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Review Article

Advancements in Skin Aging Treatment: Exploring Antioxidants and Nanoparticles for Enhanced Skin Permeation

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ABSTRACT

Many people have always aspired to have skin that is young-looking and vibrant. The natural aging process of the skin, which is impacted by both internal and external factors, has sparked further research into its origins and the creation of efficient therapeutic approaches. This review aims to give a thorough understanding of the skin's composition, the causes and variables that contribute to skin aging, the difficulties in treating skin aging, and the methods used to treat skin aging. It will also go into detail about the obstacles antioxidants face while trying to permeate the skin and their potential role as essential players in the fight against skin aging. In addition, it will discuss the intriguing use of nanoparticles (NPs) in reversing skin aging, emphasizing their involvement in enhanced skin penetration. Due to their distinct size-dependent characteristics and ability to integrate medicines, NPs in general provide a variety of therapeutic benefits for antioxidant drug delivery to control skin aging.

Keywords: *Drug delivery; Wrinkles; Oxidative stress; Nanoscale particles; Topical delivery.*

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1. Introduction

Skin aging generally starts in the mid-20s and causes wrinkles and brown spots. Ultraviolet (UV) radiation, smoking, and gravity are some of the factors that cause skin aging. UV rays damage the elastin and collagen causing wrinkles. Anti-aging treatments can reverse the symptoms of chronological and photographic aging. Anti-aging methods for the skin can be grouped into two main approaches; invasive skin procedures such as chemical peels, visible light therapy, fractional laser resurfacing, dermal fillers and injectable skin rejuvenation, botulinum, toxin, autologous platelet-rich plasma and microneedling and the other approach is the noninvasive skin procedures as preventing extrinsic aging-related factors and alterations to behavior and lifestyle. Daily skin care and photoprotection are essential components of cosmetological care. Additionally, systemic agents, including hormone replacement therapy, and topical medicinal treatments, such as antioxidants and cell regulators, play crucial roles in maintaining skin health. Antioxidants play a crucial role in anti-aging strategies but unfortunately, they face many barriers that limit their function. Herein, nanoparticles (NPs) play

their role in helping antioxidants to fully function, overcoming barriers, and enhancing their efficacy. The charge and size of NPs play a key role in NP-based topical drug delivery. Nanotechnology has opened up new opportunities and concepts for skin aging with different types of NPs being investigated such as liposomes, polymeric NPs, nano-emulsions, metallic NPs as well as nanocrystals. Due to their distinct size-dependent characteristics and ability to integrate medicines, NPs in general provide a variety of therapeutic benefits for antioxidant drug delivery to control skin aging.

The skin, the body's outermost tissue, is the largest organ in terms of body weight or surface area. It makes up nearly 2 m^2 of the body's surface area and around 10% of the weight of the body **[1]**. The skin is composed of three tissue layers: the epidermis, which is the outermost layer, the dermis, which is in the middle, and the hypodermis, which is the bottom and fatty layer. Skin's poor permeability to water, hydrophilic, and lipophilic compounds is caused by its lipid makeup. It acts as a strong barrier against a variety of environmental stresses, such as dehydration, dehydration, changes in temperature and pressure, stretching, shearing, bending, compression, ultraviolet (UV) radiation, chemicals, toxins, dangerous bacteria, and infections **[2]**. The skin also acts as a protective layer as it controls the transport of substances into or outside the body via its highly selective properties. Nevertheless, drugs can pierce the skin through three main routes; the sweat ducts, the stratum corneum (SC), and the hair follicles, which significantly restricts their absorption and limits their bioavailability. The hair follicle has been determined to be a target for hair follicle-related diseases, including acne vulgaris and androgenetic alopecia (AGA) in addition to serving as a crucial entrance point for percutaneous absorption. Hair follicle-targeting drug delivery systems are a potential approach for treating hair follicle-related dysfunctions because they enable controlled medication release and greater treatment efficiency with fewer adverse effects **[3]**. The drug's physicochemical characteristics as well as the carrier type used in the formulations determine the drug's preferential accumulation in hair follicles. Many drug delivery systems, such as lipid nanoparticles, microneedles, and polymeric nanoparticles (NPs), have been extensively studied to improve the precise administration of pharmaceutically active substances to hair follicles **[4]**. Only 0.1% of the skin's surface allows for these direct passageways, but hair follicles and sweat ducts are excellent entry points for drugs into the bloodstream. As a result, the SC, which acts as the primary impediment to drug transport, is where the bulk of pharmaceuticals pass through. The SC is a thick, corneocyte-based structure that controls water flow and acts as a physical barrier. Typically, only extremely tiny lipophilic molecules can transcellularly diffuse to the keratinized corneocyte layers with the aid of permeation enhancers like glycols and alcohols. Other medications need carriers to travel through intracellular routes for percutaneous absorption because their physicochemical qualities are less favorable **[5]**.

The horny cells of the SC are the peripheral non-viable layers of the epidermis that represent the transdermal absorption rate-controlling barrier that is directly related to drug lipophilicity. The appearance of one's skin is a primary age indicator that distinguishes between old and young people **[6]**.

Extrinsic aging, which is influenced by environmental factors and overlaid with the consequences of chronological aging, has been defined as aging that is not caused by genetics but rather by external influences. Age, gender,

ethnicity, exposure to air pollution, diet, smoking, and sunlight are all significant risk elements for different skin aging phenotypes **[7]**.

The goal of skin-aging treatments is to improve skin appearance by reducing wrinkles, sun damage, scarring, and age spots. This can be achieved by different techniques such as chemical peels, in which the skin's outer layer can be removed using a chemical solution. Retinoids, vitamin C, and alpha hydroxy acids are topical antioxidant products that may help with early signs of aging. Moreover, laser resurfacing, microneedling, dermabrasion, and ultrasound energy devices are more invasive procedures that stimulate the skin to produce new elastin and collagen thus decreasing the signs of aging. BOTOX®, which relaxes the muscles that cause wrinkles, and soft tissue fillers, which inject substances under the skin to plump up and smooth out wrinkles, are two other treatments. The selected treatment is determined by the individual's areas of concern, skin type, preferences, and previous results.

NPs can help prevent and treat hyperpigmentation and premature aging of the skin. They are beneficial in the sun and radiation-stressed skin care regimen. They can penetrate the horny skin's barrier layers owing to their composition. This procedure causes the barrier layers to temporarily fluidize, allowing the encapsulated active ingredients to be released and penetrate via means of a skin barrier.

