancer, mutation, reproductive toxicity and endocrine disruption [31]. Plant-based bioactive compounds’ bioavailability to target areas can be boosted by topical application assisted by nanotechnology-based carriers or simply called nano-carriers. The minute droplet topical delivery systems (TDS) encapsulate the active plant ingredients with low water or lipid solubility. The system also simultaneously protects the components from physical and chemical degradation, enable their controlled and sustained release at the target site.

Moreover, product skin spreadability is also improved by nano-carriers, making the cosmetic formulations more enjoyable, thus enhancing public adherence [32]. The TDS circumvent issues with the product’s administration, including drastic pH changes, deleterious presence of food and enzymes, and the liver’s first-pass effect. TDS is also non-invasive and suitable for needle phobes and can be self-administered with minimal side effects. However, TDS is less apt for delivering large hydrophilic molecules due to the very low skin permeation rates of the system. The continuous stratum corneum (the outer layer of skin) poses a significant challenge for the active ingredients to penetrate deeper into the skin layers [33].

Phytobased cosmeceuticals are set to play a highly significant role in the near future in enhancing protection and skin beauty, as well as other health benefits. The safety of over-the-counter cosmeceuticals is often dubious since most are without any commercial approval. The increasing awareness among consumers has seen a higher preference for plant-based cosmeceuticals since the ingredients are generally accepted as safe. In this regard, this review focuses on several plant phytochemicals and their bioactivities for topical applications. The selection of plant-based bioactive compounds in nanoemulsions used in clinical skin improvement studies, and their mechanisms of action for skin repair, namely for melanogenesis, collagenesis and anti-aging through the anti-oxidant process, are also discussed.

Plant-based bioactive compounds in cosmeceuticals for skin therapies

Cosmeceuticals are a niche of cosmetic products in which active ingredients impart their cosmetic benefits, evidence therapeutic effects capable of changing skin
function and structure. Cosmeceuticals are basically functionalized cosmetics with beauty and health applications [32,34]. On the other hand, cosmetics are products used to care for and clean the human skin, to make it more attractive and beautiful, and promote well-being without affecting body organs and parts or functions [31,35]. Plant-based bioactive compounds are highly sought-after active ingredients in the cosmeceuticals industry due to their therapeutic effects, such as moisturizing, rejuvenating, anti-aging, UV protection and prevention of skin-related diseases. Natural bioactive plant compounds are preferable for being eco-friendly and compatible with different skin types, without the artificial aspects of synthetic chemical ingredients that often cause skin irritation [32,36]. Several types of nano-carrier systems such as nanoemulsion, liposomes, solid lipid nanoparticles, hydrogels, dendrimers and smaller-sized nanoparticles have been developed to deliver plant-based bioactive compounds in cosmetics products [10,37]. Some of the plant-based bioactive compounds and their association with bioactivities for skin repair or improvement are listed in Table 1. Figure 3 illustrates the structures of several popular plant-based bioactive compounds.

**Quercetin**

Quercetin (C_{15}H_{10}O_{7}) is a well-known plant pigment and polyphenolic flavonoid found in leafy vegetables, citrus fruits, berries, rich in anti-oxidants [48]. Chemically, quercetin features a catechol B-ring and three additional hydroxyls on carbons 3, 5 and 7. Previous studies had demonstrated that the anti-oxidative property of quercetin is enhanced by higher concentrations of hydroxyl groups in conjunction with the adjacent hydroxyl groups in a benzene ring-C, which forms a resonance stabilized quinone structure. It is the third most active flavonoid after epicatechin gallate and epigallocatechin gallate [49]. Generally, quercetin exhibits anti-inflammatory action by reducing edema, leukocyte formation and irritation and helps tissue regeneration by promoting new collagen fibers and producing ground substances for skin restoration [50,51]. Also, quercetin inhibits various inflammatory mediators such as interleukins (IL), prostaglandins (PGs), produced by COX, LOX, LPS. Quercetin is responsible for reducing the expression of matrix metalloproteinase-1, which is vital for skin wrinkling and loss of elasticity in healthy and photoaged skin, at both the mRNA and protein levels [52]. Basically, quercetin partakes in inhibiting all the mediators, which leads to oxidative stress, thus producing the anti-oxidant effect [53] and inhibits the secretion of the mast cell, which contributes to the anti-allergic effect of the compound [54].

Despite this, quercetin has poor water solubility and low skin permeability, which somewhat hinder its use in cosmetics products. Notwithstanding the low bioavailability of quercetin, it produces several therapeutic benefits and constitutes an essential intermediary of its bio-actives [48]. The issue can be overcome by formulating quercetin in nano-carriers, i.e. nanoemulsions, to improve bioavailability. Fasolo et al. [42] formulated an O/W topical nanoemulsion containing quercetin extracted from *Achyrocline satureioides* Lam D.C. The low solubility of lipophilic quercetin was circumvented through an O/W nanoemulsion, as confirmed by the higher quercetin recovery. The spontaneously emulsified quercetin nanoformulation demonstrated excellent antiviral activity, reduced the infectivity of herpes simplex virus type-1 and the intracellular virus replication. The nanoemulsion showed sizes lower than 200 nm, with flavonoid contents recovery at 0.991 ± 0.006 at the skin extracts [38,42] performed a similar experiment for topical nanoemulsions containing flavonoids, namely quercetin, luteolin, and 3-O-methylquercetin extracted via maceration of the *A. satureioides* extract. The nanoemulsion was formulated by spontaneous emulsification in which medium chain triglycerides

