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Review

Trends and challenges in phytotherapy and phytocosmetics for skin aging

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ABSTRACT

Oxidative stress and inflammation mostly contribute to aging and age-related conditions including skin aging. The potential of natural products in the form of naturally-derived cosmetics, cosmeceuticals, and nutricosmetics have, however, not been fully harnessed. This review, thus, critically analyzes the potential roles of natural products in inflammation-related skin aging diseases due to the increasing consumers' concerns and demands for efficacious, safe, natural, sustainable, and religiously permitted alternatives to synthetic products. The information and data were collated from various resources and literature databases such as PubMed, Science Direct, Wiley, Springer, Taylor and Francis, Scopus, Infilbnet, Google, and Google Scholar using relevant keywords and Medical Subject Headings (MeSH). The role of green extraction solvents as promising alternatives is also elucidated. The potential enhancements of the bioavailability, stability, solubility and controlled release profile of the bioactives using different delivery systems are also presented. The current potential global market value, motivators, drivers, trends, challenges, halal, and other regulatory certifications for cosmeceuticals and nutricosmetics are equally discussed. The adoption of the suggested extractions and delivery systems would enhance the stability, bioavailability, and target delivery of the bioactives.

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Contents

1. Introduction	2
2. Anti-inflammatory therapy	3
3. Antioxidants, free radicals, inflammation, and skincare	4
3.1. Free radicals and inflammation	4
3.2. Antioxidants and inflammation	4
3.3. Aging and inflammation	4

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3.4. Skin aging and inflammation 5
 3.5. Aging and skincare 5
 4. Cosmetics, cosmeceuticals, and nutricosmetics 6
 5. Delivery systems in cosmeceutical and nutricosmetics 8
 5.1. Natural products and delivery systems 8
 5.2. Application of nanotechnology for bioactives 9
 5.3. Global market value for cosmeceutical and nutricosmetics 9
 5.4. Motivators and drivers of cosmeceutical and nutricosmetics market 9
 5.5. Trends and challenges. 10
 5.6. Halal certification and other common certification systems 11
 6. Conclusion 11
 Declaration of Competing Interest 11
 Acknowledgement 11
 References 11

1. Introduction

Skin aging is induced by multiple factors including intrinsic skin aging (such as genetic and physiological factors) and extrinsic (photoaging) skin aging (such as environmentally-induced and personal lifestyle factors (Ahmed et al., 2020; Franco et al., 2022). Free radicals, oxidative stress, and inflammation have been strongly implicated in aging as well as most other chronic diseases such as atherosclerosis, stroke, cancer, diabetes, and neurodegenerative diseases (Korovila et al., 2017; Mikail et al., 2016). Inflammation is a protective physiological response to tissue injury or infection, and it is characterized in its acute phase by an increase in vascular permeability and plasma extravasation, resulting in the accumulation of fluid, leukocytes, and mediators to the inflamed site. Heat, fever, loss of function, and pain, redness, and swelling (edema) are also common manifestations of inflammation. The simultaneous occurrence of both tissue injury and active inflammation, however, results in a prolonged inflammation otherwise called chronic inflammation which is the hallmark of most pathological conditions such as allergies, arthritis, atherosclerosis, cancer, metabolic syndromes, immune system homeostasis disturbance as well as other autoimmune diseases (García-López et al., 2019; Jin et al., 2019; Jitta et al., 2019; Saito et al., 2019). Sterile

inflammation otherwise known as chronic low level or pathogen-free inflammation can also be induced by some sterile stimuli such as certain environmental cues, ischemia, mechanical trauma, and stress. These stimuli lead to the secretion of damage-associated molecular patterns (DAMPs) which are responsible for the activation of some innate immune effectors such as families of NOD-like and toll-like receptors (Feldman et al., 2015; Land, 2020; Relja & Land, 2020). The prolonged inflammation is also linked to the overproduction of mediators such as inducible type cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), interleukins (IL 1β, IL-6, IL-8), intercellular adhesion molecule-1 (ICAM-1), tumor necrosis factor (TNF-α), nuclear factor-κB (NF-κB), prostaglandin E2 (PGE2), and 5-lipoxygenase (5-LOX) by the pro-inflammatory and immune cells such as macrophages and monocytes (Fig. 1). The role of the transcription factor, NF-κB, is mainly to regulate the expression of several pro-inflammatory cytokines and enzymes such as COX-2, iNOS, IL-1β, and TNF-α (Azul et al., 2020; El Assar et al., 2013; Khoo et al., 2017; Taofiq et al., 2016a; Taofiq et al., 2016b).

Superoxide ion (O₂⁻), hydroxyl (HO), hydroperoxyl (HO₂), peroxy (ROO), alkoxy (RO) ozone (O₃), hydrogen peroxide (H₂O₂), nitric oxide (NO), peroxy nitrate (ONOO), nitrogen dioxide (NO₂), dinitrogen trioxide (N₂O₃), leukotrienes (LTB₄), platelet-

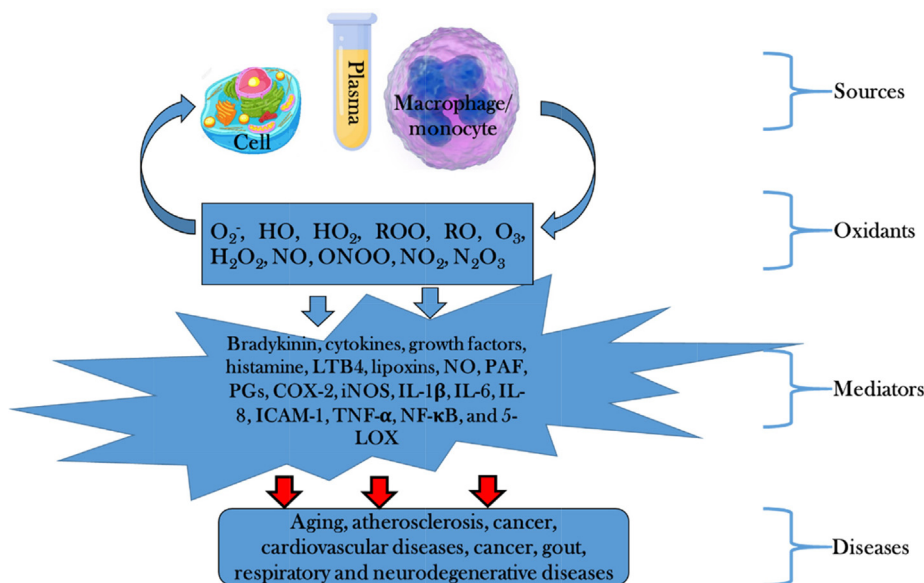


Fig. 1. Role of reactive oxygen species and other free radicals in inflammation. The various oxidants attack the pro-inflammatory cells thereby generating different inflammation mediators and leading to various inflammatory diseases.

activation factor (PAF), prostaglandins (PGs), cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), interleukins (IL), intercellular adhesion molecule-1 (ICAM-1), tumor necrosis factor (TNF- α), nuclear factor- κ B (NF- κ B), and 5-lipoxygenase (5-LOX).

The action of arachidonic acid and prostaglandin derivatives has also been attributed to inflammatory reactions (Khoo et al., 2017; Zaidi et al., 2019). Prostaglandins are a subclass of prostanoids and the enzyme involved in the metabolism of arachidonic acid and synthesis of prostanoids is cyclooxygenase (COX), a prostaglandin-endoperoxide synthase (E.C. 1.14.99.1). There are at least two isoforms of COX in mammalian cells, namely COX-1 and COX-2. COX-1 is regulated as a housekeeping enzyme for various physiological functions such as tissue homeostasis maintenance, cell signaling, maintenance of gastrointestinal epithelium integrity, regulation of angiogenesis in endothelial cells, and formation of thromboxane in blood platelets. Thus, it is expressed constitutively in almost all cell types. COX-2, however, is inducibly expressed and stimulated to produce prostaglandin during tissue damage or inflammation (Khoo et al., 2017; Shaikh et al., 2016; Xu et al., 2022).