This review article delves into the skin and its composition, the causes of skin aging, and various techniques used for skin aging treatment. It emphasizes the role of antioxidants in combating skin aging and explores the challenges they encounter in penetrating the skin. Furthermore, the article examines the potential of different types of nanoparticles (NPs) as carriers for antioxidants, enhancing their skin penetration and overcoming barriers for optimal efficacy.

2. Skin

The skin is the biggest and most intricate organ in the body. The skin's main role is to shield the body from the surrounding environment and disease-causing infections (germs). Furthermore, it aids in regulating body temperature and accumulates sensory information about the surroundings. The skin's three primary layers are composed of numerous specialized cells and structures **[8]**.

The skin's epidermis is its topmost layer. Depending on where it is situated on the body, it has a different thickness. The eyelids have the thinnest layer (about half a millimeter), whereas the palms and soles have the thickest layer (1.5 millimeters). The epidermis itself is composed of five layers; the top layer of the epidermis is the SC. Its function includes assisting the skin to retain moisture and preventing hazardous chemicals from entering the body **[9]**.

It consists of corneocytes, which are flattened dead cells that are shed every fortnight. The fibrous protein, keratin -produced by keratinocytes- participate in the construction of the nails, hair, and skin. The first line of defense for the body is the SC which is known as a brick wall because it is made of corneocytes, that are connected by keratin and organic moisturizers. Infectious viruses and hazardous toxins could enter your body without it, leading to major health issues **[10]**.

Only on the soles of the feet and the palms of the hands does the second layer -the stratum lucidum- exist as a separate layer. Its cells and functions are incorporated into other layers in thinner areas. The lucid stratum allows for skin stretching, it contains a protein that aids in the degeneration of skin cells; protecting the soles and palms from the impacts of friction and making the skin impervious. This layer is made up of flattened, dead keratinocytes as well.

Third is the stratum granulosum which has keratinocytes that are slowly being pushed towards the skin's surface. Cells begin to lose their shape and features as they progress through this layer, resembling the flattened, dead keratinocytes of the outermost layers more and more. Lipids, a type of fatty acid, are also present in this skin layer, contributing to the formation of an impermeable shield that protects the fluid loss from the body through the skin **[11]**.

Fourth is the thickest layer of the epidermis, known as the squamous cell layer or stratum spinosum. It has newly formed keratinocytes and Langerhans cells, both of which function to fight infection. This is the main barrier keeping pollutants from the environment from entering the body **[12]**.

Last is the epidermis's lowermost layer which is called basale, commonly known as the basal cell layer. It contains several significant cell types, including Merkel cells, which sense touch, Melanocytes, which create the pigment that gives the skin its color, and columnar stem cells, which force more mature keratinocytes to the skin surface where they flatten and perish **[7]**.

The skin's middle layer, known as the dermis, is made up of capillaries, nerve endings, connective tissue, and hair follicles as well has glands like sebaceous and apocrine glands that generate sebum (body oil) and perspiration, respectively.

There are two sections in the dermis **[13]**. First, the papillary dermis which is the thin top layer of skin that has capillaries, which regulate the skin's temperature, supply the epidermis with nutrition. Also, this skin layer includes Meissner corpuscles which are receptors that transfer delicate touch sensations, and lamellar corpuscles which are receptors that transmit vibration and pressure sensations **[14]**.

Second is the reticular dermis which is a thick, lower layer of connective tissue and thick collagen bundles. Collagen is the main protein that gives connective tissues and skin its structure. It is in charge of the suppleness and toughness of the skin. The breadth of the dermis varies according to its location on the body. It is approximately 0.6 millimeters thick on the eyelids and three millimeters thick on the back, palms, and feet soles **[15]**.

Subcutaneous tissue is the skin's bottom layer. It is mostly composed of fat, connective tissues, larger blood vessels, and nerves. The subcutaneous layer stores the majority of body fat. It protects muscles and internal organs from impacts and falls by insulating the body against changing temperatures. The subcutaneous layer also stores fat cells for energy reserves, giving the body its smooth and contoured appearance. Additionally, the body temperature is controlled by the contraction and dilation of blood vessels in this layer. Moreover, it serves as a point of attachment for bones, muscles, and other organs to the skin, contains deep pressure sensors, and produces leptin, a hormone that aids in maintaining homeostasis.

The skin is a complex network of cells, proteins, fatty acids, and lipids. Proteins are the building blocks of physical skin structures as well as key signaling molecules for the skin's ability to regulate itself. Fatty acids, such as ceramides and hyaluronic acid (HA), are chemical building blocks that aid in the strengthening and retention of the skin barrier. Skin lipids form a barrier to prevent water from evaporating from the skin's surface. These elements give the skin its structure and aid in the attraction and trapping of water.

Natural moisturizing factors in the skin also help to keep the skin hydrated and the barrier strong. These elements consist of amino acids, lactic acids, and urea, which attract and bind water molecules. Furthermore, the skin has an acid mantle, which is a thin protective layer of

fatty acids and sebum that helps to maintain the pH balance of the skin and protect it from bacteria and other pathogens **[16]**.

This barrier has unique characteristics as it enables the slow passage of some molecules while preventing the passage of others, including medicines. Passive diffusion is the primary mechanism by which chemicals enter the skin, with active transport being far less important. Chemicals can cross the upper skin structures, including the SC, penetrate the living epidermis, and then passively continue into the basal membrane. Since diffusion is passive, the concentration gradient along with a chemical's preference for a lipophilic or a hydrophilic environment acts as the driving force. As a result, a lipophilic molecule will easily traverse the SC, but once it reaches the more hydrophilic epidermis, the rate of penetration will decrease. In these cases, we may see the formation of a temporary reservoir in skin compartments. Based on these findings, substances soluble in both the lipophilic layer and more aqueous structures are expected to have the highest rate of permeability through the skin barrier **[17]**.

3. Skin aging

Skin aging is a multisystem degenerative biological process that might be expressed as skin sagging, losing its suppleness, and changing in texture and substances necessary for the preservation of smooth skin, damaged barrier function, the appearance of spots, modification of surface line isotropy, reduction in skin thickness, loss of collagen, and finally wrinkles **[18]**. Skin aging can be influenced by the combination of endogenous or intrinsic factors such as genetics, cellular metabolism, hormones, and metabolic processes which generally start in the mid-20s. Additionally, exogenous or extrinsic factors such as chronic light exposure, pollution, ionizing radiation, chemicals, smoking, gravity, repetitive facial expressions, sleeping positions, and toxins also participate in the skin aging process, where the skin becomes thinner and more easily damaged **[19]**.