| Bioactive compounds | Plant origin | Particle size (PDI) | Bioactivities | References |
|---------------------|--------------|--------------------|--------------|------------|
| Quercetin           | *Achyrocline satureioides* | 237.35 nm (0.09) | Anti-herpes activity evaluation | [38] |
| Catechin            | *Phyllanthus emblica* L. | 191.63 nm (0.20) | Anti-oxidant, anti-melanogenesis, anti-aging and anti-inflammatory | [39] |
| Gallic acid         | *Tamarindus indica* L. | 130 nm (<0.20) | Anti-oxidant, anti-tyrosinase, anti-bacterial | [40] |
| Gallic acid         | *Punica granatum* | 169 nm (0.12) | Anti-oxidant activity against UV radiation | [41] |
| Quercetin           | *Achyrocline satureioides* | 200–300 nm | Antiviral activity against herpes virus | [42] |
| Catechin            | *Eugenia dysenterica* | 27.0 nm (0.14) | Antioxidant activity | [43] |
| Kaempferol          | *Equisetum arvense* | <100 nm | DPPH free radical scavenging activity | [44] |
| Curcumin            | *Curcuma longa* | 10.57 nm (0.094) | Anti-psoriatic activity | [45] |
| Curcumin            | *Curcuma longa* | 84.032 nm | Wound healing property | [46] |
| Resveratrol         | – | 66–68 nm | Antioxidant activity against UV radiation | [36] |
| Lycopene            | *Solanum lycopersicum* | – | Antioxidant activity against UV radiation | [47] |
Figure 3. Structures of plant-based bioactive compounds (a) catechin, (b) quercetin, (c) gallic acid (d) kaempferol, (e) gallocatechin, (f) epicatechin, (g) epigallocatechin, (h) catechin gallate, (i) gallocatechin gallate, (j) epicatechin gallate, (k) epigallocatechin gallate, (l) curcumin, (m) resveratrol and (n) lycopene
catechins are a group of flavan-3-ols from the flavonoid family. The name is derived from ‘catechu’ from the extract of *Acacia catechu* L., which is a 3,3′,4′,5,7-pentahydroxyflavan having two steric forms of (+)-catechin and (−)-catechin. Catechins and the analogs endowed galloyl moiety such as propyl gallate have significantly demonstrated exceptionally high inhibition capacity of free radicals. Researchers have identified and confirmed that the galloyl moiety of green tea catechins is the critical structural feature for any given bioactivities. Catechins are commonplace compounds in an array of herbs and foods, including apples, cacaos, tea, grapes, berries and persimmons [57]. However, the *Camellia sinensis* (*C. sinensis*) and *C. assumica* are said to have the highest catechin content. Catechins possess many benefits that include skin damage prevention or reduction and intensive anti-oxidant and representative physiological activities [39]. Catechins function indirectly as anti-oxidants through their effects on transcription factors and enzyme activities. As a matter of fact, the compounds strongly scavenge free radicals and retard extracellular matrix degradation induced by ultraviolet (UV) radiation and pollution. The swift and extensive metabolism of catechins by the human body further underscores the importance of their *in vivo* anti-oxidant activity [58,59]. The emulsification of catechins also improves their permeation through the skin, alongside better protective capability against UV rays and anti-aging effects [60].

_Ipsa facto_, catechins have since found applications in the cosmeceutical industry since the compounds can augment the penetration and absorption of bio cosmetics into the skin, thus improving their utility [61]. Studies have also shown that catechins positively affect the skin by activating collagen synthesis and interfere with the matrix metalloproteinase enzyme production [59]. The highly effective free-radical scavenging activity of catechin derivatives, the (−)-epigallocatechin and (−)-epicatechingallate than the standard anti-oxidants, viz. ascorbic acid, tocopherol and Trolox, has to do with the presence of the hydroxyl in the gallates [61–63].

To date, catechins from the extract of *Phyllanthus emblica* L. branch extract have been formulated into a topical nanoemulsion comprising of isopropyl myristate (0.6% w/w), Brij 78 (0.35% w/w), *P. emblica* extract (0.15% w/w), and water (98.9% w/w). The catechin-rich nanoemulsion containing epicatechin gallate, epigallocatechin, epigallocatechin gallate and gallocatechin in *P. emblica* showed excellent anti-oxidant properties, alongside astringent, antimelanogenesis and anti-inflammatory MMP-I properties, thus implying its potential use as an anti-aging product. Likewise, the minute droplet size (< 200 nm) of the O/W nanoemulsion indicated better penetration through the stratum corneum, as well as excellent storage stability for up to 90 days [39].

Catechins are excellent bioactive ingredients in topical nanoemulsions due to their high solubility in W/O and O/W systems. Several studies have consistently shown that catechin-rich nanoemulsions could permeate across the stratum corneum and enter the deeper skin layers, including the viable epidermis and dermis [61]. Another study experimented on catechins obtained from the leaves extract of *Eugenia dysenterica* DC as the bioactive ingredient for dermatological and cosmetics applications. The resultant topical nanoemulsion achieved the smallest droplet size of 27.0 ± 1.02 nm and 191.0 ± 7.20 nm for the W/O and O/W microemulsions, respectively, with long-term storage stability as long as three months. Further, *in vivo* studies revealed that catechins from the *Eugenia dysenterica* DC leave extract could reach the viable epidermis and dermis layers of the skin [43].

**Gallic acid**

Gallic acid (GA) is a phenolic compound known as 3,4,5-trihydroxy benzoic acid with the molecular formula of C₆H₃(OH)₃CO₂H. The GA molecule has two types of functional groups, hydroxyl groups and a carboxylic acid group, which can interact to yield different salts and esters, including digallic acids [64]. The unique coplanar and bent configuration of the
ortho-bonded hydroxyl groups were shown to be responsible for the favorable antioxidative activities seen in GA [65]. GA is widely distributed in the plant kingdom as a large family of secondary plant metabolites and natural anti-oxidants. The compound exists in both a free state and a component of tannins, such as the gallotannin, and GA derivatives. The compounds are found in almost every part of the plant, for instance, the bark, leaf, fruit, wood, seed and root. In particular, processed beverages such as red wine and green tea are exceptionally rich in GA. This naturally occurring phenolic compound forms white, yellowish-white, or pale fawn-colored organic acid crystals with good solubility in alcohol and ether but poorly soluble in water [66,67]. Aside from the potent anti-oxidant property, GA and its derivatives are also recognized for their antimicrobial, anti-inflammatory, and even antidepressant properties [27,68].