Thus, inflammation is a complex pathophysiological defense mechanism and the fundamental protective response of the body to eliminate and/or limit the spread of the injurious agent. Following the increasing understanding of inflammation, the basic three distinct phases involved in the inflammatory response are increased vascular permeability, leukocyte infiltrations as well as granuloma formation, and tissue repair (de Oliveira et al., 2014; Nile and Park, 2013; Yang et al., 2022). The mediators and signaling molecules of inflammation that originate either from cells or plasma include bradykinin, cytokines, growth factors, histamine, leukotrienes (LTB₄), lipoxins, nitric oxide (NO), platelet-activation factor (PAF), prostaglandins (PGs), and serotonin (Dzoyem and Eloff, 2015; Nile and Park, 2013). The development of inflammation is usually initiated by a wide range of toxic oxidative reactions in the body which occur as a result of free radicals and highly reactive oxygen species (ROS) causing lipid peroxidation, inhibition of membrane sodium-potassium ATPase activity, inhibition of metabolic enzymes as well as oxidative modifications of proteins. ROS include hydrogen peroxides, hydroxyl radicals, hypochlorite radicals, peroxy radicals, singlet oxygen, superoxide radicals, nitric oxygen radicals, and various lipid peroxides (Nile and Park, 2013; Xiao et al., 2022). An excessive amount of ROS is also produced by both mononuclear cells (such as lymphocytes and macrophages) and polymorphonuclear leukocytes (such as eosinophils and neutrophils) of the phagocytic cells as a mechanism for host defense. These excessive ROS, however, lead to a deregulation of the cellular functions through cellular and tissue damage, which in turn, accentuates the inflammation state (Shaikh et al., 2016; Xiao et al., 2022). Generally, the interaction of ROS with cellular components (such as membrane lipids, nucleic acids, proteins, various metabolic enzymes, and other small molecules of living systems) leads to cellular damage and tissue injury which, in turn, prompts inflammation. Furthermore, ROS is majorly linked to the initiation and progression of various diseases such as aging, atherosclerosis, cancer, cardiovascular disease, cancer, gout, respiratory diseases, and neurodegenerative diseases (Nile and Park, 2013; Xiao et al., 2022).

Despite the high-cost implication of managing these inflammatory diseases, the outcomes have not been encouraging because a reductionist approach or a monotherapy model has always been adopted such that a single drug or single bioactive compound is used to attack one target of the disease. The trend now is to explore a group of compounds that are naturally present in foods, known as nutraceuticals or functional foods, for the management of these chronic degenerative diseases, owing to their cheapness, natural-

ness, safety as well as remarkable preventive and therapeutic potentials (Ibrahim et al., 2018a,b; Santana-Gálvez et al., 2019; Aldaddou et al., 2022; Zamakshshari et al., 2021; Zamakshshari et al., 2022). Our objectives in this review are to critically analyze the setback and limitations of the current anti-inflammatory therapy, the role of free radicals and natural antioxidants in inflammation, the role of inflammation in aging, the potential roles of naturally-derived cosmetics, cosmeceuticals, and nutricosmetics in inflammation-related diseases, the alternatives to common extraction techniques of bioactives vis-à-vis green extraction solvents such as natural deep eutectic solvents and electrochemically reduced water, the enhancement of the bioavailability, stability, solubility, and controlled release profile of the bioactives using different delivery systems as well as the potential global market value, motivators, drivers, trends, challenges, halal and other common certifications for cosmeceuticals and nutricosmetics. The information and data were collated from various resources and literature databases such as PubMed, Science Direct, Wiley, Springer, Taylor and Francis, Scopus, Infilbnet, Google, and Google Scholar. The keywords and corresponding Relevant Medical Subject Headings (MeSH) terms used for searching databases include aging, cosmetics, cosmeceuticals, certifications; delivery systems, eutectic solvents, free radicals, hormesis; Inflammation, and nutricosmetics. The process of selection of relevant articles involved a list of titles obtained from the electronic database, followed by an evaluation of the abstracts of all selected titles and analyzed titles based on predetermined inclusion criteria. Full texts of relevant articles were then carefully studied.

2. Anti-inflammatory therapy

Both corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) agents are the major classes of drugs commonly used as the first line of anti-inflammatory therapy worldwide (García-López et al., 2019; Jitta et al., 2019; Shimada et al., 2022; Zhang et al., 2022). Common examples of NSAIDs include, but are not limited to, carboxylic and heterocyclic acid derivatives (indomethacin), phenylacetic acid derivatives (diclofenac), propionic acid derivatives (flurbiprofen, ibuprofen, ketoprofen,) and salicylate derivatives (aspirin). These carboxylic (organic) acid-containing drugs mainly act by inhibiting the cyclooxygenase enzymes responsible for the production of prostaglandins from arachidonic acid. In other words, the drugs act at the active site of the enzyme to prevent the enzyme from accessing arachidonic acid thereby able to stop the cyclooxygenase pathway (Shaikh et al., 2016; Shimada et al., 2022). The toxic and highly undesirable adverse effects of these synthetic drugs such as bone marrow depression, cardiovascular and gastrointestinal complications (such as bleeding, obstruction, perforation, and ulceration), hypertension, nephrotoxicity, salts, and water retention, in addition to their exorbitant cost and questionable efficacy, have generated more interests in natural alternatives of plant origin which are not only safe and efficacious but also readily accessible and affordable to patients (de Oliveira et al., 2014; Jitta et al., 2019; Meshram et al., 2016; Park et al., 2018; Shaikh et al., 2016; Zaidi et al., 2019; Zhang et al., 2022). Furthermore, the selectivity of NSAIDs toward inhibition of COX-1 over COX-2 also underlies the gastrointestinal side effects of NSAIDs. Thus, a major thrust area of anti-inflammatory research is searching for selective COX-2 inhibitors with little or no influence on the normal physiological functions of COX-1 (Shaikh et al., 2016). The extracts of plant-derived natural products, however, characteristically contain complex mixtures of various inactive, partially active, and active components, thus, representing an important lead and source of new effective compounds against a panoply of diseases including inflammatory

disorders (Sharifi-Rad et al., 2020). According to the literature, many dietary polyphenols can inhibit arachidonic acid peroxidation as well as modulate various inflammatory mediators such as COX-2, inducible nitric oxide synthase (iNOS), IL-1 β , IL-10, and TNF α (de Oliveira et al., 2014; Domínguez-Perles et al., 2019; Shaikh et al., 2016). The potential benefits of the pharmaceutical active and bioactive compounds from most natural and herbal products underlie their usefulness and applications in various skin disorders such as acne, eczema, premature skin aging, and wounds (Barreira et al., 2019). Nevertheless, these natural plant bioactives, similar to mild stress, follow hormetic pathways or hormetic dose responses through either direct stimulation or overcompensation (Ahmed et al., 2020; Calabrese, 2020). Hormesis is characterized by a stimulation effect of a low dose and an inhibitory effect of a high dose. Besides, hormesis underscores the life-supporting homeodynamic space as well as the beneficial nonlinear biphasic dose-response effects of foods and food components (Agathokleous et al., 2019; Ahmed et al., 2020; Demirovic and Rattan, 2013; Kadlecová et al., 2019).

Having discussed the common anti-inflammatory therapies and their challenges, the authors deemed it fit to review the role of antioxidants and free radicals in inflammation and skincare.

3. Antioxidants, free radicals, inflammation, and skincare

3.1. Free radicals and inflammation

Free radicals are highly reactive chemical species with an unpaired electron in the outer shell of their molecules. They are formed from the metabolism of oxygen as well as byproducts of the various physiological reactions. They are either reactive oxygen species (oxygen-derived) or reactive nitrogen species (nitrogen-derived). Major examples of the oxygen-derived molecules include free radicals such as superoxide ion (O₂⁻), hydroxyl (HO), hydroperoxyl (HO₂), peroxy (ROO), and alkoxy (RO) as well as non-radicals such as ozone (O₃) and hydrogen peroxide (H₂O₂) [Pisoschi and Negulescu, 2011]. The nitrogen-derived free radicals, on the other hand, include nitric oxide (NO), peroxy nitrate (ONOO), nitrogen dioxide (NO₂), and dinitrogen trioxide (N₂O₃). Free radicals, especially, reactive oxygen species (ROS) are, generally, electrophilic possessing a strong oxidizing property. Substances such as oxygen, cholesterol, DNA, proteins, phospholipids, and polyunsaturated fatty acids are the main targets of ROS (Mikail et al., 2016). The major steps involved in the oxidation process via free radical-mediated chain reactions include initiation, propagation, branching, and termination steps. The action of external agents such as heat, light, and ionizing radiation as well as chemical agents such as metal ions and metalloproteins are responsible for the initiation step (Pisoschi and Negulescu, 2011). While a normal cell has an appropriate oxidant: antioxidant balance, the balance, however, is swiftly shifted with increasing production of oxidant species or decreasing levels of antioxidants to create oxidative stress which ultimately leads to the damage of biopolymers and inflammation (Korovila et al., 2017; Mikail et al., 2016).