Direct sunlight might damage the elastin and collagen resulting in wrinkles and brown spots. UV radiation is an essential component that contributes to an imbalance between pro-oxidants and antioxidants leading to oxidative stress and photoaging of the skin **[20]**. The constant skin exposure to UV rays diminishes the antioxidants existing in the skin over time which are commonly present in SC and are susceptible to UV rays.

There is a general agreement that reactive oxygen species (ROS) and skin antioxidant capability play key roles in skin aging. Oxidative stress occurs when the generation of ROS exceeds the body's natural antioxidant defenses, damaging the skin's lipids, proteins, and DNA **[21]**. ROS are required to maintain healthy cell signaling and the skin's microbial defense. Excess ROS production, on the other hand, can exceed the cellular antioxidant (AO) capacity and alter the cellular redox balance, resulting in oxidative stress. Extrinsic and intrinsic aging in the skin is both driven by oxidative stress. Sunlight exposure has been linked to the skin's extrinsic photoaging, as its oxidizing components interfere with the balance of redox and iron, causing harm from oxidation to skin cells and other tissue components **[22]**.

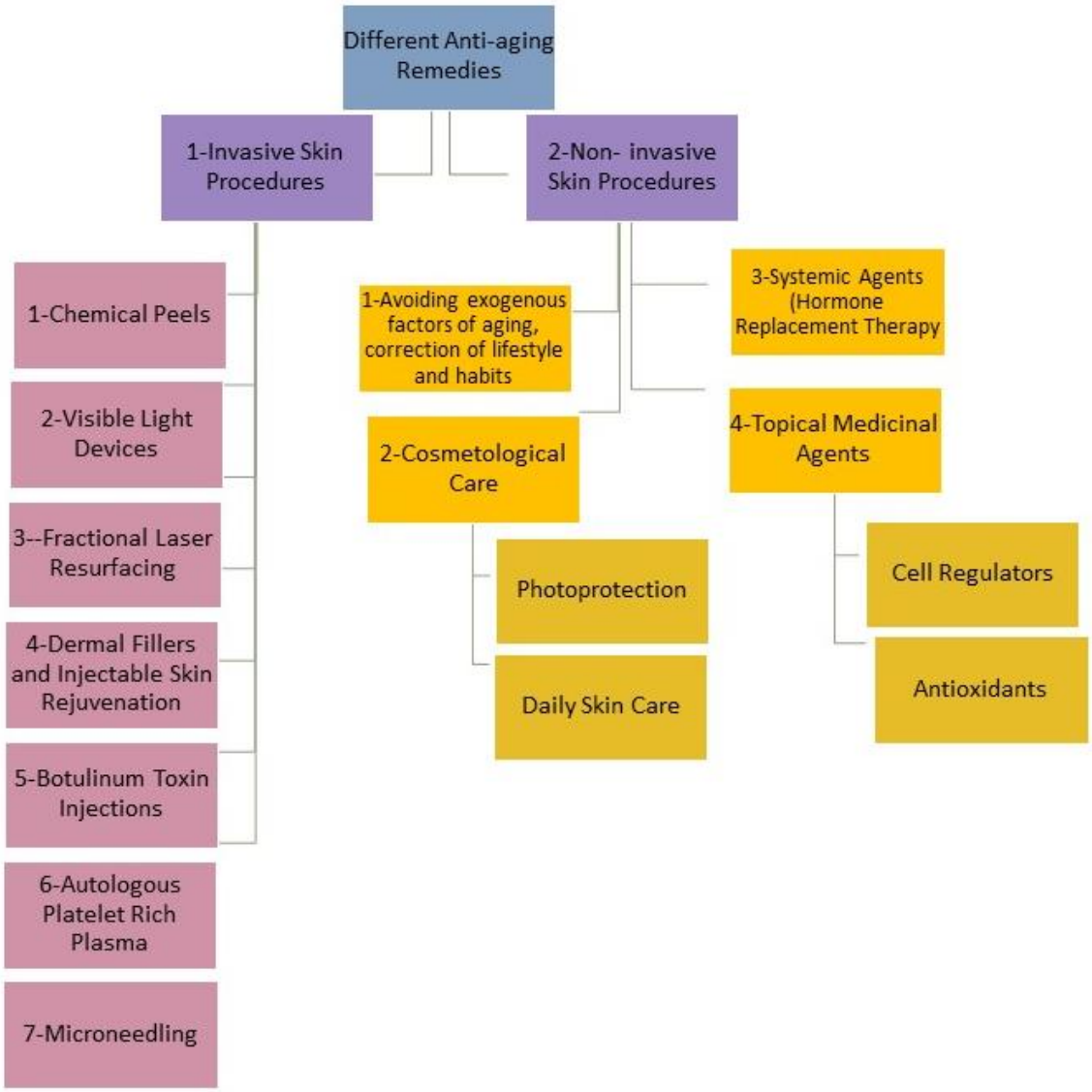
Smoking also contributes to elastin damage and reduction in blood flow to the skin. Additionally, gravity pulls our bodies with the loss of elastin and collagen causing sagging. Moreover, sleeping positions cause creases that then become wrinkles along with facial expressions where muscles produce grooves that gradually become etched in the face **[23]**. Skin aging may intensify after menopause as decreased estrogen causes collagen loss where estrogen stimulation may promote keratinocyte

growth, thickening the epidermis and avoiding atrophy **[23]**.

4. Different anti-aging remedies

Upon aging, wrinkles and sunken cheekbones are only two examples of skin-related problems that start to emerge. However, anti-aging treatments can be quite effective in reducing these signs of aging and aid in maintaining a youthful look.

The following methodologies can be used to categorize the skin anti-aging techniques used to aid in reversing the dermal and epidermal indications of photo- and chronological aging: ranging from changing lifestyle habits to invasive procedures as outlined in **scheme I.**



Scheme 1. Different techniques are used as skin anti-aging remedies**.**

4.1. Invasive skin procedures

An invasive procedure involves breaking the skin in some way. This is a broad category that includes nearly all major surgeries as well as numerous diagnostic tests. It's most likely an intrusive surgery if it leaves a scar. There are a variety of in-office techniques, the majority of which aim to "resurface" the epidermis, or to remove the damaged epidermis and replace it with remodeled skin layers and, on rare occasions, to stimulate the synthesis of new collagen. It's likely that shortly, technical development and creativity in the growing disciplines of gene therapy and tissue engineering could finally enable us to harness the power of GF, cytokines, and telomerase **[24]**.

