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Review Article

Phytoextract Loaded Nanoemulsions for Age-Defying Effects: A Review

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ABSTRACT

Aging is an inevitable process that results in folds, ridges, and wrinkles in the skin as a result of body mass reduction, insufficient hydration, and breakdown of the connection between the dermis and epidermis. The process of skin aging involves numerous alterations arising from a combination of external factors (such as chemicals, ultraviolet radiation, pollutants, and toxins) and intrinsic factors (such as gene mutation, and hormonal factors). Several pharmacological formulations, such as nanoemulsion, can be used to treat and protect the skin against the damaging effects of reactive oxygen species. Nanoemulsion is a biphasic mixture of two immiscible liquids. Compared to other drug delivery techniques, nanoemulsions can improve drug bioavailability by increasing the absorption rate, reducing variability in absorption, protecting against hydrolysis and oxidation, delivering lipophilic pharmaceuticals and water-soluble drugs. Many drugs may benefit from an aqueous dosage form and increased bioavailability because of the extremely large surface area and low interfacial tension of the whole emulsion system; nanoemulsions have better component penetration ability. Nanoemulsions are also non-toxic and non-irritant and their physical stability can be enhanced. This review article highlights *in vitro* herbal anti-aging studies on nano emulsions loaded with phytoextracts such as *Calendula officinalis, Ocimum basilicum, Coriandrum sativum* (coriander), *Phyllanthus emblica* (Indian Gooseberry), *Punica granatum* (pomegranate), *Tagetes erecta* (marigold), *Chilli* peppers (Capsicum), *Oryza sativa* (Rice bran), *Azadirachta indica* (Neem), *Daucus carota* (Carrot), *Camellia sinensis* (Green tea), *Citrus reticulate* (Orange peel) *Curcuma longa* (turmeric) *Morus alba* (White mulberry) etc which have anti-aging potential.

Keywords: Antioxidant, Aging, Nanoemulsions, Phytoextract skin.

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INTRODUCTION

Skin aging

The skin is one of the major parts of the human body, and its primary purpose is to defend against external causes such as unwanted bacteria, stop the body from losing water and electrolytes, and protect from Ultraviolet (UV) radiation.[1] Most of the pathogens transmitted through the skin are stopped by the human skin as the first line of defence and barrier.[2] In 2019, getting older and exposure to the sun were shown to be the primary causes of skin aging, according to a study conducted with Mongolian tribes in Nepal living in Chennai, India's fourth-most populous city, which was identified as a risk factor for skin aging since the skin is prone to conditions at work, such as outdoor work and part-time labour, which may bring major changes. Skin aging is of two types: age-related aging, and premature aging. This premature aging condition is caused by external sources and includes dry skin and deep wrinkles. The free radical concept of aging, first stated by Hermann in the 1950s, is one of the most popular ideas to explain aging[3] which is directly associated with skin aging such scars impair the skin's regulatory systems, causing photo-aging and the formation of skin cancer.[4] UV light is the most significant external contributor to skin aging which leads to skin photo-aging. A preventive method of protecting human skin against cancer and photo aging is called photo protection.[5] An increased level of Reactive Oxygen Species (ROS) and resultant oxidative stress are highly correlated to age-related diseases, and[6] many enzymes overproduction or some change in them may cause aging. (e.g., hyaluronidase, tyrosinase, collagenase, and elastase) that play a role in the skin's protein matrix degeneration. There are blemishes, rough skin texture, wrinkles, uneven pigmentation, and a noticeable lack of skin elasticity in the skin. The epidermis, dermis, and subcutaneous tissue of the skin are all affected differently by the aging process. However, the effects of skin aging are most visible in the dermis, which is prone to wrinkling when both internal and external causes act on it, also reducing the elasticity of the skin. Cutaneous degeneration is associated

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with decreased levels of the Extracellular Matrix (ECM), which includes collagen, elastin, proteoglycans, glycosaminoglycans, fibronectin, and other glycoproteins. Hyaluronic Acid (HA), a glycosaminoglycan with a high molecular weight, can fill the holes in the ECM with water, providing the skin with a tighter and younger physical appearance.[7] Cellular aging happens continually after birth, affecting not only internal organ biofunctions but also physical appearances. Accordingly, oxidative stress causes a wide range of cellular degeneration, including lipid peroxidation, damaged DNA, and inflammation, resulting in skin wrinkles and a loss of skin strength and structure.

Mechanism of aging

There are several mechanisms involved in skin aging, including changes in the Extracellular Matrix (ECM), inflammation, oxidative stress, and a decrease in skin cell renewal. Elastase and collagenase are specific types of MMPs that target elastin and collagen, respectively.[8] This leads to reduced levels of fibers and collagen type VII (Col-7). This impairs the epidermis-dermis relationship, resulting in outside-aged skin. The skin aging process involves various changes induced by a combination of endogenous (cellular metabolism, gene mutations, and hormonal variables) and exogenous (pollutants, chemicals, UV Radiation, and toxins) factors. UVB radiation promotes the generation of ROS as shown in Figure 1. Melanin is a color pigment that plays a significant role in minimizing harm to the skin caused by the effects of solar radiation. The melanin deficiency impairs the skin's regulatory system, leading to photo-aging and the formation of skin cancer. These adverse effects include erythema, edema, sunburn cells, hyperplasia, immuno suppression, and photocarcinogenesis.[4]

Treatment of skin aging

Nowadays there are many anti-aging methods available to dermatologists with other preventive measures, cosmetic methods, topical and systemic therapeutic substances to manage skin aging. There are varieties of treatments available to manage skin aging (Figure 2).