3.2. Antioxidants and inflammation

Antioxidants, which are generally of low molecular weights, however, delay or inhibit the oxidation processes through the scavenging of free radicals, stabilization of polymeric products, and biocomponents in the human body as well as cosmetics, foodstuffs, petrochemicals, and pharmaceuticals. Antioxidants are required for the body's defense mechanism against various free radical-associated pathologies. Antioxidants are either endogenous or exogenous. Endogenous antioxidants are either enzymatic or

non-enzymatic. Endogenous enzymes include catalase, glutathione peroxidase, and superoxide dismutase while endogenous non-enzymatic compounds include albumin, bilirubin, metallothioneins, and uric acid. Exogenous antioxidants are needed to support endogenous factors for the complete protection of the organism against the reactive oxygen species. Most essential exogenous antioxidants include vitamin C, vitamin D, vitamin E, vitamin K, β -carotene, flavonoids, and minerals. These exogenous antioxidants are derived both from natural sources such as anthocyanins, flavonoids, vitamins, and some mineral compounds as well as synthetic compounds such as butyl hydroxyanisole, butylhydroxytoluene, and gallates (Ahmed et al., 2015; Pisoschi and Negulescu, 2011; Mikail et al., 2016; Ahmed et al., 2019). The health benefits of antioxidants, particularly concerning free radicals, oxidative stress, and inflammation-related complications such as aging, atherosclerosis, arthritis, brain stroke, cancer, diabetes, immunological incompetence, neurodegenerative diseases, Alzheimer's disease, Parkinson's disease, and rheumatoid arthritis have been well reported in the literature with phenols and polyphenols being the target analytes in most cases (Ahmed et al., 2015; Pisoschi and Negulescu, 2011; Nirmala et al., 2018; Zamakshshari et al., 2021). These analytes may be detected by enzymes like tyrosinase or other phenol oxidases. Dietary plant antioxidants include phenolic compounds, carotenoids, flavonoids, benzoic acid derivatives, proanthocyanidins, stilbenes, coumarins, lignins, and lignans. The antioxidant properties of plants and foodstuffs are enhanced by the additive, cumulative, potentiation, and synergistic effects of these bioactive molecules. Thus, the level of single antioxidants does not necessarily reflect their total antioxidant potential. And the total antioxidant potential or profiling of plants is difficult, in part, due to the diversity of plant chemical compounds with antioxidant activities as well as geographical differences in food composition (Pisoschi and Negulescu, 2011; Santana-Gálvez et al., 2019).

3.3. Aging and inflammation

The global demographics, particularly, in both the developing and developed high-income nations have been transformed into hyper-aging societies from the previously known young societies, mainly due to the putative improvement in the population life expectancy due to better nutrition, and advances in medicine as well as improved standards of living. People are now living longer worldwide with those aged 60 and above now numbered 962 million in 2017, as compared to 901 million in 2015 and 382 million in 1980. This number is already projected to reach nearly 2.1 billion by 2050. Furthermore, older people are expected to outnumber children under age 10 (1.41 billion versus 1.35 billion) by 2030 and by 2050. There will, more probably, be older persons aged 60 or over than adolescents and youth ages 10–24 (2.1 billion versus 2.0 billion) (Nations, 2015, World Population Aging Report). The unintended consequences of these transformations include significant shifts in the population's attitudes towards beauty, aging, and health. In other words, it has put a tremendous impact not only on the economies but also on the social aspirations, health as well as well-being with chronic and degenerative diseases emerging as the top causes of global morbidity and mortality (Sabaragamuwa et al., 2018). According to the world health organization (WHO), it is expected that the proportion of the world's population aged 60 years or over will nearly double from 12% to 22%, between 2015 and 2050 (WHO, 2018). Though the biological mechanisms underlying the aging process are yet to be comprehensively understood, aging is known to be a complex multifactorial process involving genetics, physiology, and the environment as well as accompanied by the occurrence of cognitive dysfunctions, dementia, progressive memory loss, schizophrenia, Parkinson's

disease, and Alzheimer's disease to mention but a few. Aging has also been theorized as a cumulative accumulation of damaged primary biomolecules such as DNA, lipid, and protein over time, which, in turn, culminates into several pathophysiologies and negative functions at the cellular as well as organ level, which then results in disease and ultimately death (Zhang et al., 2016; Zhong et al., 2013).

According to the literature, free radicals, oxidative stress, and other genotoxic stressors are the main culprits for most chronic and neurodegenerative diseases, particularly aging (Ahmed et al., 2015; Ahmed et al., 2017; Pisoschi and Negulescu, 2011; Dzoyem and Eloff, 2015; El Assar et al., 2013; Ibrahim et al., 2017; Ibrahim et al., 2018a,b; Nirmala et al., 2018). Furthermore, the associations between ROS generation, inflammation, and disease progression are well established through the stimulation of cytokines release and activation of enzymes (such as lipoxygenases) from the various inflammatory cells (Dzoyem and Eloff, 2015; Yin et al., 2016). The various inflammatory processes have also been linked with significant alterations in several cellular metabolisms. Neuroinflammation events are fundamentally responsible for the activation of brain immune cells, like astrocytes and microglia (Yin et al., 2016). Oxidative stress is responsible for telomere shortening and attrition which have been implicated in the acceleration of the aging process through telomere dysfunction-mediated cellular senescence (Zhang et al., 2016).

Though aging cannot be prevented, it, however, could be made to progress gracefully, healthily, and positively. One of such dependent variables that can positively influence senescence is nutrition, whose role in healthy aging has led to significant global concerns by health-conscious consumers to increasingly demand functional whole food and superfoods with exceptional health benefits. It is, thus, trending to explore the functional properties of herbal and medicinal as conventional foods, especially as a therapeutic ingredient in age-related health issues (Domínguez-Perles et al., 2019; Sabaragamuwa et al., 2018). Physiologically, nutrition modulates blood pressure, endothelial dysfunctions, inflammation, insulin sensitivity, and subclinical oxidative stress (Domínguez-Perles et al., 2019).

3.4. Skin aging and inflammation

Though an increase in the mortality and morbidity risks with age is a known defining property of the aging process, there is also a non-linear and sometimes exponential increase in the incidence of cancer, cardiovascular as well as neurodegenerative diseases with age (Gruber et al., 2019). According to the inflammaging theory, however, the classic hallmark of aging is chronic and subclinical low-grade inflammations. It has, thus, been postulated that the production of the danger-associated molecular pattern (DAMP) induces inflammation which, in turn, is induced by aging (Alencar-Silva et al., 2018; Franceschi et al., 2017; Franco et al., 2022). Similarly, the protective function of the skin is greatly affected by aging which is responsible for the inflammatory processes, skin barrier disruption, a decrease in wound reparability, and an increase in the risk of skin cancer. Thus, skin aging is characterized by elasticity reduction, pigmentation, and some harmful effects on the skin extracellular matrix (ECM) as well as increased ROS production, which leads to an imbalance in the free radicals production, decrease in the number of fibroblasts and keratinocytes, reduction in the epidermis turnover, decrease in collagen and proteoglycans, increase in the matrix metalloproteinases (MMPs) expression and decrease in the MMP inhibitors expression. Though sunlight (infra-red radiation, visible light, and ultraviolet radiation) has a pronounced causative effect on oxidative stress and skin inflammation, photoaging as well as photocarcinogenesis, sleep deprivation, stress, and other environmental factors such as

air pollution, cosmetic products, nutrition, and tobacco smoke also influence skin aging and carcinogenesis (Bellei & Picardo, 2020; Gruber et al., 2019; Krutmann et al., 2017; Parrado et al., 2019; Seok et al., 2016). ROS also stimulates the inflammation process through the upregulation of COX-2, synthesis of prostaglandin E2, and skin erythema induction (Masaki, 2010). There are also yet-to-be well-understood biological differences between premature senescence and the chronological aging phenotype. Nevertheless, cellular senescence has some underlying common molecular and cellular traits and it is also associated with a vast range of human pathologies. Telomeric dysfunction from repeated cell division, on the other hand, is also mainly implicated in replicative senescence (Bellei and Picardo, 2020; Franco et al., 2022). Furthermore, caveolin-1 (Cav-1) also contributes pathophysiologically to hyperproliferative and inflammatory skin aging. Normal expression of Cav-1s is required by the cells for regular functioning. Its overexpression or deficiency, however, results in premature cellular senescence. An up-regulation of Cav-1 expression has been demonstrated in the skin fibroblasts both in UV-induced and chronological aging conditions whereas mitochondrial dysfunction can lead to Cav-1 deficiency (Kruglikov et al., 2019).