4.1.1. Chemical Peels

During a chemical peel, a chemical solution is applied to the skin to remove its outermost layers. The commonly-used chemical solutions include glycolic acid, trichloroacetic acid, salicylic acid, lactic acid, or carbolic acid (phenol). The skin that regenerates is softer. It might be needed to have a light or medium peel multiple times to obtain the desired results.

Chemical peels are frequently used to heal scars, discolored skin, and wrinkles on the face. They may be performed separately or in conjunction with other cosmetic procedures. Additionally, they can be performed superficially or into deeper skin layers. Deeper chemical peels result in more dramatic outcomes, yet require longer healing time **[25]**.

The concentration, pH, and timing of application of the chemical are further factors that affect the depth of peeling **[26]**. If corneosomes are the target of superficial peelings, which also result in desquamation, increased epidermal enzyme activity, epidermolysis, and exfoliation, then medium-depth peels coagulate membrane proteins, kill epidermal living cells, and, depending on the concentration, also affect the dermis **[27]**.

4.1.2. Visible Light Devices: Intense Pulsed Light therapy (IPL), Lasers, Radio Frequency (RF)

Non-ablative skin rejuvenation also referred to as "sub-surfacing," is a low-risk, quicker surgery that can undo structural changes brought on by aging without harming the skin's structure. It uses lasers and other techniques to treat age spots, wrinkles, and loss of skin tone. The skin layers and small skin imperfections like fine wrinkles and dark spots are removed during this process using a non-injuring laser. With fewer sessions, shorter recovery times, and long-lasting results, the procedure addresses various skin flaws **[28]**.

The heat from the laser tightens the skin and makes it appear young and healthy by encouraging collagen synthesis **[28]**.

4.1.3. Fractional Laser Resurfacing

A well-known anti-aging procedure known as laser resurfacing, laser peeling, or light therapy employs light radiation to rejuvenate and repair skin cells, boosting collagen production to grow new skin cells for a youthful skin look.

Fractional laser skin resurfacing is the finest anti-aging laser therapy for eliminating pigmentation disorders and softening wrinkles on numerous parts of the body, including the face, chest, neck, arms, and hands **[29]**.

The procedure accurately focuses pulsating light beams on the skin to eliminate the damaged top layer and improve the skin texture.

Another cutting-edge anti-aging procedure that uses stem cells to rejuvenate the skin is called a stem cell facelift. The key advantages of this treatment are that there is no downtime and no need for surgery. However, there hasn't been a lot of research done on the advantages and

effectiveness of this anti-aging procedure **[30]**.

4.1.4. Dermal fillers and injectable skin rejuvenation

As you age, your skin naturally loses HA, collagen, and elasticity, which causes wrinkles to appear. Dermal fillers; (HA) and calcium hydroxyapatite (CaHA) are injected around the cheeks, nose, eyes, jawline, and lips to improve the appearance of the skin.

Dermal fillers, an injectable procedure carried out under the guidance of a licensed medical professional, can help reduce wrinkles and replace lost volume, giving the skin a more youthful appearance **[31]**.

Skin bio rejuvenation aims to enhance fibroblasts' capacity to produce new proteins thus, recreating an optimum physiologic environment to improve cell activity and hydration, and produce collagen, elastin, and HA. This can be achieved by microinjection of HA, vitamins, minerals, nutrients, hormones, GF, amino acids, autologous cultured fibroblasts, homeopathic products, etc. into the superficial dermis. The injected materials either contain only one active ingredient or a combination of different substances that are perfectly biocompatible and fully absorbable. *In vitro*, the various formulations can cause fibroblasts to go through remarkably different molecular and cellular processes **[32]**.

4.1.5. Botulinum Toxin Injections

The main purpose of Botox, also known as botulinum neurotoxin, is to temporarily relax the muscles in the face.

Botox injections block the nerve impulses to tissues when administered into muscles. This reduces muscle activity, thus leadings to a smoother skin appearance. The current alternatives to cure crow's feet and glabellar lines, and accentuated frown lines, like implants or surgery, do not discuss the excessive nerve stimulation that is the primary source of these lines. Botox is a perfect agent to focus on the main root of these dynamic lines due to its mode of action. Presynaptic neurons of particular muscles are precisely and quickly (within an hour) bound by the toxin **[33]**.

An increase in the region of the muscular membrane responsive to acetylcholine may be another mechanism explaining the recovery of muscle function by Botox **[34]**.

4.1.6. Autologous Platelet-Rich Plasma (PRP)

Autologous platelet-rich plasma (PRP) has gained interest for its potential to rejuvenate skin. Fresh whole blood, which has a high platelet concentration, is used to make PRP. The concentrated platelet granules that are activated by aggregation inducers produce a variety of GF, including insulin-like growth factor (IGF), platelet-derived growth factor (PDGF), transforming growth factor (TGF), and vascular endothelial growth factor (VEGF). By binding to particular cell surface receptors, these substances are known to affect many functions, such as cell motility, adhesion, differentiation, and proliferation, as well as extracellular matrix (ECM) buildup **[35]**. It has been demonstrated that PRP can rejuvenate the skin by causing the creation of collagen and other matrix elements by activating fibroblasts **[36]**.

4.1.7. Microneedling

The use of microneedling, a collagen-inducing technique, can enhance skin texture, and reduce the fine lines appearance, enlarged pores, acne scars, and sun damage. Microneedling uses small needles that are calibrated to reach the skin's outer layer at various depths **[37]**. It can be used with serums and other beauty care products for deeper skin penetration and more effective skin treatment. Minor scarring from wounds, acne, and age can be treated with this skin

technique which is thought to be both effective and safe. After the procedure, the skin will probably look more radiant and firmer. However, it takes several sessions to get the best outcomes **[38]**.

Using invasive anti-aging skin procedures can have many disadvantages. Complications from these procedures include bleeding, infection, scarring, and nerve injury. These operations can potentially have a long recovery period.

Dermal fillers and injectable skin rejuvenation are invasive procedures as well that may cause irritation, edema, bruising, and redness.

4.2. Non-invasive skin Procedures:

Non-invasive operations do not entail cutting the skin or otherwise entering the body, whereas invasive procedures do. In general, non-invasive procedures are less intrusive as they don't involve making any incisions in the patient's body.