A dimeric derivative of GA, which is ellagic acid, found mostly in fruits and berries, i.e. raspberries, strawberries, blackberries and pomegranates, has been explored as an active ingredient in topical nanoformulations [41,69]. The pomegranate, specifically known scientifically as *Punica granatum* L., is a fruit-bearing deciduous shrub in the family Lythraceae. High anti-oxidant properties in the fruit peels have been reported because of the inherently high GA content. Extract of pomegranate peels strongly inhibited free radicals formed by harmful UV radiation and, was shown to protect skin from UV-induced erythema, burns, DNA fragmentation and depigmentation [70]. The in-vitro skin permeation study of the *P. granatum* peel extract O/W nanoemulsion found that the UV radiation was well absorbed by the spherical-shaped GA droplets (a combination of allic acid, ellagic acid and punicalagin) before the harmful rays reached the viable skin layers. This confirmed the compounds’ ability to quench free radicals produced by UV radiation [41]. Another study reported that polyphenols’ low surface-active ability, such as GAs could beneficially reduce the surface tension at the O/W interface. This indicated the plant-based active ingredient’s suitability to be formulated as either O/W or W/O nanoemulsions [71]. It is reported that phenolic acids in the crude extract of tamarind (*Tamarindus indica* L.) fruit pulps possessed potential skin lightening, antityrosinase, anti-inflammatory properties, and are promising anti-aging and skin whitening nanoemulsions [40]. Both studies consistently proved that the GA-rich pomegranate peel extract nanoemulsion is a promising topical anti-oxidant delivery system for the skin.

**Kaempferol**

A member of flavonoids, kaempferol or 3,4,0,5,7-tetrahydroxyflavone (*C15H10O6*), is a natural plentifully flavonoid found in apples, beans, broccoli, tea and strawberries. This compound’s pure form is a yellow colored powder, known for having a multitude of pharmacological properties, for instance, anticancer, anti-tumor growth, anti-oxidant, anti-inflammatory and anti-allergic activity, as reported in numerous research publications [72]. Kaempferol can augment the body’s anti-oxidant defense against free radicals as it is a powerful anti-oxidant capable of averting oxidative damage to our cells, lipids and DNA. Conversely, the substance seemingly conserves normal cell viability, in some cases, exhibits a protective effect. The number of hydroxyl groups in this compound and their disposition increased the superoxide and free radical scavenging activity. Also, the substitution of the hydroxyl groups by methoxyl groups reduced their scavenging activity. Kaempferol and quercetin are thought to act synergistically in delaying cancer cell proliferation, where a combined therapy of quercetin and kaempferol is more potent than the effects of each flavonoid alone [73,74]. Studies have consistently shown that kaempferol reduces the resistance of human cancer cells lines to anticancer drugs [73], induces apoptosis in human glioblastoma cells, and is better absorbed than quercetin in humans, even at low doses [75].

Kaempferol is naturally lipophilic like other flavonoids and is absorbed by passive diffusion, facilitated diffusion, and active transport due to its lipophilicity. Consequently, the variety of nano-carrier systems can better improve kaempferol’s bioavailability for topical or cosmeceutical applications [32,76]. Novel topical delivery systems are continually being developed to enable the controlled-release of the kaempferol at a predetermined rate and prevent interaction with the gastric and intestinal fluids that can unwantedly degrade the substance [51]. Given this, a wide range of nano delivery systems, i.e. kaempferol-containing nanoemulsions, has been prepared [51]. Hernández-Jaimes et al. [44] formulated a kaempferol-loaded nanoemulsion from *Equisetum arvense* extract, oil, water, using pseudo-ternary phase diagram, in which Tween 20 and ethanol were used as surfactant and co-surfactant, respectively. The droplets in the nanoemulsion were between 54.0 to 110nm and fitted well with a first-order kinetics model [44]. Kaempferol acts as a novel agent in treating UVB-induced tumorigenesis and photo-inflammation. Kaempferol was studied in skin cancer, where the COX 2 enzymes’ level was elevated. It inhibits the AP-1...
Resveratrol

Resveratrol, 3,5,4′-trihydroxy-trans-stilbene (C_{14}H_{12}O_{3}), is a member of stilbenoids, abundantly found in grapes, blueberries, peanuts, cranberries, soybeans and pistachios. Resveratrol analogs can be further divided into three different groups: catechol, resorcinol and pyrogallol depending on the hydroxyls’ positions. However, resveratrol and its hydroxylated analogs at ortho position are shown to exhibit higher anti-oxidant activity. This compound also possesses several interesting pharmacological properties: anti-tyrosinase, anticancer, anti-oxidant and anti-inflammatory ones.

In comparison to other anti-oxidants, resveratrol is an excellent skin protector against UV-B radiation. The compounds are capable of inhibiting the activities of certain kinases and tyrosinases and induce cancer cell apoptosis and senescence. Nevertheless, the downside to resveratrol’s clinical use is its poor water solubility (less than 1%), which reduces its bioavailability to target skin sites. Studies attempted to overcome this limitation by formulating a resveratrol-loaded nanoemulsion with 66–68 nm particle sizes, successfully boosting its bioavailability for protection against ultraviolet radiation. Recent in-vitro and in-vivo studies explored the potential of a nano-formulated resveratrol gel to prevent oxidative skin damage, which afforded a novel delivery system with enhanced permeability, free radical scavenging and retention effects.

Lycopene

This compound is a form of natural pigment that hails from the carotenoids group and is exceptionally abundant in tomato seeds. Lycopene is widely used in skin care products because of its capacity to nullify harmful oxidants by scavenging and neutralizing free radicals’ negative effects. However, biolycopene suffers the same limitation as resveratrol as it is strongly lipophilic (log p~15). This feature complicated lycopene absorption from the stratum corneum to other inner layers, mainly because of the compound’s affinity for the stratum corneum components and tended to be retained in this layer. The solution to this drawback is nano-encapsulation to enhance lycopene’s bioavailability through the skin. It is important to note that all trans-lycopenes have a linear chain and were 1.4 and 2.7 fold more efficient in quenching the reactive oxygen species (ROO•) than the cis isomers.

According to the literature, the prolonged diet of consuming tomatoes may prove useful in the repair of UV-induced sun-burned skin. In 2013, Ascenso et al. created a lycopene-rich nano-sized topical formulation that better protected the skin from UV-induced damage, as a result of the phytoconstituents’ improved bioavailability to the cutaneous level.