3.5. Aging and skincare

Aging is, undoubtedly, an integral part of life affecting all body systems including the human integumentary system, the skin, which is certainly the largest organ in the body and which does not only keep the body functioning and protects it against external factors (biological, chemical, and physical) but also maintains body homeostasis and prevents the loss of biomolecules, electrolytes, and more importantly water (Barreira et al., 2019; Ratnasooriya et al., 2014; Wang et al., 2019a,b; Franco et al., 2022). The role of the skin tissue in drug delivery is also well reported in the literature (Martins et al., 2019; Rehman et al., 2015). The three layers of the skin are the epidermis, dermis, and hypodermis. The epidermis is the outermost layer with five separate sub-layers, namely: stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum, and stratum basale. The base layer of the epidermis, stratum basale, connects the dermis and also contains melanocytes. The dendrites of the melanocytes help to transfer melanin to keratinocytes. Melanin protects against damage by ultraviolet (UV) light and its synthesis is responsible for the darkening of the eyes, hair, and skin (Wang et al., 2019a,b). The mechanism of

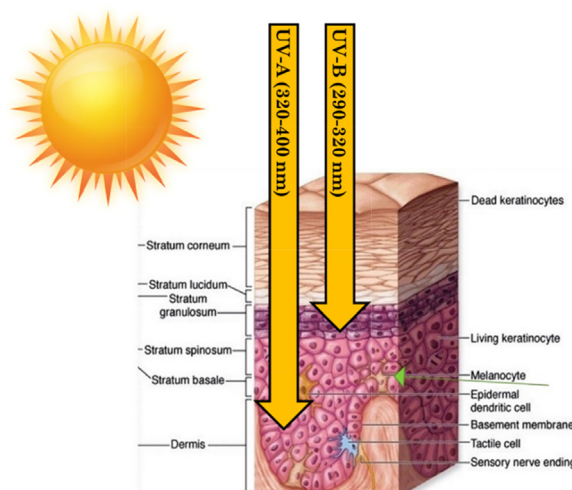


Fig. 2. Structure of the skin. The epidermis layer of the skin contains five main sub-layers, namely: stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum, and stratum basale. The ultraviolet (UV) radiations UV-A (320–400) and UV-B (290–320 nm) reach the dermis and epidermis, respectively.

melanin synthesis is through the oxidation of tyrosinase or L-3,4-dihydroxyphenylalanine (L-DOPA) via the activity of tyrosinase and tyrosinase-related protein 1 (TRP-1). Skin plays a significant role in identifying human aging. And the most important factors attributed to skin aging are free radicals and ROS which induce oxidative stress in skin cells causing significant damage to DNA and biomembranes (Siavash et al., 2011). The two types of skin aging are chronologic aging (intrinsic or endogenous) and exogenous aging (photoaging). While chronologic aging, due to the passage of time, is mainly accompanied by the progressive deterioration of the structure and function of the skin, environmental factors such as long-term exposure to sunlight (UV radiation) are responsible for photoaging wherein skin texture changes (Alencar-Silva et al., 2018; Espinosa-Leal and Garcia-Lara, 2019; Gruber et al., 2019; Lee et al., 2019; Mukherjee et al., 2011; Park et al., 2018; Thakur et al., 2022). The two main deleterious types of UV are UV-A and UV-B with the spectrum in the range of 320–400 nm and 290–320 nm, respectively (Fig. 2). The UVA rays are mainly absorbed by various cellular chromophores such as bilirubin, heme, melanin, riboflavins, porphyrin, pterins, and urocanic acid upon penetrating the skin. Though both UV-A and UV-B rays directly harm the skin, UV-A radiation, alone gives more than 80% of daily UV and damages the collagen and elastic tissue by penetrating more deeply to the dermal-epidermal junction as well as the dermis (Burke, 2018). Skin sagging and wrinkles, due to weakening of the skin strength and elasticity, are, thus, the commonly visible imperfections in the repaired dermal matrix as a result of repeated exposure to solar radiations as well as the effect of some endopeptidases, the MMPs which degrade ECM components (Alencar-Silva et al., 2018). The role of connexins as important key determinants of epidermal homeostasis has also been reported (Levit and White, 2015).

Other common consequences of acute and chronic sun exposure are DAMP generation, changes in skin pigmentation as well as photo-induced skin cancer. The deleterious effects of sun rays on the skin are mainly due to its ultraviolet rays (Madan and Nanda, 2018; Seok et al., 2016; Thakur et al., 2022). On the other hand, intrinsic/age-dependent aging is mainly due to conditions such as hormonal changes, telomere shortening, as well as an imbalance between free radicals and antioxidants. Most of these conditions lead to a dramatic reduction in the level of collagen, elastin, and hyaluronic acid (HA). Collagen, alone, makes up 80% of dry skin weight and is responsible for tensile strength and skin flexibility maintenance. Elastin is required for skin elasticity while HA also helps to retain skin moisture contents, elasticity, and structure, as well as rapid tissue proliferation, tissue regeneration, and repair (Espinosa-Leal and Garcia-Lara, 2019). Thus, potential antiaging materials should be able to inhibit collagenase, elastase, and hyaluronidase (which degrade collagen, elastin, and HA, respectively) in addition to possessing antioxidant and anti-inflammation activities. The growing association, particularly in recent times and globally, between beauty and health as well as well-being, has resulted in an unprecedented increase in natural-based cosmetics, otherwise known as natural and organic cosmetics, a trend and a market that continues to grow faster than the overall cosmetic industry. Furthermore, the richness of the plant kingdom and marine organisms in bioactive compounds that can protect, heal and maintain human skin beauty is known since ancient times (Barreira et al., 2019; Espinosa-Leal and Garcia-Lara, 2019; Hossain et al., 2021). Mukherjee and colleagues have reported naturally sourced bioactive compounds commonly used against skin aging (Mukherjee et al., 2011). It is, however, worthy of note that natural products are not necessarily safe and effective. Thus, it is very important to evaluate both their safety and efficacy to ensure the best conditions for their use (Barreto et al., 2017; Costa and Santos, 2017).

Having reviewed the role of antioxidants and skincare in tackling the menace of free radicals and inflammation, it is highly essential to address the potential roles of naturally-derived cosmetics, cosmeceuticals, and nutricosmetics in inflammation-related skin diseases. The various approaches to enhance the potential benefits of these natural products also require appropriate awareness.