Role of Phytoextracts in Aging

In the last few decades, there has been a noticeable increase in the use of herbal extracts or phytochemicals. Phytochemicals are chemical substances derived from plants that have attracted the attention of both biologists and the general public due to their ability to enhance both lifespan quality and quantity.[9] Plants produce a large range of secondary metabolites, ranging in structure from simple to complex. These compounds include flavonoids, terpenoids, phenolic, and alkaloid compounds. Chinese, Indian, and Egyptian people apply plant powders and herbs to look attractive and young.[10] Several ideas have been proposed to explain the typical aging process. According to one of the ideas, extremely reactive oxygen-derived molecules (free radicals) damage proteins, lipids, and DNA. Over the last decade, the concept of oxidative stress has gained popularity, and a significant study has been conducted reviewing the use of vitamins such as Vit A, B_{12}, Vit C, Vit D, Vit E, and folic acid and their influence on lowering oxidative stress.[11] Phytoconstituents have been shown to promote longevity and prevent and treat many types of aging-related diseases.[12] The concept of beauty and cosmetics is as old as man and society. Women are focused on maintaining their appearance. They employ a range of herbal-infused beauty products to look attractive and young. The utilization of Indian herbs is well-known around the world. Herbal cosmetics, a priceless gift from nature, are becoming increasingly popular on the global market. Herbal compounds are chosen over synthetic ones due to their widespread availability and mild negative effects. Additionally, these medicines are becoming increasingly popular due to their compatibility with various skin types and lack of side effects.

Tocopherols, flavonoids, phenolic acids, nitrogenous chemicals (indoles, alkaloids, amines, and amino acids), and monoterpenes are examples of phytoconstituents obtained from herbal drugs. Furthermore, studies indicate that they have additional benefits for preserving skin tone, texture, and looks.[13] Bioactive ingredients such as (phenols, flavonoids, stilbenes etc.) and various conventional herbal formulations of the Indian system of medicine have long been utilized to effectively regulate melanogenesis and associated disorders on the Indian continent.

Comparison of Herbal and Available Synthetic Cosmetics

Herbal treatments have been widely used around the world since ancient times, and their better therapeutic efficacy due to fewer side effects in comparison to modern drugs has been recognized by scientists, researchers, physicians, and patients. The areas of preserving and improving the overall beauty of the face and other body parts, including the lips, eyes, hair, hands, fingers, neck, etc., can be achieved by using various cosmetic formulations like-creams, face packs, powders, lotions, moisturizers, shampoo, hair oil, and conditioners. Smooth, gleaming, healthy skin and hair are attributes of a human. A variety of chemicals, toxins, bacteria, etc. found in the environment cause skin harm and affect aging naturally and free of potentially harmful synthetic ingredients that can cause injury to the skin. Synthetic antioxidants such as BHT (Butylated Hydroxytoluene) and BHA (Butylated Hydroxyanisole) are employed as preservation agents in several lipsticks and moisturizer products. The International Agency for Research on Cancer has identified BHA as a likely cause of cancer in humans.[14] Also, colors generated from coal tar are commonly used in synthetic cosmetics. It has already been identified in a study that coal tar is a confirmed human carcinogen.[11] Synthetic cosmetics alone are insufficient to care for skin and body parts; therefore, a combination of active components is not only required to prevent skin damage and aging but also to minimize

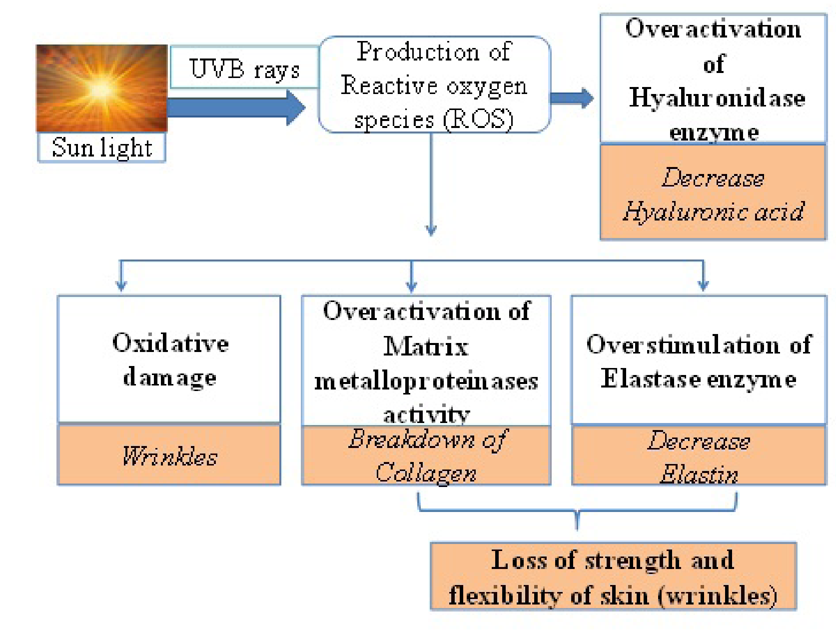


Figure 1: Systematic representation of the molecular mechanism of skin aging.