Curcumin

Curcumin is a polyphenolic compound from the Curcuma longa (turmeric) rhizomes. This root vegetable has been used widely to treat various skin diseases, for example, acne, alopecia, melanoma, psoriasis, and for wound healing. Curcumin has a wide range of biological and pharmacological activities, such as anti-cancer, anti-oxidant, antimicrobial, anti-inflammatory, and so forth. Interestingly, information on the structure–activity relationship of curcumin divulged its important role in various bioactivities that the compound displays. The o-diphenoxyl and o-dimethoxyphenoxyl groups in the curcumin structure exhibited higher DPPH scavenging due to the increased presence of electron-donating groups (methoxy and hydroxy) in the o-position of 4-OH. Curcumin, however, is poorly soluble in an aqueous medium following its lipophilic nature. Recent studies attempted to package curcumin into nanoemulsion systems to resolve this significant limitation and improve bioactivity through increased bioavailability. This is done to enhance the absorption or permeability of curcumin into the stratum corneum for local and systemic delivery, as well as for topical bioavailability.

The encapsulation of curcumin has been described to enhance its delivery and increase the anti-oxidant activity, in particular, for nanoformulations that have been specifically designed to cease the aging process in the stratum corneum. In addition, curcumin was shown to significantly expedite the wound healing process in the stratum corneum, boost granulation in the tissues, and promote more effective cellular content and neo-vascularization and re-epithelialization of the wound.
of the skin. Lycopene is also proven to have corrective roles in photo-damaged and preneoplastic keratinocytes, supporting the amenability of nano-formulated lycopene over conventional cosmetic products [47,89].

**Cosmeceutically relevant crude plant extracts**

The highly diverse plant kingdom is a reservoir for cosmeceutically exceptional crude extracts, packed with compounds that could be transformed into nanoformulations for delaying physiological aging. The wide range of phytoconstituents in plant crude extracts would render an array of synergically-significant bioactive effects compared to single bioactive compounds. Furthermore, naturally-occurring anti-oxidants from the crude extract of plants offer potential function in skin therapy against skin aging by benefiting from the complex composition of flavonoids, alkaloids, tannins, stilbenes, lignins, etc [90].

For instance, the commonly found *Prunus dulcis* Mill from the Mediterranean and Middle East countries could be valuable as the active ingredient in nanocosmetics for skin repair [90]. Its oleic- and linoleic acid-rich compositions were found comparable to almonds (80–90%) [91]; hence, it is naturally endowed with exceptional anti-oxidant capacity. This is related to the myriad of polyphenols (flavonoids, phenolic acids) in the crude extracts from various parts of the plant [92]. Another interesting plant extract from the *Murraya koenigii* belonging to Rutaceae family, commonly known as ‘curry leaves’ was high in free radicals-quenching compounds such as alkaloids, flavonoids, terpenoids and polyphenols. All the above-said compounds were found in leaves, roots, stem bark, fruits and seeds, indicating the plant is an excellent source of natural anti-oxidants for anti-aging formulations [93].

**Actions of plant-based bioactive compounds in cosmeceuticals**

Advancements in nanoformulation technology attract many scientists who are increasingly in favor of nano-cosmeceuticals to prepare more effective moisturizers, anti-wrinkle, anti-acne, or even whitening creams to treat problematic skin with greater efficiency. Nanotechnology, particularly nanoemulsions loaded with naturally occurring bioactive compounds in the form of plant extracts, has been effective in boosting skin hydration or oiliness and reducing wrinkles’ formation. Efficiencies of such formulations have been reported to supersede commercial synthetic cosmetics products [94]. For instance, moisturizers are applied to the skins’ surface to help with moisture retention in the stratum corneum surface and keep human skin hydrated over a longer duration. W/O moisturizers are formulated to go well with dry skin or skin-types that would benefit from the added oiliness on the stratum corneum and protect the human skin from extreme moisture loss. The applications or intended end-uses of anti-aging nanoemulsions are broad, and the following sub-sections further discuss their mechanism of action. The plant-based nano-sized formulations and their respective end-uses are presented in Table 2.

**Moisturizer**

The moisturizer is vital in cosmetics as it forms a thin protective film on the stratum corneum when applied to the skin surface and prevents dehydration of the stratum corneum. As a matter of fact, moisturizers are standard in cosmetic products to support skin beauty and enhance skin flexibility, as well-hydrated skin is a sign of healthy, young and uncompromised skin.

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**Table 2. Bioactive compounds, plant origin, delivery method, particles size, PDI and end use of nanoemulsions.**

| Bioactive compounds | Plant origin | Delivery method | Particles size (PDI) | End use | References |
|---------------------|--------------|-----------------|----------------------|---------|------------|
| Vitamin E, fatty acids | *Clinoacanthus nutans* (L.) | Nanoemulsion | 97.8 nm (0.25) | Moisturizer | [95,96] |
| Quercetin, kaempferol | *Opuntia ficus-indica* (L.) | Nanoemulsion | 92.17 nm (0.2) | Moisturizer | [97] |
| Polysaccharides | *Agave sisalana* | Nanoemulsion | 174.81 nm (0.11) | Moisturizer | [98] |
| Flavonoids | *Achyrocline satureoides* | Nanoemulsion | 250 nm (< 0.2) | UV Protective | [99] |
| Isoflavone | *Soybean* | Nanoemulsion | 144.38 nm (0.16) | UV Protective | [100] |
| Phenolic acids | *Tetraselmis tetrathele* | Nanoemulsion | 160 nm | Anti-wrinkle | [35] |
| Cinnamaldehyde p-cimene | *Cinnamonum bunianii* | Nanoemulsion | 25.8 nm (0.475) | Anti-acne | [101] |
| Tocopherols | *Mauritia flexuosa* L. | Nanoemulsion | 142.1 nm (0.198) | UV protective | [102] |
| Quercetin | *Moringa oleifera* | Nanoemulsion | 51.0 nm (0.22) | Anti-wrinkle | [103] |
| Quercetagetin | *Tagetes erecta* Linn. | Nanoemulsion | 201.80 nm | Anti-wrinkle | [104] |
| Polyphenols | *Mangifera indica* L. | Nanoemulsion | 26.14 nm (0.16) | Anti-acne | [105] |
| Kojic acid | *Aspergillus oryzae* | Nanoemulsion | 110.01 nm (0.25) | Whitening agent | [106] |
| Ellagic acid | *Pomegranate peel* | Nanoemulsion | 24.28 nm | Whitening agent | [107] |
| Artocarpin | *Artocarpus incicus* | Nanoemulsion | 225 nm (0.31) | Whitening agent | [108] |
Various skin problems such as dry skin disorders, psoriasis, atopic skin, ichthyosis, and contact dermatitis can benefit from a moisturizer’s consistent applications [109]. The incorporation of moisturizers in nanoemulsions can boost skin hydration by two different pathways: a) by forming an occlusive thin film on the stratum corneum where the rate of water evaporation or dryness from the skin is controlled and, b) by transporting hygroscopic substances capable of binding and retaining water into the stratum corneum, for instance, glycerin [62].