4. Cosmetics, cosmeceuticals, and nutricosmetics

A “cosmetic product” is a substance with soft action that is rubbed or sprinkled on the various parts of the human body for beautifying, cleansing, increasing attractiveness, smoothing, reinforcing, restoring, protecting, and keeping the body in good condition with the skin, hair, nail and oral being the most focused primary action areas. Examples include, but are not limited to, creams, lotions, ointments, toilet soaps, shower preparations, make-up powders, deodorants, perfumes, depilatories, and antiperspirants. The world’s cosmetic industry is worth hundreds of billions of US dollars and euros. The variety, diversity as well as potential of natural products to compete with the existing natural and synthetic materials have made the industry remain fixated on the constant search for novel and improved natural products as alternatives and more suitable raw materials. The fundamental cosmetic formulation components include simple ingredients such as emollients, humectants, thickeners, emulsifiers, preservatives, stabilizers, and neutralizers as well as biologically active ingredients such as antioxidants, anti-acne substances, fragrances, dyes, and sunscreens (Costa and Santos, 2017). Cosmeceutical, on the other hand, denotes a combination of cosmetics and pharmaceuticals. Thus, it refers to products with bioactives having medical drug-like benefits and are applied topically to esthetically influence the biological function of the skin through the supply of the needed nutrients for healthy skin to improve its appearance, anti-aging activity, texture, and radiance. Though the skin and hair are the most focused primary action areas, modern cosmeceuticals offer both immediate response (like a cosmetic) as well as a prolonged effect (like a pharmaceutical) with a strong consideration for well-being. And according to Raymond E. Reed, the first to describe “cosmeceutical” in the late twentieth century, a cosmeceutical is any product that is scientifically designed for external application, produces a desired useful result, has desirable esthetic properties, and meets rigid chemical, physical, and medical standards (Barreira et al., 2019; Costa and Santos, 2017; Espinosa-Leal and Garcia-Lara, 2019; Rahul et al., 2018; Taofiq et al., 2016b; Hossain et al., 2021). In the natural personal care industry, cosmeceuticals have become the fastest-growing segment and, thus, assume the future generation of skincare owing to the various advances in the world of dermatological products (Wanjari and Waghmare, 2015). Despite the putative consensus on the scope of cosmeceuticals, however, there is no official definition commonly agreed upon by all countries. While most governmental offices, like the US FDA, do not recognize the term, the Korean and Japanese offices legally recognize 3 distinct categories of products, namely; cosmetics, functional cosmetics, and drugs. One of the newest trends in skincare, in recent times, is “nutricosmetics” which combines cosmetics with food and pharmaceutical. In other words, it refers to the use of edible ingredients with excellent and effective skin-repairing bioactives. It symbolizes the enhancement of the health and visual appearance of the skin through the consumption of functional foods. It underlies beauty promotion from within (Dini and Laneri, 2019). It is trending in the cosmetic industries to develop nutricosmetics with high contents of several bioactives such as ceramide, collagen, elastin, and hyaluronic acid which are capable of enhancing or maintaining the skin as well as hair

Table 1
Common materials with nutricosmetics potential.

Ingredients	Relevant properties	References
Marine macroalgae (seaweed) for Edible mushroom (<i>Schizophyllum commune</i>)	Various cosmetic applications Strong antioxidant and anti-tyrosinase effects	(Mazarrasa et al., 2014) (Abd Razak et al., 2019)
Sericin from tasar silk fiber wastes	Free radical scavenging potential; anti-tyrosinase; anti-elastase and anti-GST activities	(Jena et al., 2018)
Liverworts from Marchantia species	Anti-melanoma and tyrosinase inhibitory properties of marchantin A	(Gawel-Bęben et al., 2019)
Ferns (<i>Stenoloma chusanum</i>)	Antioxidant and anti-tyrosinase activities	(Wu et al., 2017)
Medicinal halophytes (Tamarix gallica; <i>Daucus carota</i> ; Frankenia laevis; <i>Raphanus raphanistrum</i> ; <i>Inula crithmoides</i> and <i>Plantago coronopus</i>)	Antioxidant; antibacterial and anti-tyrosinase activities	(Jdey et al., 2017)
Degraded polysaccharide from brown algae (<i>Sargassum fusiforme</i>)	Improved antioxidant and anti-tyrosinase activities	(Chen et al., 2016)
Alkali-extractable polysaccharides from Mushroom (<i>Agaricus bisporus</i>)	Antioxidative; antiaging, and hepatoprotective activities	(Li et al., 2017)
Mycelial polysaccharides from <i>Lepista sordida</i>	Antioxidant and anti-aging activities	(Zhong et al., 2013)
White grape pomace extracts	Antioxidant, anti-tyrosinase, and anti-inflammatory activities	(Ferri et al., 2017)
Bird's nest fern (<i>Asplenium australasicum</i>) frond extracts	Anti-melanization and anti-tyrosinase activities	(Zeng & Lai, 2019)
Aerial parts of <i>Eryngium tricuspidatum</i> L.	Antibacterial; antioxidant; tyrosinase inhibitory activities	(Benmerache et al., 2016)
<i>Phyllanthus emblica</i> fruit extract	Inhibitions of melanogenesis	(Wang et al., 2019a,b)
<i>Kummerowia striata</i>	Anti-melanogenic and anti-oxidant activities through down-regulation of TRP-1, TRP-2, and MITF expression	(Lee et al., 2019)
Rhizomes and flowering aerial parts of <i>Iris albicans</i> extracts	Antioxidant and anticholinesterase activities	(Hacıbekiroğlu and Kolak, 2015)
Leaves of <i>Burkea africana</i> , <i>Leucaena leucocephala</i> , <i>Lippia javanica</i> , <i>Englerophytum magaliesmontanum</i>	Anti-inflammatory; anticholinesterase and antioxidant activities	(Dzoyem & Eloff, 2015)
Aerial part of <i>Achillea cucullata</i> (Asteraceae)	Antioxidant; antimicrobial; anticholinesterase; and antidiabetic activities	(Eruyur et al., 2019)
<i>Arceuthobium oxycedri</i> (D.C.) M. Bieb (dwarf mistletoe).	Antioxidant and anticholinesterase activities	(Erdogan et al., 2019)
Brazilian red macroalgae (<i>Hypnea musciformis</i> ; <i>Ochtodes secundiramea</i> ; <i>Pterocladia capillacea</i> ; Santelices & Hommersand (Rhodophyta)	Acetylcholinesterase inhibitory activity	(Machado et al., 2015)
<i>Rhodolirium andicola</i> : a new renewable source of alkaloids with acetylcholinesterase inhibitory activity	Acetylcholinesterase inhibitory activity	(Moraga-Nicolás et al., 2018)
Virgin coconut oil	Improved cognitive status of Alzheimer's patients	(Hu et al., 2015)
<i>Centella asiatica</i> (Gotu Kola)	Wholesome anti-oxidative, neuroprotectant, anti-inflammatory, neuron, neurotoxicity inhibition effect, anti-anxiety, and anti-depressive properties	(Sabaragamuwa et al., 2018)
<i>Oryza sativa</i> L. (brown rice and bran oil)	Reduce hypercholesterolemia and cardiovascular risk; anti-inflammatory; immunostimulatory; and antioxidant activities; dermatologic and cosmetic applications	(Burlando and Cornara, 2014)
Tea (<i>Camellia sinensis</i>)	Anti-cancer; anti-diabetic; antioxidant; anti-inflammatory; cardioprotective activities; good for cardiovascular, infectious, and neurological diseases	(Sanlier et al., 2018)
Bamboo culm, leaves, rhizome, shaving, roots, seeds, and shoots	Antioxidants activities; effective against age-related chronic and neurodegenerative diseases, cancer, and diabetes.	(Nirmala et al., 2018)
Apple pomace	Rice in bioactive compounds with potential food and pharmaceutical applications	(Barreira et al., 2019)
<i>Bacopa monnieri</i>	Neuroprotective effects; amelioration of cognitive impairment and neurodegeneration	(Khan et al., 2015; Saini, Singh, & Sandhir, 2012)
Pomegranate	Antioxidant; antimicrobial, antihelminthic; immunity-boosting, anti-carcinogenic; anti-hyperlipidemic; and neuroprotective activities; synthesizing different nanoparticles	(Karimi et al., 2017)
Cocoa (<i>Theobroma cacao</i> L.) pod husk	Antioxidant; anti-elastase; antityrosinase; antibacterial; and larvicidal activities; encapsulating agent and UVB sunscreen potential	(Campos-Vega et al., 2018)
Safranal from <i>Crocus sativus</i> Linn. (saffron flowers)	Antioxidant; anti-elastase; anti-collagenase; anti-hyaluronidase; and sun protecting activities	(Madan and Nanda, 2018)
Orange pekoe grade black tea (<i>Camellia sinensis</i> L.).	Anti-hyaluronidase activity	(Ratnasooriya et al., 2014)
Bangladeshi medicinal plant <i>Pothos scandens</i>	Anti-estrogenic, anti-hyaluronidase; and histamine release inhibitory activities.	(Muhit et al., 2016)
<i>Aesculus hippocastanum</i> flower extracts	Treatment of inflammation	(Dudek-Makuch et al., 2019)
<i>Ocimum sanctum</i> Linn.	Skin anti-aging compounds	(Chaiyana et al., 2019)
Sri Lankan <i>Artocarpus altilis</i> ; <i>A. nobilis</i> ; <i>Eleocarpus serratus</i> & <i>Mesua ferrea</i>	Anti-tyrosinase; anti-elastase; anti-hyaluronidase; antioxidant	(Liyanaarachchi et al., 2018)
<i>Hypericum origanifolium</i> Willd	Anti-aging potential; antioxidant; anti-elastase; and anti-collagenase activities	(Boran, 2018)
Tunisian propolis	Antioxidant and anti-inflammation activities	(Gargouri et al., 2019)
<i>Tagetes erecta</i> Linn flower	Anti-elastase; anti-hyaluronidase; and MMP-1 inhibitory activities	(Maity et al., 2011)
Black seed (<i>Nigella sativa</i> L.)	The oil is used to treat various skin conditions	(Hossain et al., 2021)