the side effects. Herbal cosmetics supply nutrients to the body, enhance health, bring satisfaction, and are favored over synthetic chemicals for personal care by today's youth. Natural substances, along with their active phytoproducts, such as polyphenols, have been investigated worldwide for their anti-aging properties, and are generally considered safe with the least adverse effects than synthetic compounds. Natural colors derived from herbs, on the other hand, are safer.[13] Synthetic antioxidants that should not be used in cosmetics because they are harmful to the skin include Butylated Hydroxyanisole (BHA), Propyl Gallate (PG) and Tert-Butylhydroquinone (TBHQ), Butylated Hydroxytoluene (BHT), which can deteriorate the skin. Plant-based bioactive chemicals such as flavonoids, linalool, quercetin, and kaempferol in topical nanoemulsions for improving skin quality may be a more desirable and safer alternative to synthetic antioxidants.[14]

Advantages of Nano Emulsion Based Formulations

Nano-emulsion technology is a very effective and promising method for topical delivery systems of potent plant-based ingredients that rejuvenate and protect skin aging.[15] Nanoemulsions have excellent stability against sedimentation or creaming because of their very small droplet size. A biphasic dispersion of two immiscible liquids is a nanoemulsion[16] which either produces an Oil-in-Water (O/W) or a Water-in-Oil (W/O) nanoemulsion that can be stabilized by an amphiphilic surfactant. Nanoemulsions are colloidal particle compositions with submicron dimensions that can be used as a drug delivery mechanism.[17] Because of the extensive surface area and low interfacial tension of the entire emulsion system, nanoemulsions have better component penetration capabilities. In the cosmetics sector currently, the most pressing need is to create nanotechnology-based (e.g. nanoemulsions, niosomes, etc.) dosage forms that may not only increase the delivery of active cosmetic chemicals into the skin but also give enhancement, get better therapeutic efficacy of the medication, and cut down on side effects and dangerous reactions when used as a drug delivery technique[17] because of various formative advantages (e.g., greater shelf-life stability, and improved textural qualities), the usage of nanoemulsions in cosmetic products has expanded over the past decades. Furthermore, as compared to conventional emulsions, nanoemulsions appear to improve active ingredient penetration through human skin because of their smaller globules size (<200nm). The capacity of nanoemulsions to improve permeability results in a significant danger of high systemic exposure of the consumer to the synthetic ingredients. But this disadvantage may prove to be an advantage in the case of using herbal nanoemulsions because herbal drugs are has the fewest side effects, so they may provide maximum therapeutic effects. Overall, the results showed that nanoemulsions can considerably modify the permeation patterns of molecules based on their physicochemical features. Notably, as compared to traditional emulsions, O/W nanoemulsions greatly improve the penetration profiles of polar active components, although no difference was observed for polar molecules.[18]

Recent research on herbal nanoemulsions was carried out on curcumin- an active phytoconstituent to enhance its antioxidant profile. In this research, the researchers analyzed encapsulating curcumin nanoemulsions. Curcumin is the least stable bioactive component. The researchers included whey protein concentrations of 70% and tween 80 as an emulsifier. Reactive oxygen species are protected by curcumin. The prepared nanoemulsions had an average diameter of 141.6±15.4 nm and contained particles with a zeta potential of 6.9±0.2 mV. The slow release of curcumin from the nanoemulsions resulted in enhanced bioavailability. The produced nanoemulsions were pasteurization stable, and the pH ranged from 3.0 to 7.0. In this study, the researcher discovered significant impacts on the formulation and production of encapsulated bioactive systems.[19] The combined use of nanotechnology-based formulations in traditional herbal medicine could provide a valuable tool for developing future medicinal products that have greater bioavailability profiles and reduced toxicity. The link between plant sciences and nanotechnology has the potential to create a desirable and beneficial relationship with actual prospects for reducing the application and manufacture of hazardous chemicals that damage living creatures.[20]

Phytoextract Loaded Nanoemulsions

If a simple formulation containing phytoextracts as antioxidants were compared with nano emulsion-based herbal formulations, extract-loaded nanoemulsions are thought to be more effective against aging and have the least side effects. Table 1 represents some of the examples of nanoemulsions containing phytoextract along with their mechanism of action of preventing skin aging. All references cited in this review are taken from PubMed, Google Scholar, Web of Science, and Scopus index journals.

Molecular Mechanism of Phytoconstituents

Quercetin

In human skin tissue, quercetin treatment reduced the production of the enzyme's Matrix Metalloproteinase-1 (MMP-1, Cyclooxygenase-2 (COX-2) and inhibited UV-mediated collagen breakdown. Both Nuclear Factor-Kappa B (NF-B) and UV-induced Activator Protein-1 (AP-1) activity were significantly inhibited by quercetin. Additionally, quercetin inhibits the activation of protein kinase B (Akt), c-Jun N terminal Kinases (JNK), Extracellular signal-Regulated Kinases (ERK), and Signal Transducer and Activator of Transcription 3 (STAT3) by UV light. Moreover, quercetin has been shown to directly reduce Protein Kinase C delta (PKC) and Janus Kinase 2 (JAK2) kinase activity. In pull-down tests, quercetin was discovered to bind to PKC and JAK2. According to these results, quercetin may directly affect JAK2 and PKC in the skin to provide anti-UV actions that slow down the aging process.[21]