The effect of kaempferol, quercetin, galacturonic acid, glucose, rhamnose and arabinose in topical nanoemulsions of the Opuntia ficus-indica (L.) extract was investigated [110]. They found that when galacturonic acid, glucose, rhamnose and arabinose are associated with a nanoemulsion, the compounds function as a humectant and proceed through a nonocclusion mechanism to hydrate the skin [110]. Miller [111] investigated as potential anti-aging and moisturizing agent on the stratum corneum [111]. The hydrophilic O/W nanoemulsion of the 1% plant extract developed by [8] successfully increased the moisture content of the stratum corneum on the forearm for 5h after application, thereby proving its moisturizing efficacy. The formulation was also stable for at least 60days [8]. Vitamin E and fatty acids were found abundantly in Clinacanthus nutans (L.) leaf extract, which showed moisturizing efficacy. The O/W nanoemulsion reduced the water loss and improved the hydration level in the stratum corneum [95,96].

UV protection

With an increasing number of reported skin cancer cases, sunscreen products have become more critical than ever to protect the skin against ultraviolet (UV). Natural plant secondary metabolites, viz, phenolic acids, flavonoids, polyphenols, terpenoids and amino acid, alkaloids and tocopherols, are increasingly being used as UV blockers in sunscreen formulations due to their remarkable anti-oxidant properties [112]. The compounds prevent harmful UV radiation from penetrating healthy skin and halt the inflammation process, oxidative stress and DNA damaging effects [30]. Thus, topical nanoemulsion containing the aforementioned photo-protective compounds can better penetrate the skin’s stratum corneum compared to microemulsions [113].

Drug delivery abilities and penetration enhancement by various lipid-based colloidal carriers to treat dermatological disorders such as photoaging and skin inflammation were investigated for retinoids, including vitamin A, retinyl palmitate and other derivatives. The studies found that fatty acid esters were intrinsically more stable and showed reduced irritant effects and immunogenic responses [110,114]. Nanoemulsions of retinyl palmitate gave the highest permeation and reached deeper skin layers [115]. Nanoemulsions of the retinoids exhibited an increased tretinoin-induced anti-inflammatory response in ex vivo skin over other tested retinoids. The nano emulsified retinol microcapsules also induced other biological processes that shielded the skin against extracellular matrix lipid metabolism reactions, oxidative stress and cell proliferation when tested against a leading commercial product containing microencapsulated retinol or tretinoin [110,114,116].

In 2016 [117] proved that the quercetin-rich ethanolic extract of Achyrocline satureioides showed adequate anti-oxidant capacity after it was formulated into a nanoemulsion. The minimal dose of the nano emulsified A. satureioides extract exhibited a higher anti-oxidant effect over thiobarbituric acid. This indicated the possible applicability of the nano formulated A. satureioides extract as a photo-protective product [117]. Other bioactive compounds, namely, isoflavones in soybeans, aglyconeform glucosides daidzein, genistein, genistin and glucosidesdaidzin glycitin, genistin as well as malonylgucosides showed remarkable antioxidant properties, too. In 2018, a study by [100] proved that isoflavone-rich soybean extract nanoemulsions were excellent photo-protective formulation to shield the human skin against oxidative damage caused by UVA/UVB [100].

Mazzarino et al. [118] reported that nanoemulsions containing the fruit peel extract of Plinia peruviana showed promising anti-oxidant capacity, namely as active ingredients in anti-aging cosmetic products. This is because the P. peruviana peel extract is rich in phenolic anti-oxidants, such as anthocyanin, gallic acid, ellagic acid, isoquercitrin, quercimeritrin, quercitrin, myricitrin and quercetin. Likewise, anti-oxidant assays of nanoemulsions using jaboticaba extract as the active ingredient revealed the strong 1,1-diphenyl-2-picrylhydrazyl (DPPH) and ferric reducing power thus feasible as a topical anti-aging cosmetic product [118,119].

Anti-wrinkle

The first noticeable signs of skin aging begin with the appearance of wrinkles on the surface of the stratum corneum. Wrinkles are formed as a result of environmental or nutritional instigated changes that are manifested as the degradation of the skin’s three primary structural constituents, namely, collagen, elastin and
A study by [103] showed that the nanoemulsion contains Moringa oleifera seed oil to be an effective anti-wrinkle treatment when used topically on human skin. This has to do with the M. oleifera seed oil being rich in anti-oxidants. The treated skin appeared nourished, and fine lines and wrinkles disappeared upon topical application of this nanoemulsion. They believed that the W/O nanoemulsion of M. oleifera was well-dispersed and delivered through the stratum corneum due to its smallest droplet size of less than 100 nm. The anti-oxidative effect of the M. oleifera seed oil nanoemulsion stemmed from the colloidal system’s ability to prevent the loss of elastin and collagen. When topically applied at an extended duration, this eventually caused a profound reduction in skin wrinkles [103].