structure and function. The presence of these bioactives in some natural products, which are consumed, has also been linked to the significant inhibition of enzymes such as collagenase, elastase, hyaluronidase, and tyrosinase, thereby maintaining the structural stability, elasticity, moisture content, and blocking melanogenesis, respectively (Abd Razak et al., 2019; Taofiq et al., 2016b). A few examples of common natural products with nutricosmetics potential is provided in Table 1.

Similar to cosmeceuticals, there exists no official definition which is commonly agreed upon by all countries for functional foods. Nevertheless, the four main aspects of functional foods are the health benefits through enhancement of the target function or prevention of the disease occurrence; the nature of food by being a traditional food; the level of function which should be beyond the food's basic nutritional function and the consumption pattern which is through normal routine diet (Nazir et al., 2019). Generally, food-derived bioactives are putatively safer than those obtained through synthesis or from herbal medicines. Furthermore, functional foods with multiple-targeted and multipotent agents have the advantages of lower risks of drug-drug interactions as well as better predictable pharmacokinetic behaviors (Zhang, 2007). On the other hand, there has been a paradigm change in the way the anti-aging campaign is approached owing to the significant development in anti-aging skincare. The emergence of advanced technology and biological treatments has culminated in the increasingly growing use of growth factors, stem cells, neural rejuvenation, DNA-customized formulas, youth-promoting nanotechnologies, mitochondria, enzyme boosting treatments, plasma therapies, and hormone replacement therapies to regenerate damaged skin (Siavash et al., 2011).

The following sections would address the various approaches that should be adopted to enhance the potential benefits of naturally-derived cosmetics, cosmeceuticals, and nutricosmetics.

5. Delivery systems in cosmeceutical and nutricosmetics

5.1. Natural products and delivery systems

Natural products refer to chemical compounds that are derived or obtained from living organisms found in nature with the capability of significantly enhancing human health or treating different kinds of diseases. The main sources of natural products are plants,

animals, and microbes which are obtained from both land and marine organisms. Natural products such as organosulfur, phyto-sterols, polyphenols (e.g. stilbene, simple phenolic acids, curcuminoids, flavonoids, isoflavonoids), and terpenoids (e.g. carotenoids) also play an important pathological role against aging, cancer, diabetes and its complications, hepatotoxicity, oxidative stress, and obesity. Thus, about 80% of the African and Asian populations depend on natural medicines for their primary health care, according to the World Health Organization (WHO).

In general, the topical use of antioxidants and vitamins in cosmetics, cosmeceutical, and nutricosmetics are known not to only better protect the skin but also possibly to neutralize the damages of the free radicals. Antioxidants and vitamins also play significant anti-inflammatory roles in stimulating collagen production, suppressing skin pigmentation and bruising as well as refining keratinization (Siavash et al., 2011). Nevertheless, the issues of permeability, bioavailability, low water solubility, stability, rapid catabolism, and excretion as well as ingestion efficiency are some of the challenges facing the application of natural products and their bioactives. Exposure of these bioactives to adverse pH and temperature conditions, enzymatic activities, light, metal ions, oxygen, and water usually results in the alteration and/or destruction of their beneficial properties.

A summary of the success of various colloidal delivery systems, their conventional and advanced preparation methods, and common characterization techniques has been reviewed by Kapoor et al. (2019). Liposome, for instance, is a lipid-based delivery system to deliver natural products. It is also one of the most common carriers used for the encapsulation of bioactives both in cosmetics and various pharmaceutical applications. The biodegradability, safety, enhancement of the transcellular transport through transient disruption of cellular lipophilic bilayers as well as improvement of the *para*-cellular drug transport by altering the tight junctions make the self-assembling and cell-resembling lipid-based colloidal delivery system a promising approach to encapsulating and protecting both hydrophilic and lipophilic compounds (Shishir et al., 2019). A critical review of the major problems complicating liposomes development for bioactives delivery, issues related to its preparation techniques and encapsulation efficiency, the loss of its protective function, its inefficiency of skin permeability, its alternative development strategies as well as their respective advantages and drawbacks have been reported (Van et al.,

Table 2
Common delivery systems for bioactives.

Delivery system	Benefits	Potential applications	References
Liposome	Sustained and targeted drug delivery; reducing drug-induced toxicity; improving drug solubility; increasing circulation time; overcoming multi-compound resistance; and improving the therapeutic index	Agrochemical; pharmaceutical; cosmetic; and food industries	(Shishir et al., 2019)
Micro and nanoencapsulation	Production of stable capsules; protection of the core compound from moisture, oxygen, and UV rays; allows the modification and/or improvement of the properties of the active substance; increase the shelf life of a volatile compound; control release; reduces agglomeration of fine powders; improve the handling properties of sticky materials, and prevent chemical reactions with external factors	Agrochemical; cosmetic, food; pharmaceutical; and textile industries	(Ribeiro et al., 2020)
Nanoemulsion, nanoparticles, phytosomes, nanovesicles, nanoliposomes, and niosomes	Enhanced penetrability and bioavailability of the active compounds; penetration to the cell membranes; encapsulating both hydrophilic and hydrophobic drugs; slowing the rate of drug break down, extending the drug half-life, stabilizing sensitive drugs, lessening the toxic and side effects of drugs; improving entrapment efficiency	Cosmetics; agrochemical; food; and pharmaceutical industries	(Karimi et al., 2017)
Bilosomes and Double emulsions (duplex or multiple emulsions)	Easy availability and high potency as penetration enhancers to improve the oral bioavailability, co-delivery of nutraceuticals, fat and salt reduction e in foods without altering the food's native sensory properties	Agrochemical; food; cosmetics and pharmaceutical industries	(Aditya et al., 2017)
Polymeric and inorganic nanoparticles, Protein-based nanocarriers, Lipid-based and vesicular delivery systems, and exosomes	Improved drug bioactivity, low toxicity, the capability of evading the immune system, ability to cross the permeability barrier of the skin, enhanced drug penetration into and through the skin	Agrochemical; food; cosmetics and pharmaceutical industries	(Lagoa et al., 2020)

2019). A comprehensive review of the microencapsulation concepts, methods, characterization, release studies, media, and kinetics has also been discussed by Ribeiro et al. (2020).

Therefore, different delivery systems (such as emulsions, microencapsulation, microemulsions, microgels, phytosomes, liposome, nanoliposomes, nanoemulsions, niosomes, nanoparticles, nanovesicles, solid-liquid nanoparticles, and biopolymer-based nanoparticles) have been developed for the incorporation of natural products or purified plant extract to improve the bioavailability, stability, solubility as well as to control and protect the release profile of natural products within GI tract (Shishir et al., 2019; Karimi et al., 2017; Ribeiro et al., 2020). The commonest delivery systems for bioactives are itemized in Table 2.