α-Pinene

NF-B and MAPK are suppressed by alpha-pinene, which has anti-inflammatory properties. It has been found that alpha-pinene (-pinene) inhibits the (NF-B) pathway and Mitogen-Activated Protein Kinases (MAPKs) in mouse peritoneal cells. Using mouse peritoneal macrophages, researchers investigated the inhibitory effects of α-pinene on inflammatory responses elicited by Lipopolysaccharide (LPS). The production of Interleukin-6 (IL-6) and Nitric Oxide (NO) produced by LPS was significantly reduced by α-pinene. Furthermore, in LPS-stimulated macrophages, α-pinene decreased the production of (COX-2) and the Induction of NO Synthase (iNOS).[22]

Linalool

Many cellular signaling components are induced by ultraviolet-B light (285-320 nm). The natural monoterpene linalool protects Human Derma Fibroblast (HDF) cells from UVB-induced oxidative imbalance, (MAPK), and (NF-B) signaling. The results of the Comet experiment show that linalool strongly inhibits UVB-induced Cyclobutane Pyrimidine (CPD) generation, rather than UVB-mediated 8-deoxy guanosine development (DNA damage by oxidative). This may result from its ability to prevent the formation of ROS caused by UVB and restore the equilibrium of oxidative species in cells. UVB-induced increases in MAPK and NF-B signaling levels have been found to reflect this. The findings indicate that linalool can reduce UVB-induced activation of MAPK family proteins ERK1, JNK, and p38.[23]

Kaempferol

A study investigated the efficacy of the phytochemical kaempferol and its ability to inhibit Phosphoinositide-Dependent Kinase-1 (PDK1) to prevent cell degeneration and the decline of age-related skin factors *in vitro*. The phytochemical significantly reduced cell degeneration and increased collagen fibers. These findings suggest that PDK1 inhibition is a potentially beneficial anti-aging therapy in the MAPKs studied, kaempferol decreased JNK, MAPK, and p38 activation.[24]

Alpha-Tocopherol

α-Tocopherol can block hydroxyl free radicals. Improvements in the G0/G1 and G2/M phases of the cell cycle, as well as cell viability, mitochondrial membrane potential, and Ki-67 expression, were identified. Following these findings, there was an increase in Glutathione (GSH) levels and a decrease in the production of ROS. Furthermore, iNOS expression, NO release were inhibited, and the expression of pro-inflammatory cytokines was degraded, indicating the suggested anti-inflammatory effects of α-tocopherol.[25]

Epigallocatechin gallate

According to several studies, the epidermal growth factor receptor (EGFR; ERBB-1; HER1) is suggested to be a cell-surface receptor for extracellular protein receptors that are a part of the EGF family. Downstream signaling proteins then initiate various signal transductions. The MAPK, JAK, and Akt pathways are the primary pathways that promote DNA synthesis and cell growth. The innate immune response in human skin depends on the activation of the receptor. Furthermore, when EGFR binds with other receptors, its kinase domain can cross-phosphorylating their tyrosine residues, stimulating them. Epigallocatechin gallate may be beneficial in keeping skin healthy and reducing the signs of aging.[26]

Table 1: Nanoemulsions-based phytoextract with their mechanism of action of preventing skin aging.

Sl. No.	Botanical name	Family	Parts used	Active phytoconstituents	Therapeutic activity	Type of nanoemulsion	Name of emulsifier used	Mechanism of action	References
01	*Calendula officinalis* (Pot marigold).	Compositae	Flowers	Flavonoids (quercetin, rutin), volatile essential oil (α-pienene, sabinene, geraniol), (Figure 1).	Antioxidant Anti-aging Anti-inflammatory properties.	Oil in water nanoemulsion	Lecithin and tween 80	Prevent the absorption of UVB rays. Antioxidant activity using DPPH free radical scavenging method.	45
02	*Ocimum basilicum* (Basil).	Lamiaceae	Leafs	Essential oil, Linalool- (Figure 2) oxygenated monoterpenes.	Antioxidant (phenolic compound), Anti-acne, Anti-aging, Remove dead skin cells.	Oil in water	Polysorbate 80	Antioxidant activity using DPPH free radical scavenging method.	46
03	*Moringa oleifera* (Drumstick).	Moringaceae	Seed	Quercetin, Kaempferol (Figure 3), Moringinie, niazinine A, niazirin	Anti wrinkles, Antioxidant, Fine lines.	Oil in water	Sodium caseinate.	Prevent the loss of collagen, and elastin Rejuvenate the skin, and give a youthful appearance.	15
04	Helianthus (Sunflower).	Compositae	Seed	Alpha-tocopherol (Figure 4)	Natural sunscreen Anti-aging.	Oil in water	Tween 80 and span 80.	Absorb UV rays.	47
05	*Coriandrum sativum* (Coriander).	Apiaceae	Seeds	Linalool, α-Pinene (Figure 5).	Anti-aging Anti-wrinkles Antioxidant Anti-inflammatory.	Oil in water	Tween 80, span 20.	Collagenase, elastase, hyaluronidase, and tyrosinase inhibitory activities.	48
06	*Phyllanthus emblica* (Indian Gooseberry*)*	Phyllanthacea	Branches and stems	Epigallocatechin, (Figure 6) Epigallocatechin gallate, gallic acid.	Anti-aging Anti-inflammatory Antioxidant Anti melanogenesis	Oil in water	Tween 80, Span 80.	Inhibit melanin synthesis and act as a skin-lightning agent in the treatment of dark circles.	49
07	*Punica granatum* (Pomegranate)	Lythraceae	Peel	Polyphenols, flavonoids and tannins, anthocyanins, catechin, epicatechin, and quercetin (Figure 7) (ellagitannin and gallotannin)	Anti-elastase activities Prevent ultraviolet radiation Antioxidant, and sunburn	Oil in water	Polysorbate 80, soy lecithin.	Stimulate the production of collagen, Absorb UV rays before radiation reaches the dermis and the epidermis, Promoting skin renewal.	50
08	*Tageteserecta L* (Marigold)	Asteraceae	Flowers	Flavonoids, carotenoids, quercetin and essential oils	Anti-wrinkles Antioxidant Anti-aging	Water in oil	Span 80, PEG 40, hydrogenated castor oil.	DPPH, reducing power Superoxide radical scavenging activity.	51
09	Capsicum (Chilli peppers)	Solanaceae	Fruits	Capsaicin (Figure 8) and Vitamin C, carotenoids.	Anti-inflammation anti-aging.	Oil in water	Span80, tween20, tween 80.	Capsaicin inhibits Reduction in collagen.	52
10	*Oryza sativa* (Rice bran)	Poaceae	Seeds (RICE husks)	Ferulic acid, (Figure 9) γ-oryzanol, and Phytic acid	Protect UV radiation (Sunscreen formulation) Anti-aging, and treatment of skin disease (psoriasis) Antioxidant Improvement of skin lightening.	Oil in water	Sorbitan oleate/PEG-30 castor oil.	Increase skin hydration Growth stimulation of human fibroblasts Inhibition of MMP-2.	53