The flavonoid-rich Marigold (Tagetes erecta Linn.) flower extract containing the hexahydroxyflavone quercetagetin was loaded into nanoemulsion and assessed for antiwrinkle efficacy on the stratum corneum [122]. The active compound, quercetagetin, was successfully delivered into the skin and reduced skin wrinkles. Clinical studies using the T. erecta nanoemulsion revealed that the skin hydration on the stratum corneum was also improved. The wrinkle parameters, such as surface, volume, Ra, and Rz, decreased significantly. The ability of the quercetagetin-rich nanoemulsion to reduce wrinkles may be explained by the compound’s ability to inhibit the UVB-induced phosphorylation of c-Jun and AK by binding to the signaling molecules c-Jun NH2-terminal kinase-1 and phosphatidylinositol 3-kinase [122]. Quercetagetin also strongly suppresses thymus and activation-regulated chemokine and macrophage-derived chemokine production in HaCaT human keratinocytes. Therefore, this nanoemulsion has a promising use as an anti-wrinkle cosmetic product [104].

### Anti-acne

Acne currently affects approximately 9.4% of the global population, characterized by physical symptoms as soreness and itchiness. However, individuals inflicted with acne also suffer psychological issues such as self-esteem and degraded confidence. Acne-related inflammation is an immunomodulatory response towards the gram-positive anaerobe Propionibacterium acnes, which mainly inhabits the human pilosebaceous unit [123]. Acne can be treated through the following pathways where i) P. acnes moieties stimulate the toll-like receptors (TLR-2,4,6) on keratinocytes, and ii) the activated TLRs trigger the release of inflammatory cytokines (TNF-α, IL-6 and IL-8) by keratinocytes [124]. The researchers found that the polyphenol-rich kernels of Mangifera indica L. formulated into a topical nanoemulsion that effectively reduced acne. The formulation exhibited notable antibacterial and cytokines anti-inflammatory properties. The ethanol fraction encapsulated nanoemulsion showed increased minimum inhibitory concentration (MIC) and minimum bacteicidal concentration (MBC) when tested against P. acnes during the 90 days of storage. The M. indica L. anti-acne nanoemulsion showed long-term stability and better skin permeability [105].

Likewise, nanoemulsion loaded with oregano essential oil of Origanum vulgare L. was developed by [125] for acne skin. Their in vitro findings indicated that the nanoemulsion showed intense antimicrobial activity when tested against two acne-causing bacteria. The MIC and MBC of the Origanum vulgare L. was 0.34 mg/mL and 0.67 mg/mL for the Pseudomonas acnes, and was 0.67 mg/mL and 1.34 mg/mL against the Staphylococcus epidermidis, signifying the potential of the nanoemulsion as a topical anti-acne agent [125]. Another promising plant extract comes from cinnamon, widely known as a traditional medicine for various bacterial related diseases. A cinnamon extract anti-acne topical nanoemulsion was recently formulated and effectively inhibited Staphylococcus aureus that caused acne. The smallest particle size and PDI for the n-hexane extract of Cinnamomum burmanii loaded nanoemulsions were 25.8 nm and 0.48, respectively [101].

### Whitening agent

Skin hyperpigmentation is the most prevalent and worrisome phenomenon for both men and women. This has to do with the unsightly, excessive production of melanin or melanogenesis in both the dermis and epidermis layers of human skin. Nevertheless, melanogenesis or any related concerns, such as freckles, can be cured by avoiding UV exposure, the inhibition of tyrosinase and melanocyte metabolism, and preventing further melanin production by corneal ablation. The application of kojic acid may also help. This compound is a fungal metabolite from Aspergillus oryzae, well-known for its tyrosinase inhibitory property [126]. Tyrosinase is instrumental in the metabolic
action that causes hyperpigmentation of the human skin. This copper-containing membrane-bound enzyme's role is to catalyze the biosynthesis of melanin in the human body [127].

A relatively recent study experimented on a kojic monooleate (KMO)-enriched nanoemulsion for in-vitro cytotoxicity using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) on the 3T3 cell of mouse embryonic fibroblast cells. The IC_{50} value of below 30 μg/mL indicated that the nanoemulsion was safe for topical application [106]. In 2019, Ting et al. nano emulsified the adlay bran oil (ABO) and produced minute particles in the range of ~150 nm, and the formulation exhibited potent topical whitening property. Tyrosinase activity and melanin production was reduced in both in-vitro and in-vivo assays, using the B16F10 cells and zebrafish embryos [128]. Likewise, nano-encapsulated ellagic acid from pomegranate peels showed the most potent inhibition effect against tyrosinase enzyme with an IC_{50} value of 38.3 ± 0.09 μg/mL, making it the ideal whitening agent [107].

### Plant-based bioactive compounds and their mechanisms of action for skin improvement

Synthetic anti-oxidants, including butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate (PG) and tert-butylhydroquinone (TBHQ), are not safe to be used in cosmetics. The substances may pose unwanted side effects such as skin allergy or perhaps cancer, with extended use [129]. Natural plant-based bioactive constituents are the more attractive and safer substitutes over synthetic anti-oxidants as active ingredients in topical nanoemulsions to improve skin quality. Anti-aging properties in compounds, phenolic acids, terpenoids, polyunsaturated fatty acids, lycopene, resveratrol, lignan, tannins, indoles, flavonoids, coenzyme Q, polysaccharides and anthocyanins have been investigated and studied extensively [130]. The anti-oxidants mentioned above can be extracted from other parts of the plant, including fruits, grains, seeds, roots, leaves, stems and flowers. Then, they are formulated into nanoemulsions for topical applications [18]. Table 3 summarises the plant-based bioactive compounds and their inhibition mechanisms with corresponding IC_{50} values of their in-vitro assays.

### Melanogenesis

Melanin is a color pigment whose pertinent role is to protect human skin against damaging UV radiation. The pigment is synthesized by melanocyte cells through the melanogenesis biosynthesis process. However, prolonged exposure to sun and skin conditions, such as hyperpigmentation, namely, melasma, freckles or ephelides, can cause melanin to be over secreted and cause undesirable skin darkening [137]. Reactive oxygen species, i.e. hydrogen peroxide, resulting from overexposure to the sun, are produced in keratinocytes. The reaction subsequently triggers UV-induced melanogenesis or skin pigmentation [138]. There are two categories of melanin pigments, the first being the black-brown eumelanin (darker melanin), and the second is the yellow to reddish pheomelanin (lighter melanin). Melanogenesis involves two steps, which are mediated by the

### Table 3. Bioactive compounds, plant origins, inhibition mechanisms, particles size, PDI and inhibition values at IC_{50} for nanoemulsions.