4.2.1. Systemic Agents (Hormone Replacement Therapy (HRT))

It is generally known that hormone production decreases with age. The amounts of dehydroepiandrosterone (DHEA) (sulfated form and its urinary 17-keto metabolites), estrogens, testosterone, thyroid stimulating hormone (TSH), and insulin-like growth factor-1 (IGF-1) are reduced with aging. Andropause, menopause, and partial androgen shortage in the aging male are the three main hormonal abnormalities in humans. Hormones lost during aging are supplemented through HRT. The goal of HRT is to restore the hormones lost during aging Melatonin production declines with aging **[39]**.

The type of hormone replacement therapy (HRT) being utilized will determine whether the HRT approach will be systemic or local. Systemic hormone therapy is offered topically or intravenously, whereas local hormone treatment is available in the form of lotions, pills, and rings. It has long been believed that HRT, which includes estrogen and progesterone, has anti-aging properties. However, the results from larger trials, especially those carried-out as part of the women's health initiative do not always guarantee an anti-aging effect **[40]**. Although HRT has also been accused of raising the risk of cardiovascular disease and breast cancer **[41]**, it delivers beneficial osteoporosis prevention with early, low-dose estrogen therapy **[40]**.

4.2.2. Lifestyle modifications:

Healthy habits can have a significant impact on your biological age and longevity. These lifestyle habits can be attributed to delaying skin aging as exercise routines, dietary habits, levels of stress, alcohol consumption, sleep duration, tobacco use, and other toxins in the environment.

Although the technology needed to effectively carry collagen and elastin into the skin has not yet been established, certain products as Vitamin C-rich foods include broccoli, kiwi fruit, bell peppers, and citrus fruits, as Tofu, nuts, seeds, milk, and cottage cheese are all high in protein and encourage the natural synthesis of both elastin and collagen **[42]**.

According to interventional studies, administering specific nutritional supplements can slow down the skin's aging process and enhance skin problems. Free radicals (FRs) scavengers are the majority of nutritional antioxidants, which function via numerous pathways and in a variety of compartments. First, they immediately neutralize FRs, second, they lower peroxide levels and restore damaged membranes, third, they quench iron to limit ROS formation, and fourth, they neutralize ROS via lipid metabolism, short-chain free fatty acids, and cholesteryl esters **[43]**. Endogenous antioxidant defenses present in the body are either non-

enzymatic (such as nutritional ingredients as vitamins and phenols and other non-enzymatic as glutathione, bilirubin, thiols, albumin, and uric acid) or enzymatic (such as superoxide dismutases, glutathione peroxidases (GSHPx), and catalase) **[44]**. Nutrition is the most significant source of antioxidants. Vitamins C and E are among the most well-known systemic antioxidants along with carotenoids and copper and selenium as trace elements. Studies have also shown that ferulic acid and vitamins C and E can work as an antioxidant and sunscreen when combined **[45]**.

4.2.3. Cosmetological care

Skin and hair care are referred to as cosmetological care. The study and treatment of conditions affecting the skin and hair are the focus of this area of dermatology. Protecting the skin from dehydration and permeation of various bacteria, allergies, radiations, reactive oxygen species, and irritants are all part of cosmetic care. Daily skin care, the appropriate use of photoprotection, minimally invasive cosmetic procedures, topical medicinal agents, and systemic agents are also included.

4.2.3.1. Daily Skin Care

A strong and healthy skin barrier is an important defense against radiation, ROS, dehydration, and penetration of numerous pathogens. Accordingly, it is essential to maintain a regular skin care routine such as face cleansing, toning for balancing the skin, and moisturizing for hydrating and softening the skin. This can improve the skin's condition by enhancing skin regeneration, suppleness, and smoothness. Wrinkle appearance can be delayed by stopping the degeneration of the skin's primary structural proteins such as elastin and collagen **[46]**.

4.2.3.2. Photoprotection

Skin aging caused by chronic photo-damage is known as extrinsic skin aging (photoaging). DNA photodamage and UV-generated ROS cause the majority of the typical histological and clinical symptoms of chronic photodamage of the skin, which are the initial molecular events. The most significant cutaneous signs of premature photo-aging are wrinkles and pigmentary alterations. Sun protection and sun avoidance are essential to prevent photo-aging. This can be achieved by the use of sunscreens to block or minimize skin exposure to UV radiation, retinoids to inhibit collagenase synthesis and increase collagen creation, and anti-oxidants, especially when combined, to lessen and combat free radicals **[47]**.

Sunscreens -available as a counter product- are essential for primary photoaging prevention. There are two categories of sunscreen ingredients: inorganic/physical blockers that reflect and scatter UV radiation such as titanium dioxide, and zinc oxide. Organic/chemical agents that absorb particular UV photons such as sulisobenzone (benzophenone-4), dioxybenzone (benzophenone-8), and oxybenzone (benzophenone-3), and organic UVB filters such as PABA (para-aminobenzoic acid) **[48]**.

4.2.4. Topical medicinal agents

The two primary types of ingredients that can be found in anti-aging lotions are cell regulators and antioxidants. Antioxidants such as flavonoids, vitamins, and polyphenols decelerate the breakdown of collagen by reducing the amounts of FR in the tissues. Growth factors (GF), retinol, and peptides, which are cell regulators, directly affect collagen metabolism and have an impact on collagen production.

4.2.4.1. Cell regulators

Cell regulators that directly affect the

metabolism of collagen and encourage the formation of collagen and elastic fibers include vitamin A derivatives and polypeptides.

Because of its beneficial effect on collagen metabolism, vitamin A (retinol) and its derivatives (retinaldehyde and tretinoin) are currently the most widely utilized anti-aging drugs. It dramatically lowers the appearance of premature aging indicators such as elasticity loss, pigmentation difficulties, and fine wrinkles by their ability to lower the expression of MMP 1 and increase collagen production (collagenase 1) **[49]**.

Tretinoin -a first-generation non-aromatic retinoid- has been approved for use as an anti-aging medication at a concentration of 0.05% **[50]**. It has been demonstrated that it can reduce all signs of UV-induced early aging of the skin such as wrinkles, elasticity loss, and pigmentation. Retinol is found to be less irritating to the skin than tretinoin, accordingly, it is currently the most commonly used anti-aging substance. Moreover, retinol has beneficial effects on the metabolism of collagen as well as on intrinsic and extrinsic skin aging.

Polypeptides (or oligopeptides) such as Acetyl hexapeptide-3 and pentapeptide-3 work similarly. This sort of component is made up of amino acids, which help collagen and elastin formation and make the skin look smoother, suppler, and younger [51]. Polypeptides can increase skin metabolism and activate collagen production when applied topically **[52-54]**.