Sl. No.	Botanical name	Family	Parts used	Active phytoconstituents	Therapeutic activity	Type of nanoemulsion	Name of emulsifier used	Mechanism of action	References
11	*Azadirachta indica* (Neem)	Meliaceae	Seed, leaf	Phenols (catechins, gallic acid) (Figure 10), polyphenols.	Antioxidant Anti-aging Treating the symptoms of skin aging such as water loss erythema, and wrinkles.	Oil in water	Tween 20	Neem leaf extract can be boosted by type I procollagen and elastin, Prevent water loss, DPPH radical scavenging.	54
12	*Daucus carota* (Carrot)	Apiaceae	Seed	Essential oil, carotenoids, flavonoids, beta-carotene, Vitamin A, and Vitamin C (Figure 11).	Anti-inflammatory Anti-aging Antioxidant Anti- wrinkles.	Oil in water	Span 20, tween 80	Protection of DNA, Production of new cells proteins, and lipids.	55
13	*Piper nigrum* (Black pepper)	Piperaceae	Fruits	Phenol, Total flavonoids, piperine (Figure 12).	Anti-aging Anti-inflammatory.	Oil in water	Tween 80	Radical scavenging activity for DPPH, Radical scavenging action by the ABTS.	56
14	*Camellia sinensis* (Green tea)	Theaceae	Leaf	Epigallocatechin gallate, epicatechin, catechin (Figure 13) epicatechin.	Antioxidant Anti-inflammatory Anti-wrinkles.	Oil in water	Tween 80	Inhibition of collagenase, elastase, tyrosinase-related protein activities. Inhibition of tyrosinase, MMP-2, and reactive oxygen species.	57
15	*Tamarindus indica* (Tamarind).	Fabaceae	Fruit pulp,	Tannin, Flavonoids, Polyphenols coumarin (Figure 14) and quinone.	Antioxidant Anti-aging Anti-inflammatory.	Oil in water	Tween 80, span 80	Inhibited tyrosinase synthesis. Improved skin melanin.	58
16	*Lycium barbarum* (matrimony vine or Chinese wolfberry).	Solanaceae	Leaves, fruit	Phenols, Alkaloids, carotenoids (zeaxanthin and β-carotene) riboflavin, thiamine, betaine, (Figure 15) and ascorbic acid.	Reducing DNA damage Anti-oxidative Anti-inflammatory effects Anti-aging.	Oil in water	Tween 80	Inhibit lipid peroxidation, ROS scavenged and DNA damage is reduced.	59
17	*Citrus reticulata* (Orange peel)	Rutaceae	Peel	Ascorbic acid, (Figure 16) Polyphenols, carotenoids, flavonoids (narirutin, hesperidin, naringin and eriocitrin).	Prevents the skin from free radical damage, oxidative stress Skin hydration, and prevents blemishes, acne, wrinkles, and aging.	Oil in water	Tween 80 and Span 80	Inhibition of tyrosinase, collagenase, and elastase enzyme.	36
18	*Curcumalonga* (Turmeric)	Zingiberaceae	Rhizomes	Curcumin (Figure 17)	Antioxidant Photoprotection Anti-aging Moisturizer Anti-inflammatory.	Oil in water	Tween 80	Curcumin inhibits reactive oxygen species.	19
19	*Morus alba* (White Mulberry)	Moraceae	Leaf	Protocatechuic, antioxidants, polyphenols caffeic acid, Vanillic, vitamin C, calcium, iron, zinc, phosphorus, oxyresveratrol and resveratrol (Figure 18)	Anti-aging, Antioxidants, Anti- wrinkles Skin lightening.	Water in oil	Tween 80	Anti-tyrosinase Anti-hyaluronidase.	60

Figure 2: Representation of types of treatments for skin aging.