5.2. Application of nanotechnology for bioactives

The incorporation of bioactives into functional products such as foods and cosmetics has been majorly hindered by their putative oxidation as well as various degradation reactions and thermal enhanced oxidation during food processing and storage. Thus, several delivery systems using nanotechnology science have been developed to protect the bioactive, improve their pharmacokinetic profiles, enhance their capabilities to cross several biological barriers, and increase their intracellular penetration and distribution to the target site (García-López et al., 2019).

Nanomedicine and nanotechnology offer an ideal solution for disease prevention, detection, and treatment. The potential possibilities of simultaneous works on different cellular mechanisms, organic molecules, and biological processes at the nanoscale are the main drivers of nanotechnology success in the healthcare sector (Kaur et al., 2014). Furthermore, the increasing consumer awareness coupled with the negative perception and strict regulatory requirements attributed to the use of synthetic antioxidant compounds has also enhanced the exploration of various natural alternatives. In recent times, the use of physical and chemical modification for both the dispersed and continuous phase approaches are being employed on the encapsulation systems such as emulsions and particles to prevent undesirable oxidative reactions of these labile ingredients thereby mitigating their losses due to oxidation. The antioxidant mechanisms of yeast, with its various internal compartments and a multilayered cell wall and ease of culturing at an industrial scale, have, however, been employed as carriers for a variety of bioactive compounds as well as biopolymers such as proteins and DNA (Young and Nitin, 2019).

The bioavailability, chemical instability, inferior biocompatibility, and poor water solubility of most bioactives have also limited their practical application. The use of nano- and microvectors such as polysaccharide-based polyelectrolyte complexes (PECs), and in particular, chitosan-based polyelectrolyte complex nanoparticles for the entrapment of bioactives is becoming more popular to enhance bioactives bioavailability, functionality, and solubility owing to their considerable bacteriostatic properties, biocompatibility, biodegradability, excellent loading efficacy, and hydrophilicity. One of the most efficient ways of improving the functional properties of natural polysaccharides is quaternization. The efficiency of the encapsulation property of quaternized polysaccharide derivatives is linked to their possession of a remarkable polycationic character as well as their ability to form stable PECs with polyanions in aqueous media (Wu et al., 2019).

Polymer-based nanoscale particles enhance controlled release rates and targeted delivery of the encapsulated components in addition to protecting them from enzymatic attack. The ability of amphiphilic biopolymers such as proteins to interact with both the solvent and encapsulated bioactives makes them perfect and ideal materials for preparing nano-sized delivery particles in addition to their low toxicity. The low aqueous solubility of water-

insoluble protein-based nanoparticles like zein and gliadin except in the presence of surfactants for the synthesis of and stabilization of lipophilic drugs due to relatively low percentages of either charged or hydrophilic amino acids has hindered their practical and functional application. Furthermore, the use of large amounts of organic reagents (such as ethanol and glutaraldehyde-based cross-linking agent) has also restricted the application of soy protein nanoparticles in the food industry despite their relative stability (due to the high surface charge) and facile dispersion in the aqueous phase. Alternatively, egg white protein with its excellent digestibility, nutritional value, self-assembly, and amphiphilic properties is being applied as emulsifiers and new delivery vehicles using heating gelation followed by the homogenization method (Chang et al., 2019). The use of colloidal dispersions, with average diameters lower than 500 nm, otherwise known as nanoemulsions, to carry, protect, and release bioactive lipophilic compounds in aqueous media is also a common nanostructured delivery system. Factors such as the structural and compositional properties of the emulsion system, the type of emulsifiers, and other ingredients present within the food matrix, however, greatly affect the efficiency of encapsulation and release of bioactive compounds (Artiga-Artigas et al., 2018).

The review of the green extraction solvents and the enhancement of the bioavailability, stability, solubility and controlled release profile of the bioactives using different delivery systems for naturally-derived cosmetics, cosmeceuticals, and nutricosmetics would be incomplete without discussing the potential global market value, motivators, drivers, trends, challenges, halal issues, and other common certifications for cosmeceuticals and nutricosmetics.

5.3. Global market value for cosmeceutical and nutricosmetics

The cosmetic industry is continuously growing into a highly competitive and highly desirable industry and is currently worth about 445 billion dollars in annual sales with the natural-based cosmetics growing even faster than the entire cosmetic industry (Barreira et al., 2019; Espinosa-Leal and Garcia-Lara, 2019). The major players are the Asia Pacific, Western Europe, and North America regions contributing about 40%, 29%, and 14%, respectively of the total market. Japan and South Korea are considered the largest skincare markets ranking No.1 and No.3 in the global skincare sales (Siavash et al., 2011). Though the global market trends are heterogeneous, evolving, and growing at different rates within and across various countries and continents, the reasons for these differences are not far-fetched. The socio-demographic and socio-cultural differences among consumers as well as their acceptance are the major factors. Furthermore, functional foods alone have an annual average growth rate of 8.5% with the global market value anticipated by 2020 to exceed \$305.4 billion being the fastest-growing segment of the global food market (Nazir et al., 2019). Therefore, the global market potential for the multi-billion cosmeceutical and nutricosmetics industries will continue to grow for many decades to come.

5.4. Motivators and drivers of cosmeceutical and nutricosmetics market

The role of factors such as consumers' age, education, awareness, mood, beliefs, appetite, socioeconomic status, reduction in health-care costs, access to more information, media, labeling, and product attributes, among others, are indisputably significant. Though it is difficult to practically predict with absolute certainty why a consumer would decide to buy/not buy a product, nevertheless, the three main factors influencing a consumer's decision to purchase are consumer characteristics, product characteristics,

and purchasing situation. The increase in life expectancy has also put pressure on the need for the increasing need for an improved quality of life for aging consumers. According to the U.S. State Department and the United Nations Department of Economic and Social Affairs, about 8% of the people worldwide are currently over the age of 65. And by 2030, this percentage increase is expected to reach 13% (Nazir et al., 2019).

The consumers' responses are central to the success of any new technologies. Consumers from different countries respond differently. Nevertheless, consumers are easily influenced by information; favorable to innovations that enhance the quality of life; and are critical of technologies that seem to require an excessive modification of the original product and thus portends danger to human health and the environment. The development of innovative solutions by firms is not enough to remain competitive in the progressive economic globalization but must be accompanied by the adoption of a differentiation approach such as the creation of extra value or higher value-added benefits in the minds of the consumers even beyond product attributes and functional benefits as well as efficient communication efforts to consumers. One such effective conduit to influence consumer behavior is certification and labeling systems (Sillani and Nassivera, 2015). Nevertheless, the role of external factors such as government regulations through market licenses, mandatory national standards, and administrative punishment as well as internal factors through voluntary certifications is more than essential (Guo et al., 2019). Furthermore, an integrative approach focusing on the consumers' perception and requirements, sustainable formulation process, and purposeful marketing strategies is also cardinal to successful cosmetic product development (Costa and Santos, 2017).

5.5. Trends and challenges

One of the most common trends with a lot of potential in the cosmetic industry is industrial biotechnology or the production of natural compounds through the use of suitable microorganisms as biocatalysts from different sources such as adverse environments, agro-industrial wastes, and contaminated samples (Pessôa et al., 2017). The various biotechnological techniques and transformations use are commonly employed to improve both plants and animals, develop them for specific uses or to make or modify products. Thus, biotechnology offers several benefits such as high yields in mild reaction conditions, high specificity, reduction of by-products formation as well as reduction of the overall production costs (Almeida et al., 2017).