4.2.4.2. Antioxidants

Vitamins C, B3, and E are considered the principal antioxidants as they can penetrate the skin thanks to their low molecular weight. Water-soluble, heat-labile local L-ascorbic acid (vitamin C) was reported to have skin anti-aging properties in concentrations between 5- 15% due to its ability to produce Col-1 and Col-3, as well as essential enzymes for collagen synthesis and matrix metalloproteinase (MMP) inhibitors (collagenase 1) **[55]**. Clinical research has shown that taking vitamins C and E together provides more antioxidant protection than taking either vitamin alone. Niacinamide (vitamin B3), used as an anti-aging treatment in 5% concentrations, controls cell metabolism and regeneration **[55]**. In some studies, 3 months of antioxidant topical therapy led to improvements in skin elasticity, erythema, and pigmentations **[56]**. In concentrations between 2 and 20%, vitamin E (-tocopherol), which is utilized as a component of skin care products, is reported to have anti-inflammatory and antiproliferative properties **[57]**. It works by reducing wrinkles and enhancing the SC's capacity to maintain moisture, hasten epithelialization, and contribute to skin photoprotection. However, when compared to vitamins C and B3, the effects are not as potent **[58]**.

Before exposure to UV light, applying green tea polyphenols topically increases the lowest erythema dosage, lowers the amount of Langerhans cells, and decreases DNA damage in the skin. Isoflavones from soy, for instance, are an example of another plant that functions as an antioxidant **[59]**.

5. Different categories of antioxidants used in skin aging treatment, their mechanism of action, and the barriers they face penetrating the skin

ROS results in oxidative stress both intracellularly and extracellularly, which speeds up the aging process of the skin and causes wrinkles and irregular pigmentation. Skin aging is frequently related to UV exposure since UV increases the production of ROS in cells. Antioxidants can be used as a preventative measure to stop the signs of photo-induced skin aging. Different types of antioxidants as vitamins, quinones, polyphenols, and carotenoids, how they work along with the limitations they face in topical delivery are mentioned below **(Table 1)**.

Table 1. Different categories of antioxidants used in skin care

Antioxidant type	Origin	Mechanism of Action	Limitations of topical administration
Vitamins	**1-Vitamin C:** L-ascorbic acid, also known as vitamin C, is one of the popular, strong, and extensively researched antioxidants for skin care. • It can be obtained solely from food, such as citrus fruits. • Vitamin C is the finest antioxidant for brightening pigmented skin lesions and dark spots. Vitamin C is the finest antioxidant for brightening pigmented skin lesions and dark spots.	• Ascorbic acid, which is vitamin C's reduced form, predominates in nature. • Dehydro-L-ascorbic acid, its oxidized form, can transform back into ascorbic acid and is occasionally present in trace amounts. • Diketogulonic acid, an inactive degradation product of vitamin C that cannot be transformed back into the active form, is further broken down by oxidative catabolism to stable inactive excretory metabolites, such as oxalic acid. This occurs when vitamin C formulations are oxidized, making them inefficient. To prevent exposure to UV rays or the air, vitamin C preparations should be stored in airtight, light-resistant containers. • Ascorbic acid promotes collagen synthesis in human skin fibroblasts, and ascorbate is necessary for collagen synthesis. • Elastin production may be decreased concurrently via an unidentified mechanism **[60]**. • it can reduce oxidative stress, neutralize free radicals, and boost collagen formation. This strengthens and elasticizes the skin, which can reduce wrinkles and fine lines **[61]**.	• The skin penetration of the hydrophilic, unstable, and charged L-ascorbic acid is minimal as the horny skin layer has hydrophobic nature **[62, 63]**.
	2-Niacinamide (NIA), is the biologically active amide of vitamin B3 and is also known as nicotinamide. • it's utilized to treat skin diseases like acne and rosacea **[64]**. • It enhances skin tone and texture and helps lighten black spots.	• It helps to get rid of the symptoms of aging by killing harmful FRs on the delicate skin **[65]**.	• The physicochemical characteristics of NIA point to challenges in overcoming the SC layer barrier to reach the target in the skin **[66]**. • The fact that NIA is extensively soluble in water (212.95 mg/mL), has a molecular weight of 122.1 Da, and a log p value of 0.37 suggests that it might not be suitable for topical administration on its own **[67]**.
	3-Retinol: It is a vitamin A derivative, and is undoubtedly the best over-the-counter (OTC) product for minimizing wrinkles and fine lines. • Retinol smooths the skin and accelerates cell turnover **[68]**.	• Its antioxidant's tiny molecular structure enables it to penetrate the skin deeply and neutralize FRs. • It is especially effective at promoting collagen formation and accelerating cell renewal, regrowth, and repair. • It promotes the development of new blood vessels underneath the skin, which can brighten the skin **[69]**.	•Retinoids are frequently used in skin care products and treatments [70]. • Their hydrophobic nature, substantial chemical/photochemical instability, and retinoid irritant side effects limit their conventional topical formulations **[71]**.