Gallic Acid (GA)

The hyperglycemic environment causes degradation of the Extracellular Matrix (ECM) by the enzyme MMP-1, which can accelerate the skin aging process. Additionally, evidence from past studies suggests that the GA formulation has a high potential to inhibit type I collagen deprivation in dermal fibroblast cells, which is mediated by high glucose and MMP-1. The results showed that high-glucose-induced ROS production decreased after cells were treated with GA, which prevented p38 MAPK/ERK from phosphorylating NFB, c-Fos, c-Jun, and Activating Transcription Factors (ATF-2). In cells treated with high glucose, as a result, MMP-1 mRNA and protein levels decreased. The results indicate the potential of GA formulations as anti-aging component, showing that they are more effective in inhibiting high-glucose-mediated ECM breakdown than MMP-1.[27]

Catechin

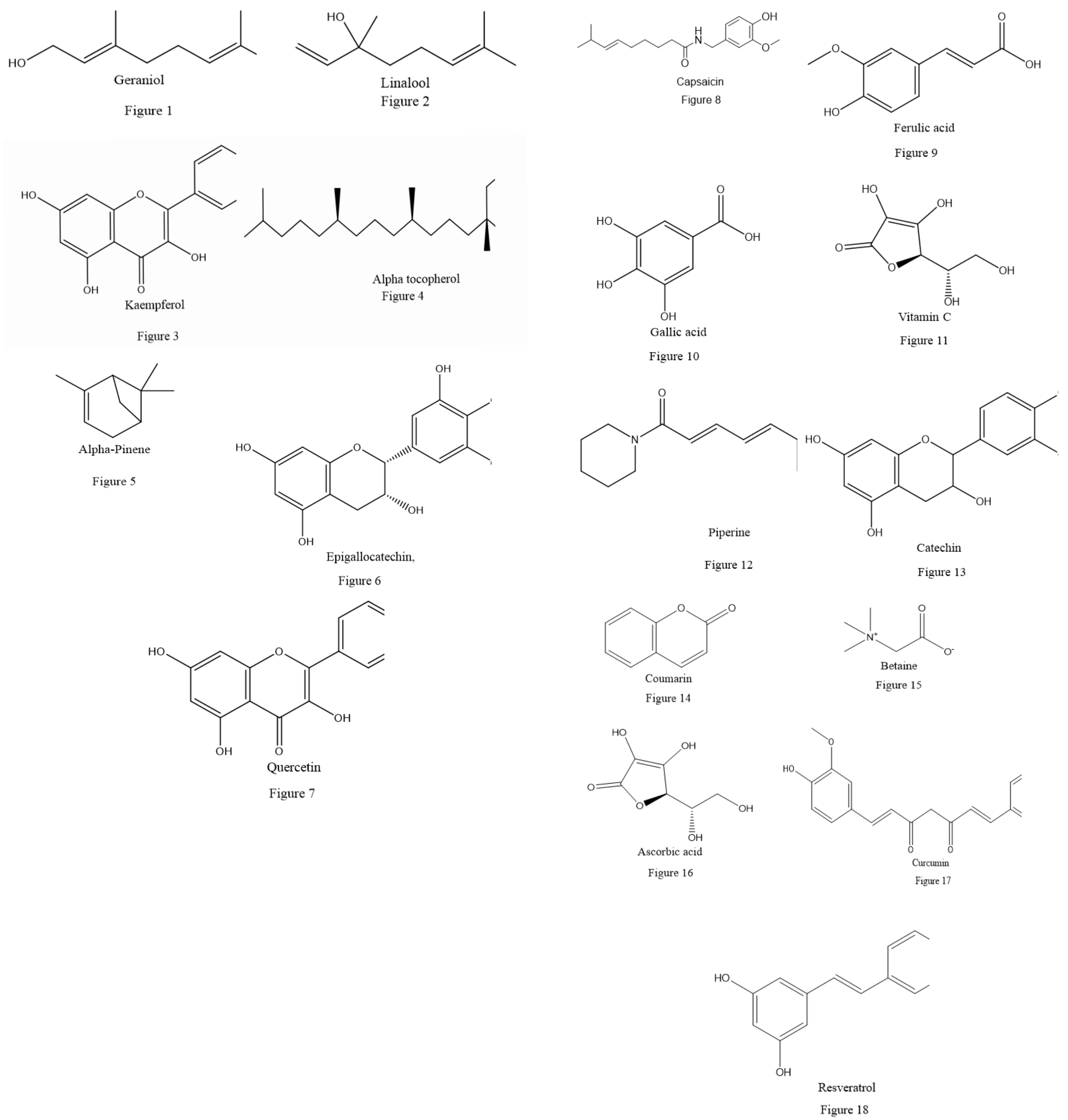
Catechin can increase collagen production while decreasing intracellular collagenase and elastase activity. Also, in Fine Dust Particles (FDP)-stimulated HDF, catechin reduced the production of human Matrix Metalloproteinase's (MMPs) by regulating the signalling pathways for NF-B, AP-1, and MAPKs. This study revealed catechin to be an achievable anti-aging agent that can be used as an independent therapeutic agent or as a component in pharmaceutical and cosmeceuticals products for FDP-induced skin aging.[28]

Capsaicin

Exposure to ultraviolet radiation reduced collagen synthesis in cultured dermal fibroblast while increasing the expression of matrix metalloproteinase's, production of ROS, and c-Jun and ErK phosphorylation, which caused skin damage. However, dose-dependent pre-treatment with capsaicin prevented the loss of dermal fibroblast collagen by reducing ROS generation in both *in vivo* and *in vitro* models.[29]

Vitamin C

Due to its capacity to encourage the creation of collagen, vitamin C has been identified as an anti-aging component. When applied topically, vitamin C increases the expression of procollagens I and III *in vitro* and collagens I and III *in vivo* at the mRNA level in skin fibroblasts. Vitamin C increases collagen production in fibroblast cells not only by enhancing hydroxylase activity but also by raising the steady-state quantity of procollagen mRNA. The human cathelicidin (LL-37) initiated ERK phosphorylation was stopped by vitamin C. Vitamin C also blocked the ETS-1(Erythroblast Transformation-Specific) developmental factor, which controls the expression of collagen by LL-37.[30]



Chemical Structure.