| Bioactive compounds | Plant origin           | Mechanisms                                                                 | Particles Size (PDI) | IC_{50} (µg/ml) | References |
|--------------------|------------------------|----------------------------------------------------------------------------|----------------------|-----------------|------------|
| Geranyl geraniol    | *Pterodon emarginatus* | Reduced levels of UVA-induced pro-inflammatory cytokines IL-6 and IL-8.     | 150 nm (0.2)         | Collagen content = 5 µg/ml | [131]      |
| Catechin            | *Punica granatum*      | Hyaluronidase activity                                                     | 83.90 nm (0.24)      | Collagenase = 4 mg/ml, Elastase = 309 mg/ml, Hyaluronidase = 95 mg/ml | [132]      |
| Eugenol             | *Syzygium aromaticum*  | Increased collagen content at wound area for early recovery                | 29.10 nm (0.026)     | Collagen content = 0.61 mg/g | [133]      |
| Erucic acid         | *Erucia sativa*        | Reduced UVA-induced cytokines, increased elasticity of skin, scavenged free radicals | 195.29 nm (0.20)     | Antioxidant = 2.10 µg/mL, Elastase = 25.1 µg/mL, SPF factor = 5.57 | [134]      |
| Geraniin            | *Phyllanthus urinaria* | Scavenged ROS free radical                                                | 30.74 nm (0.38)      | DPPH = 30.05% | [135]      |
| Myrsoinic acids     | *Rapanea ferruginea*   | Decreased edema, levels of pro-inflammatory cytokines IL-1β, TNF, KC and inhibited myeloperoxidase activity | 35.71 nm (0.40)      | DPPH = 29.89% | [136]      |
|                     |                        |                                                                           | 47.88 nm (0.23)      | Myeloperoxidase = 64.60% KC reduction = 42.72% IL-1β reduction = 40.96% TNF = 42.23% |            |

### References

[106, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138]
tyrosinase enzyme. The first step is dihydroxyphenylalanine or DOPA synthesis, while the second step oxidizes DOPA to dopaquinone [139]. Carefully selected bioactive compounds may prove useful in preventing skin darkening by inhibiting hyperpigmentation via two main mechanisms: the inhibition of tyrosinase activity and the suppression of melanosomal transfer. In the first mechanism, the bioactive compounds can suppress melanogenesis by inhibiting the activity of 5,6-dihydroxyindole-2-carboxylic acid (DHICA) polymerase, which polymerizes the 5,6-DHICA, thereby reducing the eumelanin production without interfering with the mRNA gene expression. The compounds can also interfere with tyrosinase activity in the B16 murine melanoma cells without interfering with DNA expression. In the second mechanism, translocation of melanosomes from melanocytes to adjacent keratinocytes is suppressed by photochemicals. This step essentially limits the accumulation of melanosomes-containing melanin in keratinocytes, thus keeping hyperpigmentation under control [140,141].

Since flavonoids have anti-hyperpigmentation property, the compounds are capable of altering the melanin synthetic pathway through the following detailed mechanisms: i) tyrosinase structure alteration, ii) chelation of copper, the tyrosinase co-factor, iii) tyrosinase competitive or non-competitive, and suicide inhibition, finally through iv) tyrosinase expression reduction [142]. Park et al. [70] reported that polyphenols from the *P. granatum* extract effectively inhibited UVB-induced damage in the skin. The plant extract protected UVB damage in human fibroblasts by upregulating collagen and downregulating the expression of MMP-1 [70]. The photoprotective effect of a nanoemulsion containing sucupira oil from *Pterodon emarginatus* helped minimized the UV-induced stress on human stratum corneum. IL-6 and IL-8 were effectively downregulated, implying the nanoemulsion's potential for immunomodulatory activity and minimizing inflamed skin due to UVA radiation [131].

**Collagenesis**

Collagen is the protein found throughout the human body, made of repetitive monomers of tropocollagens in tissues. Collagenesis is a necessary naturally-occurring metabolic process that happens in the human skin to replace the self-degraded fibrils. At a young age, the collagens are tightly packed and orderly arranged but are lost in photo-aged skin. Keeping the collagens intact is vital for maintaining tissues and organs’ structural integrity in terms of cell or tissue repair [143]. There are two steps for collagen biosynthesis, which are intracellular and extracellular. The biosynthesis of collagen in human skin involves translating the collagen mRNA in polysomes and the hydroxylation of the peptidyl proline and lysine using specific enzymes. Disulfide bonds form the triple helix, and, lastly, is the enzyme-aided glycosylation [144]. Prolonged exposure to UV radiation intensifies collagen degradation by producing metalloproteinase (MMP) 1 (collagenase), MMP-3 (stromelysin 1), and MMP-9 (92-kD gelatinase) in human dermal fibroblasts (dermis). UV exposure profoundly increases the cleavage of collagen by MMP 1 in the fibroblasts of human skin. It leads to excessive molecular denaturation that lowers collagen's stability and reduces its elasticity in human skin. Likewise, Kontomaris et al., showed that UV irradiation caused a significant decline in Young's modulus values in collagen fibrils and fibril diameters, length and leads [145]. The above results thus validated the destroyed structural integrity seen in photo-aged human skin, such as dryness, wrinkle formation [146]. Studies have shown that UVA rays exhibit a more substantial effect than UVB rays in destroying collagen, where wavelengths of 300-340 nm caused hardening and reduced elasticity of *in-vitro* tested collagen gels, with a pronounced effect at 330-nm radiation [147].

In the ongoing investigation for skin-improving nanoemulsions Dhawan and Nanda [132] developed a topically applied nanoemulsion using pomegranate seed oil. The formulation exhibited relatively potent anti-elastase, anti-collagenase and anti-hyaluronidase properties with an IC_{50} value of 309 mg/mL, 4 mg/mL and 95 mg/mL, respectively [132]. Nanoemulsions can boosts the action of wound healing bioactive ingredients, as demonstrated by Alam et al. in 2016 using the wound excision rat model. The orally administered rat models showed a large amount of granulation tissue, restoration of the adnexa, and extensive fibrosis, allowing the wound to recover faster [133].