Quinones	**1-Coenzyme Q10:** The fat-soluble antioxidant ubiquinone also known as coenzyme Q10 (CoQ10). • It can be found in foods like fish and shellfish and is present in all human cells. • Up to 95% of the body's energy needs seem to be met by CoQ10. • Even though it occurs naturally in the skin, it decreases with age which could result in signs of skin aging **[72]**.	• It can reduce the production of FRs, regenerate vitamin E; and reduce keratinocyte DNA damage and UVA-induced metalloproteinase production in the fibroblasts; in addition to its capacity to decrease mitochondrial oxidative damage **[73]**.	• Despite the great anti-inflammatory and healing properties of CoQ10 **[74]**, it is not ideal for topical skin application because of its inability to dissolve in water and relatively high molecular weight **[75]**.
Polyphenols	**1-Curcumin:** It is a polyphenol included in the spice turmeric and is a relative newcomer to OTC skincare treatments. It is believed to have anti-inflammatory and brightening attributes that don't cause skin stains despite the bold yellow color of turmeric **[76]**. **2-Flavonoids: Quercetin**, Hesperetin, Genisetin, Epigallocatechin, Apigenin, and Delphinidin are examples of flavonoids. • Flavonoids can be present in antioxidant beverages like green and black teas that are extracted from the Camellia sinensis plant. • The most prevalent and biologically active flavonoid is epigallocatechin 3-gallate (EGCG)**[80]**. **3-Genistein** is a soybean-derived isoflavone that can prevent UV-induced oxidative DNA damage **[83]**. • It has been demonstrated that oral or topical genistein can effectively shield human skin from UVB-induced photodamage. • It is available in a variety of products, including sunscreens, facial moisturizers, and other skin care formulas that have anti-aging properties **[84]**. **4-Silymarin:** It is a polyphenolic product of the milk thistle plant, Silybum marianum. • It's biologically active component, silybin (silibinin), is known to have strong antioxidant properties. **5-Resveratrol,** a phytoalexin polyphenol regarded as the "longevity molecule" for its powerful anti-aging properties. • It is present in red wine, berries, tea, and grapes and has anti-inflammatory and UV-protective properties. • It might increase elastin and collagen.	• Nuclear factor-KB inhibition results in free radicals' quenching and inflammation reduction **[77]**. • Flavonoids support the body's natural antioxidant systems as well as flavonoids having a broad FR scavenging activity that prevents the generation of ROS and lipid peroxidation products **[81]**. • Genistein decreases ROS levels and induces the manifestation of the antioxidant enzyme Catalase, superoxide dismutase (SOD), and manganese (Mn) **[85, 86]**. • Prevention of DNA oxidation and mutagenicity brought on by UV exposure **[87, 88]**. • Resveratrol has anti-aging properties because it inhibits the phosphorylation of survivin, a protein that stops cellular apoptosis, as well as blocking nuclear factor-kB, cyclin D1, cyclin D2, metalloproteinase matrix, IB kinase R, mitogen-activated protein kinase (MAPKK & MAPK).	• Despite curcumin's pleiotropic properties, its weak solubility and instability have constrained its clinical application **[78, 79]**. • When applied topically, their lipophilic nature, restricted solubility, and poor skin penetration may compromise their therapeutic effects **[82]**. • The clinical uses of genistein are subject to some restrictions. For instance, its poor solubility in water and low permeability through the skin contributes to its low bioavailability. • Low solubility, poor stability, poor bioavailability, and minimal penetration are the difficult issues with topical delivery routes. • Low solubility and bioavailability **[89, 90]**.

Carotenoids	**1- Lycopene**: Red fruits and vegetables include the carotenoid lycopene, a potent antioxidant that gives them their red hue **[91]**.	• A carotenoid with strong physiological activity for neutralizing singlet oxygen **[92] [93]**.	• Some negative characteristics of lycopene restrict its potential for medicinal use. • Dietary lycopene can cause intolerance or allergic reactions in certain people. • Lycopenemia is a disorder that causes an orange or red coloring of the skin upon eating a diet high in lycopene or by taking supplements that contain excessive levels of lycopene **[94]**. • When applied topically, lycopene barely diffuses through the epidermis due to its extremely low water solubility. • Lycopene is quite erratic **[95]**.

4. Nano-delivery systems for topical delivery

Nanomedicine enables targeted drug delivery, focusing the pharmacologically active agent solely on the site of action or absorption. This approach prolongs, localizes, and targets the affected tissue safely, relying on medication administration via NPs to address traditional drug delivery challenges. Two types of targeted drug delivery systems exist: passive and active targeting. Passive targeting relies on physicochemical properties, while active targeting involves attaching cell-specific ligands to NPs' surfaces for increased affinity to particular cell types.

NPs can act through various mechanisms, such as cell membrane disruption via electrostatic contact, inducing oxidative stress, releasing metal ions, or non-oxidative mechanisms. They penetrate cell membranes, interact with essential cell components, and activate cells by releasing reactive oxygen species (ROS) **[99]**.

Hydrophobic antioxidants, such as vitamin E, ubiquinone, flavonoids, carotenoids, and retinoids, are insoluble in water. Nanoparticle-based therapeutics, including micro/nanocapsules, liposomes, and polymersomes, can enhance their distribution and bioavailability. Additionally, hydrophobic medications can self-assemble into nanostructures in aqueous solutions without external carriers. Traditional non-responsive amphiphilic block copolymers' hydrophobic cores self-assemble into micelles, loaded with medicinal compounds or fluorescent dyes.

NPs' chemical and physical characteristics, such as size, surface charge, and surface chemistry, significantly influence their pharmacokinetics. Size affects circulation, organ accumulation, and elimination rates. Extremely small NPs (4 nm) can pass through the SC and into the dermis layer, while larger particles' charge and form are essential for topical delivery. Understanding nanoparticle properties and behavior requires investigation and characterization. Techniques like dynamic light scattering (DLS), transmission electron microscopy, scanning electron microscopy, X-ray diffraction (XRD), Fourier transform infrared spectroscopy (FTIR), and Raman spectroscopy are employed to characterize topical antioxidant NPs.

There are various forms of topical nanocarriers, each with distinct advantages and roles, though they all contribute to improving antioxidant delivery, some of which are outlined below.

4.1. Liposomes

The spherical vesicles known as liposomes h ave an aqueous center that is comprised of

phospholipids bilayers. They are oil-in-water (o/w) dispersions having a particle size range between 50-450 nm. They can deliver a wide range of therapies and are biocompatible, biodegradable, and able to dissolve lipophilic drugs in the lipid layer and disperse hydrophilic medications in the aqueous core. Weak knowledge exists on the precise mechanism underlying their skin penetration **[100]**. To localize medications in the viable dermis and the SC for eventual lowering of systemic absorption and hence minimal adverse effects, liposomes act as a medication carrier system that can enter the SC in the form of intact vesicles **[101]**.

To impact disease states or signal transduction pathways that are affected by oxidative stress, antioxidant liposomes offer a novel method of delivering both water and/or lipid-soluble antioxidants to tissues.

Ascorbate-loaded phosphatidylcholine (PC) liposomes displayed antioxidant and anti-inflammatory activities on human skin exposed to UVA/UVB radiation. Ascorbate-loaded PC liposomes were employed to augment topical ascorbic acid treatment of skin problems because they were able to penetrate the epidermis and allow unstable hydrophilic active components to reach the epidermis and dermis, avoiding skin photodamage **[102]**.

4.2. Polymeric Nanoparticles

Solid colloidal NPs made of either synthetic or natural polymers and sizes ranging from 10-1,000 nm are known as polymeric NPs. Polymeric NPs larger than 50 nm are stiff. They work better when applied topically to localize medications in skin appendages or on the skin’s surface.

Polymeric NPs are essential to drug carriers because they may release drugs gradually and under regulated conditions. Natural polymers such as; chitosan, albumin, and HA are frequently employed as natural polymeric NPs because they are biodegradable, non-toxic, and biocompatible. To fabricate natural polymeric NPs, various processes such as precipitation, ionic gelation, self-assembly, and polymerization are typically used **[103]**.