Ferulic acid

Acting as both an enzyme inhibitor and a free radical scavenger, ferulic acid boosts the activity of enzymes that quickly destroy free radicals while decreasing the activity of enzymes (elastase, collagenase, and tyrosinase) that quickly create them. Age and longevity have recently been associated with AMPK signalling, which controls cellular homeostasis, stress tolerance, cell survival, proliferation, death, and phagocytosis. Consequently, due to specific AMPK activation, UV exposure may inhibit procollagen synthesis by blocking the TGF-/Smad signalling pathway. The physical features of the skin are altered by glycation, becoming less elastic and stiff. The NF-B signalling pathway is similarly activated by excessive free radicals, raising levels of TNF and Matrix Metalloproteinase (MMPs) synthesis.[31]

Vitamin A

Vitamin A is an excellent antioxidant that slows the aging process. Retinoid, a class of medications made from vitamin A, have been used for years to treat and prevent the signs of aging skin. Retinol attaches to the cellular retinol-binding protein and undergoes a series of oxidation processes to produce retinoic acid (RA), or it is esterified by the enzyme Lecithin Retinol Acyl Transferase (LRAT) to produce Retinyl Esters (RE). The protein-ligand complex was formed when RA binds to Cellular Retinoic Acid, Binding Protein II (CRABP II) and penetrates the nucleus. Retinoic acid activates Retinoic Acid Response Elements (RARE) in the nucleus by binding to the Retinoic Acid Receptor (RAR), which forms a heterodimer with the Retinoid X Receptor (RXR). The improvement in the clinical phenotype of aging skin treated with retinoids is caused by the activation of RARE, which triggers the transcription of mRNA and the subsequent translation of proteins that participate in the signal transduction pathways.[32]

Piperine

Hoechst 33342 staining solution showed that the highest quantity of piperine prevented UV-B irradiation-induced cell death. Additionally, this research used ELISA, real-time PCR, and western blot analysis to show the anti-inflammatory benefits of piperine. Piperine pre-treatment inhibited the activation of phosphorylated p38, JNK, and AP-1 as well as the production of COX-2, PGE2, and iNOS, whereas UV-B radiation caused the stimulation of these signalling molecules in the cells. These findings suggest that the control of the anti-inflammatory effects of piperine may be significantly influenced by the suppression of these inflammatory signalling pathways. All of these findings indicated that piperine's anti-inflammatory abilities shielded keratinocytes from UV-B-induced harm.[33]

Riboflavin

Through an anti-oxidative stress route that involves boosting SOD1 and Catalase (CAT) activity and reducing lipofuscin accumulation, riboflavin boosts the duration of life and reproduction of fruit flies. Riboflavin's ability to delay human aging gaining more attention.[34]

Betaine

Several investigations on the antioxidant effects of betaine have recently focused on alterations in the NF-B pathway. Betaine has been shown to inhibit the NF-B kinase MAPKs-related Adrenomedullin (AM) expression which is associated with Lysophosphatidylcholine (LPC)-related LPC-related NF-B activation. LPC is an inhibitor of aging-related endothelial dysfunction in the production of adhesion molecules. Therefore, it seems that betaine can both prevent vascular disorders and reduce the age-related NF-B activities linked to uncontrolled NF-B in NF-B decibel (NIK)/IKK and MAPKs that were increased by oxidative stress. As a result, it may be effective as a defence mechanism against NF-B activation that occurs during inflammation and aging.[35]

Hesperidin

A study was conducted on the impact of hesperidin on MEK and ERK phosphorylation caused by UVB exposure.[36] According to a Western blot investigation MEK and ERK were phosphorylated as a result of UVB exposure. Results demonstrated that hesperidin therapy reduced MEK and ERK expression in mice exposed to UVB radiation which indicated that hesperidin shields mice's dorsal skin from UVB-induced deterioration.[37]

Curcumin

The turmeric spice contains curcumin, a naturally occurring yellow pigment with polyphenolic compounds that have potent antioxidant, anti-inflammatory, and antibacterial properties. These properties have contributed to curcumin's use as a treatment for acne, skin inflammation, and the prevention and treatment of skin aging. It has preventive properties against skin damage caused by ultraviolet B exposure[38] Curcumin can shield the skin by blocking free radicals and reduce inflammation by inhibiting nuclear factor-kappa B. In addition, curcumin exerts effects on the transforming growth factor- and MAPKs pathways. Phase II detoxification enzymes, which are essential for detoxification processes and oxidative stress protection, are also regulated by curcumin.[39]