One of the most important challenges, however, is the recovery of the bioactives from their natural sources, wherein extraction plays a significant role. There are many excellent reviews on major important processes involved, the extraction and delivery system of the bioactives, the common test employed as well as the trends in the development of cosmeceuticals and nutricosmetics (Espinosa-Leal and Garcia-Lara, 2019; Ribeiro et al., 2020; Van et al., 2019; Yahya et al., 2018). Though several extraction techniques using different solvent systems have been developed

(Chemat et al., 2012; Zhang et al., 2018), the choice of a suitable technique and solvent system mainly rests and depends on the target metabolite. Besides the safety of the active ingredients and all the other major excipients (Costa and Santos, 2017), other challenges include the cost, easiness, efficiency, simplicity, and versatility of the selected system. Furthermore, the potential health risk and environmental concerns of the conventional organic solvents have led to the incorporation of natural deep eutectic solvents (NADES) and ionic liquids (ILs) as an alternative, green, safe, and sustainable solvents for the extraction of the target compounds (Benvenuti et al., 2019; Martins et al., 2017). Though both deep eutectic solvents (DESS) and ILs have few things in common, the source of the starting materials, as well as the chemical formation process, are the two striking differences between the two. While ionic substances are the sources of ILs which combine through the process of ionic bonds, most DES, on the other hand, are obtained from non-ionic species (such as salts) as well as molecular components, which combine through a complexation between a hydrogen bond donor or a complexing agent and a hydrogen bond acceptor. DESS, in particular, are characterized by low melting points, low toxicity, high solubility, high biodegradability, low volatility, low vapor pressure, non-flammability, dipolar nature, chemical, and thermal stability, ease of storage, and tuneability (Mbous et al., 2017). NADES, in particular, is characteristically an alternative media to water in all living organisms. They are thought to protect living organisms from extreme conditions and are also involved both in the biosynthesis as well as the storage of non-water cellular metabolites. Their unique abilities to be formed from many abundant primary metabolites and to dissolve both non-water-soluble metabolites and macromolecules are related to their broad polarity range and supramolecular structure (Dai et al., 2013).

Furthermore, it would be a worthwhile expedition to explore the use of functional electrolyzed water both as a standalone as well as for the extraction of bioactives. There is accumulating evidence now supporting the potential health benefits of reduced water particularly, for inflammation and oxidative stress-related diseases such as arteriosclerosis, cancer, diabetes, and neurodegenerative diseases. Electrochemically reduced water, otherwise referred to as alkali-ionic water, alkaline electrolyzed water, alkaline ionized, or alkaline cathodic water is normally produced near a cathode and also contains hydrogen molecules as well as mineral nanoparticles thus exhibiting more potent reducibility (Ignacio et al., 2012; Sarshar et al., 2017; Shirahata et al., 2012). There are other excellent reviews on the major challenges as well as the potential solutions and trends in the delivery of phytochemicals (Aditya et al., 2017; McClements, 2020).

The non-universality but differences in the scope of definition and regulations of cosmetics and other related terminologies also remains a challenge. Furthermore, there are other challenges related to the successful development and incorporation of various delivery systems. These include, but are not limited to, their batch to batch reproducibility issue, cytotoxic effect, drug leakage, lack of effective sterilization methods, lack of specific protocols for pre-

Table 3
Common certification systems.

Certification system	Country	References
Hazard Free Food Certification system; Organic Food Certification system; and Green Food Certification system	China	(Guo et al., 2019)
Eco-certification (Rainforest Alliance Certified)	USA	(da Silva et al., 2019)
Marine Stewardship Council	UK	(Vince and Haward, 2019)
Hazard Analysis and Critical Control Point (HACCP).	Global	(Vilar et al., 2012)
Good manufacturing practice (GMP)	Global	(Sandle, 2019)
The International Standards Organization (ISO)	Global	(Boudouropoulos and Arvanitoyannis, 1998)

clinical studies, low drug entrapment, presence of trace amount of organic solvents in the final preparation as well as stability and scale-up problems (Kapoor et al., 2019; Kaur et al., 2014). Another important challenge facing natural products-related industries such as cosmetics, cosmeceutical, functional foods, nutricosmetics, and herbal products is the issue of the claim. Most manufacturers and marketers are culpable of false and bogus claims with regards to health, quality (nutrient content), and effectiveness (structure and function). In the European Union states, for instance, all claims are scientifically assessed and pre-approved by the European Food Safety Authority (EFSA) only (Pravst et al., 2018). However, in the US, if qualified experts have a significant scientific agreement (SSA) regarding the validity of the relationship between a substance and a health outcome, then the FDA authorizes the claim, according to the Nutrition Labeling and Education Act of 1990. However, qualified health claims can still be issued or authorized by the FDA provided it has a letter of enforcement discretion, or other scientific bodies of the US Government have concluded that the evidence meets the SSA standard, or is supported by credible evidence but does not meet SSA standard (Wang et al., 2019a,b).

Individual physiological responses to bioactives may also pose some challenges owing to genetic make-up, lifestyles, and the environment. Furthermore, the incorporation and combination of different bioactives have become customary practice in cosmetics, cosmeceutical, functional foods, nutricosmetics industries, majorly because various component compounds exhibit different interactions such as additive, antagonistic, cumulative, potentiation, and synergistic effects. Thus, the designation of a single bioactive as a biomarker or signature ingredient is not enough to determine the potential biological activity of the product.

5.6. Halal certification and other common certification systems

Certification greatly ensures traceability and safety management along the supply chain. Safety issues concerning foods, cosmetics, pharmaceuticals, and so on, have become a global problem particularly after many high-profile safety events as a result of adulteration, unintentional chemical and viral contamination, as well as complex supply chains, among others (Sun and Wang, 2019). There are several certifications, in recent times, recognized regionally and internationally. A few common examples are Kosher certification, The Leaping Bunny (Go Cruelty-Free), COSMOS, ECOCERT, EcoLogo, USDA Organic, Australian Certified Organic, Carbon Free, Carbon Neutral Certification, Certified Wildlife Friendly, Environmental Choice New Zealand, Green Seal, and Vegan. On the other hand, Guo et al. (Guo et al., 2019) have also reviewed the major global regulatory authorities and their main duties. Other common certification systems are listed in Table 3.

While Kosher, a Hebrew term, literally means 'acceptable' or 'fit', Kosher certification, which is determined by Rabbi, implies that the product conforms to the Jewish dietary laws as well as Kosher food requirements (Senter and Glass, 2016). In the same vein, *halal* certification implies that the production of food and other products is following the legally permissible Islamic Law whose primary and secondary sources are; Quran, Sunnah (prophetic tradition), and consensus (*Ijma'*) among the scholars, and analogical deduction (*Qiyas*). According to the general principles of Islamic jurisprudence accepted among the Islamic scholars, "everything is permissible except that which has been explicitly prohibited" (Taimiyah, 1997). Therefore, food and other consumer products become non-halal (*haram*) by Islamic Law (*Shariah*) if, by any means, it is proven that the aforementioned *shariah* ruling has been violated. Nevertheless, a competent Islamic Authority using relevant *halal* standards and guidelines must be responsible

for the assurance, verification, and then subsequent certification of both the final product and the entire process involved in the production and supply chain (Pauzi et al., 2019; van der Spiegel et al., 2012). Though hygiene, safety, quality, and environmental concern are among the cardinal issues in *halal* and *halalan toyyiban*, spirituality, however, is the main value. The sense of accomplishment and satisfaction can only be achieved through a combination of positive emotions, religious influences, and meaningful realization of the relationship with the Creator. The synchronization of deeds with the thoughts brings about the tranquility of the heart is the *sine qua non* of spirituality (Alzeer et al., 2018). It is also incontrovertible that the notion of spirituality or spiritual quality is not only a unique but also a cardinal *essentialia* in the three Abrahamic faiths -Christianity, Islam, and Judaism- representing almost two-thirds of the global population (Farouk et al., 2015).

Thus, the need for verification as well as the issuance of halal certification by the competent halal authority is borne out of the huge demand and growing concerns of Muslim consumers for trust and reliable guarantee (Pauzi et al., 2019). It is worthy of note, however, that halal is not exclusive to Muslims only. The fact that many non-Muslim consumers, manufacturers, corporations, and nations have embraced *halal* certification is no longer a myth but a reality.

6. Conclusion

Natural products functionalized as cosmetics, cosmeceuticals, and nutricosmetics have great potential in the management and prevention of inflammation-related skin aging diseases. The use of green solvents would enhance and maximize the extraction of bioactive compounds. Furthermore, the bioavailability, stability, solubility and controlled release profile of the bioactives would be greatly enhanced using different delivery systems. The adoption of green extraction and delivery systems would support the growing interest and demand for safe and natural alternative skincare regimens in the increasingly growing multibillion cosmetic industry. Nevertheless, the harmonization of the various global regulations and certifications, including the halal assurance system would require concerted global efforts to allay the concerns and apprehensions of the growing Muslim as well as non-Muslim consumers of processed natural products.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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