**Free radical scavenging activity**

Anti-oxidants protect against UV-induced photodamage and inhibit inflammation on human skin by scavenging the harmful free radicals. Topical formulations loaded with anti-oxidants have been proven to offer anti-aging protection by shielding the human skin by absorbing UV radiation [148]. Anti-oxidant mechanisms of polyphenols can be divided into three, with the first two mechanisms involving hydrogen atom transfer (HAT) (mechanism 1) and single electron transfer (SET) (mechanism 2) of the free radicals inactivated by the polyphenols. The polyphenols (ArOH) react with a free
radical, \( \text{R}^* \) by donating a hydrogen atom through a homolytic cleavage of the O-H bond. On the other hand, the second mechanism delineates an electron’s transfer to the free radical, \( \text{R}^* \) to form a polyphenolic cation, \( \text{ArOH}^+ \), and anion, \( \text{R}^- \). The third mechanism is transition metal chelation (TMC). The polyphenols chelate the transition metals or ligands into forming stable complexes so that the metal ions are incapable of creating free radicals for the oxidative process [149].

Encapsulated plant-based anti-oxidants or bioactive compounds in hydrophilic/lipophilic nanoemulsions can undergo oxidation or phase separation (flocculation, coalescence and sedimentation) [150,151]. Literature has shown that harmful free radicals are the primary cause of unwanted oxidation in W/O or O/W nanoemulsions. The change comes from surface interaction between lipid hydroperoxides, transition metals, or pro-oxidants in the aqueous phase and vice versa [152]. Moreover, free radical scavengers are likely effective surface-active anti-oxidants mainly found in zones where the free radicals are created. Therefore, the higher surface area of the smallest particle size in nanoemulsions impedes the lipid oxidation reaction, which mainly occurs at the oil-water interface [153,154].

Commercial applications and patented nanocosmetics

Commercial/practical applications of nanocosmetics are patented yearly by established cosmetic companies. These patents encompass nanoemulsions alongside a wide range of delivery systems such as nanoparticles, nanosomes, nanospheres, niosomes, nanocapsules and nanoemulsions. As a matter of fact, nearly all fields of application have found nanoemulsions to be highly useful. Tables 4 and 5 enlist the commercially available nanocosmetics with their corresponding applications, alongside known patented nanocosmetics, respectively. Several commercial cosmetics products are sold as anti-wrinkle, anti-acne, moisturizer, UV protection and whitening agents [155,156].

Patents numbers US 20130011348A1 and US 20090220556A1 by Tomiko Takakura and International Technology Center, respectively described nanoformulations for specific use as sunscreens or UV protection. Meanwhile, the method for stabilizing retinol (vitamin A) for wrinkle and fine lines-reducing nanoemulsion was patented by Act Co Ltd (patent number US 20130095157A1 dated April 18, 2013) and (patent number EP 2583665A2 dated April 24, 2013). The retinol polymer nanocapsule was fashioned by nano emulsifying retinol in porous polymer beads of 50–200 nm in sizes [16,157].

Conclusions and future outlook

The past decade has seen that plant-based bioactive compounds loaded nanoemulsions have found useful applications in the cosmeceutical industry, producing a wide-ranging product with photoprotection, moisturizer and anti-aging and anti-wrinkle capabilities. Nonetheless, there are many challenges ahead and also plenty of room for improvement by the formulation scientist as plant-based-bioactive compounds tend to possess low permeability into the stratum corneum. The plant bioactive ingredients’ tendency to form relatively large size droplets in the emulsion denote the impending low stability and their poorer permeation through the skin. Nanotechnology has mostly overcome this shortcoming, whereby cosmetics employing nano-sized plant-based bioactive compounds have increased their bioavailability into the skin. The phytoconstituents are retained on the surface of the stratum corneum for a more extended period, thereby improving skin hydration, skin elasticity and UV protection effects, and thus, delay skin aging [158].

Plant-based nanoemulsions in cosmeceuticals are a promising nano-delivery technique for the future. Thus,

| Bioactive compound | Product Name | Cosmetic Application | Delivery mode | Company |
|--------------------|--------------|----------------------|---------------|---------|
| Vitamin E          | Wilma Schumann Acne Kit | Anti-acne | Nanoparticles | Wilma Schumann |
| Vitamin E          | Phyto-Endorphin Hand Cream | Anti-wrinkle, Nanoeumulsion | Nanoeumulsion | Rhonda Allison |
| Arbutin            | Nanovital Vitanics Crystal Moisture Cream | Moisturizer | Nanoeumulsion | Vitacos Cosmetics |
| Vitamin            | Precision-Solution Destressante Solution Nano Emulsion Peaux Sensitivity | Moisturizer | Nanoeumulsion | Chanel |
| Q10                | Cutanova Cream Nanovital Q10 | UV protection | Nanolipid carrier | Dr. Rimpler |
| Vitamin C          | Eusu Niosome Makam Pom Whitening Facial Cream | Whitening agent | Niosome | Eusu |
| Pro-retinol A      | RevitaLift Anti-Wrinkle and Firming Face and Neck Contour Cream | Anti-wrinkle | Niosome | L’Oreal |
| Vitamin E          | Bepanthol-Protect Facial Cream Ultra | Anti-wrinkle, moisturizer | Nanoeumulsion | Bayer HealthCare |
the next decade foresees a higher market trend for nanocosmeceutical products containing primarily naturally extract compounds, replacing synthetic chemicals. This is because of consumers’ growing awareness for safer products to be used on the skin. Aside from the more refined texture and ease of applying nanoemulsions, choosing the right natural plant ingredients hinges on the cosmetic product’s requirements. Further research is needed to improve plant-based nano-cosmetics nanotechnology, thereby ensuring that nano-scaled plant extract-loaded formulation remains the best and safest choice in the coming years. Specifically, nanoemulsions are prepared for the well-being and safety of consumers. With increasing reports of evidence-based herbal biotechnology on phytohormones and their physiologic effects, future market trends will see a higher demand for nano-formulated phytohormones for repairing and/or rejuvenating human skin. By combining the cutting-edge nano-dermatology research with Ayurvedic and ancient herbal medicine based on plant stem cells, a higher preference for vegan cosmetics is expected, if not already trending, among consumers across diverse regions.

Disclosure statement
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