Caffeic acid

Caffeic acid along with S-allyl cysteine, and uracil were all examined for their anti-wrinkle properties. It was found that there was a notable change in the expression of MMP, NF-B signalling, and UVB-induced wrinkle formation. The outcomes demonstrated that all three drugs considerably reduced *in vivo* expressions of MMPs and type I procollagen degradation, as well as histological collagen fiber disorder and oxidative stress. Additionally, it was shown that caffeic acid and S-allyl cysteine reduced oxidative stress and inflammation by controlling the actions of AP-1 and NF-B.[40]

Protocatechuic (PA)

UVA-irradiated HDF cells treated with PA had considerably decreased concentrations of intracellular ROS, prostaglandins-E2, and NO. It also increases catalase and glutathione peroxidase activity while reducing malondialdehyde levels.[41] COX-2 and iNOS expression levels were also suppressed. In addition, PA significantly enhanced collagen synthesis and decreased the expression of MMP-1 and pro-inflammatory cytokines in UVA-irradiated HDF cells. This activity was regulated through the AP-1, p38, and NF-B, signalling pathways. The findings demonstrated that PA increases the UVA-irradiated photoaging's protective impact, which is linked to ROS scavenging, anti-wrinkle, and anti-inflammatory actions. As a result, PA may be an attractive option for use in the pharmaceutical and cosmeceuticals sectors to provide a protective effect against UVA-stimulated photoaging.[42]

Resveratrol

A polyphenol called resveratrol is well known for its strong antioxidant properties. Its anti-oxidant properties were tested on human Mononuclear Cells (PBMC) from donors of various ages under conditions of oxidative stress. Inhibitors of PKA, AkT/PKB, and MAPK signalling are combined with resveratrol.[43] Anti-aging benefits of resveratrol production of the Klotho gene via a signalling pathway that regulates transcription factor 3/c-Jun complex. Resveratrol treatment significantly raised the expression of Klotho mRNA and protein in the mouse kidney. ATF3 and c-Jun expression were upregulated and nuclear translocated in NRK-52E cells treated with resveratrol, which resulted in enhanced Klotho expression. Overexpression of c-Jun or ATF3 amplified Klotho's transcriptional activation. Results indicate that resveratrol has the potential to be an anti-aging substance.[44]

Chemical Structure

The chemical structure (Figures 1-18) of various phytoconstituents (from Table 1) is prepared with the help of ChemDraw professional 16.0.

DISCUSSION

This review article discusses how nanotechnology and herbal extracts are used to create cosmetic products that delay extrinsic skin aging. The article addresses the harmful effects of prolonged sun exposure as well as the increasing demand for sunscreen and anti-aging products. Due to their therapeutic efficiency and fewer side effects than synthetic medications, herbal extracts of medicinal plants are selected. As carriers for herbal bioactives, nanoemulsions are becoming more and more popular since they offer prolonged release. Selected medicinal plants mentioned in this review have anti-aging potential and antioxidant capacity to prevent skin aging and restore skin elasticity. The article also discusses the pharmacological evaluation of various plant species for their potential use as skin anti-aging products. These studies focus on wrinkle formation, elasticity, oxidative stress, pigmentation, and hydration of the skin. Plant-based bioactive compounds show promise as modulators of age-induced cellular impairment, but their therapeutic applicability is limited by issues such as poor solubility and stability. Nanotechnology offers a solution by formulating natural antioxidants with nano-delivery systems.

People nowadays need a solution to portray them as young and having smooth skin along with its complexation. Regular exposure of human skin to UV rays produced by sunlight causes many pathological changes in the cells and ultimately leads to skin aging. Photoprotection is the basic mechanism used by humans to combat photoaging which has anti-aging potential. However, herbal cosmeceuticals can also be used as a therapeutic approach. Herbal formulations are more acceptable because they are biodegradable, and have a very low toxicity profile. Among many plant metabolites, alkaloids, vitamins, and phenolic compounds like flavonoids, phenolic acids, etc. appear to be effective against damage caused by UV radiation, but evidence-based research is still required to validate their anti-aging properties. We have reviewed 19 anti-aging plants that have different types of phytochemicals such as flavonoids, essential oils, phenols, polyphenols, carotenoids, alkaloids vitamins, etc., that are responsible for age-defying effects. Depending on the study done, the following components are found to be in decreasing order of anti-aging efficacy such as polyphenols (flavonoids)>essential oils, which portray those flavonoids are the potential phytoconstituents for skin anti-aging properties.

CONCLUSION

The use of herbal nanoemulsions as an effective delivery system is gaining popularity because they can solubilize large amounts of poorly soluble drugs, offer encapsulated medicines for prolonged release, and allow these drugs to be administered orally, transdermally, directly to the skin and mucous membranes, etc. Based on this paper, we found that out of the 19 nanoformulations reviewed 17 were of oil in water type with the majority of tween 80 used as an emulsifier. The decision to use oil in water or water in oil emulsions in skin care products is often based on considerations including skin type, environment, and desired product properties. O/W formulations may be preferred by those with oily or acne-prone skin due to their lighter texture, while W/O formulations may be preferred by those with dry or sensitive skin due to their enhanced moisturizing abilities. The issue of safety considerations urgently needs to be addressed, especially when it comes to manufacturing and quality assurance processes for herbal nanoemulsions and other formulations based on nanotechnology. Thus, considering the potential of nanoemulsion-based administration of herbal drugs, it has a future for enhancing activity as well as resolving problems.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ROS: Reactive oxygen species; **ECM:** Extracellular Matrix; **HA:** Hyaluronic acid; **ERK:** Extracellular signal-regulated kinases; **PKC:** Protein kinase C delta.

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