On the other side, synthetic polymers offer the benefit of uniformity in purity and characteristics across multiple batches. During synthesis, their size, chemical composition, and other characteristics can all be precisely regulated. Poly(caprolactone-co-glycolide) copolymers (PCL), poly(lactide-co-glycolide) copolymers (PLGA), and polylactides (PLA) are polymers frequently used in NP synthesis. The most popular techniques for creating these polymeric NPs include solvent displacement, emulsification, solvent evaporation, and nanoprecipitation.

Therapeutic agents may be enclosed or trapped within the carriers, or they may be physically adsorbed on or chemically attached to the surfaces of the NPs. The two main subtypes of polymeric NPs are nanospheres with evenly dispersed loaded agents and nanocapsules with therapeutics contained within the interior aqueous or oily cavities encircled by polymeric membranes. Water solubility, tiny size, storage stability, biodegradability, long shelf life, and non-toxicity are some of these nanostructures' appealing qualities. Polymeric NPs exhibit good encapsulation efficiency as well as increased solubility and stability of hydrophobic medicines as a result of their physicochemical properties. Due to these characteristics, the toxicity of loaded medications can be reduced, allowing for a controlled release through topical application at specific locations inside the body at relatively low doses **[104]**.

Topical delivery for specific regions can also be tailored by varying the particle size; different sites in the hair follicle can be selectively

targeted.

Polymeric NPs have been used to deliver "difficult-to-formulate" drugs into the skin tissues, particularly the follicles. This has improved drug delivery to deeper skin layers and has wound-healing, anti-inflammatory, and anti-cancer properties **[102]**. The creation of wrinkle-reducing stable polymeric NPs that contain poorly soluble propolis in a cosmetic formulation was previously reported. Propolis is reported to be effective as an anti-inflammatory, antiseptic, antifungal, antimycotic, antibacterial, anticancer, antiulcer, and immunomodulatory agent. Additionally, the developed polymeric NPs were excellent at reducing wrinkles as demonstrated by Kim et al. **[105]**.

Topical solutions utilize antioxidant polymeric NPs owing to their capacity for free radicals scavenging as well as their anti-aging properties **[106]**. Topical/dermal distribution has been tested with both natural-based polymers like chitosan and synthetic polymers like PLGA, PCL, and PLA **[107]**.

Ilex paraguariensis A. St.-Hil. standardized extract-containing antioxidant polymeric NPs have been researched for topical use. Even though several compounds from Ilex paraguariensis exhibit significant antioxidant activity, there may be chemical stability issues that affect the formulation stage. Polymeric NPs employed in this situation to give these chemicals extra protection while preventing degradation events. Additionally, by including Ilex extract in polymeric NPs, the amount of chlorogenic acid that penetrated the skin was dramatically decreased. This prolonged the topical antioxidant activity of the compound **[108]**.

4.3. Metallic NP

Nanoscale metal particles include; silver, gold, copper, magnesium, aluminum, titanium, and zinc metallic NPs. Their sizes range from 1-100 nm in diameter and are increasingly used in a variety of biological applications for passive or active drug delivery. The ability to produce and modify metallic NPs with diverse chemical functional groups, to allow their coupling with various medications to target specific cells and tissues, is a crucial point. Their readily modifiable chemical composition, ease of production, biocompatibility, great stability, conjugation versatility, and changeable biophysical properties are all clear advantages in therapeutic applications **[109]**.

When the body digests food or is exposed to radiation, tobacco smoke, or other environmental variables, chemicals known as FR are generated. These molecules can harm cells and can be prevented or slowed down by antioxidants. In topical methods, antioxidants have been transported using metallic NPs. For instance, a study found that NPs containing antioxidant actives were ideal for usage as cosmetic ingredients since they were safe for topical application and demonstrated in vivo anti-aging efficacy **[110]**.

Metallic NPs have been shown to enhance the stability and the bioavailability of topical anti-aging medications, hence improving their efficacy in the context of anti-aging drug delivery. Additionally, they may increase skin moisture and elasticity.

4.4. Nanoemulsions/ Microemulsions

Combinations of immiscible liquids, such as water and oil, at the nanoscale level are called nanoemulsions. These nanosystems are often created using mechanical or chemical techniques. Chemical processes cause emulsion droplets to spontaneously form due to the hydrophobic effects of lipophilic molecules that happen in the presence of emulsifiers **[111]**. High-energy techniques can be used in mechanical procedures to break up large emulsion droplets into smaller

ones by a variety of mechanical actions. The shapes and sizes of the droplets dispersed in a suspension are the primary distinctions between conventional emulsions and nanoemulsions **[112]**.

Microemulsions are thermodynamically stable o/w emulsions with mean droplet sizes of roughly 10-200 nm, in contrast to nanoemulsions, which have mean droplet sizes < 1000 nm and are thermodynamically unstable. The fact that nanoemulsions require energy input to create while microemulsions occur spontaneously is another significant distinction between the two types of emulsions. Another significant difference is that microemulsions utilize additional surfactants and co-surfactants, resulting in a significant decrease in droplet size due to a substantial reduction in interfacial tension.

An effective way to raise the antioxidant ability, dispersibility, stability, and solubility of natural antioxidants is through their nanoemulsion-based encapsulation. Due to its controlled release and preserved antioxidant ability, the encapsulated natural antioxidant shows enhanced oxidative stability. The nanoemulsion technique is more promising than other encapsulation technologies because it produces an emulsion that is very physically stable, nontoxic, and customizable in terms of rheology **[113]**.

To provide drugs via percutaneous, peroral, topical, or transdermal routes, microemulsions are promising delivery systems. They are stable water-and-oil colloidal systems that are cosurfactant and surfactant-stabilized. Considering their potential to act as skin delivery systems for a variety of pharmacological compounds, they have come under more and more scrutiny.

Topical medication delivery systems based on microemulsions have great penetration and can enter the skin. Microemulsion improves drug absorption, solubility, and protection from outside influences.

Acne, wrinkles, dark spots, and skin aging are just a few of the skin disorders that are treated using retinyl palmitate, a vitamin A ester from the endogenous natural retinoid family. Retinyl palmitate has many well-known therapeutic benefits yet; its traditional topical application is commonly associated with negative side effects including skin irritation, redness, excessive peeling, and dryness. To increase the topical distribution and stability of retinyl palmitate, it was encapsulated in nanoemulsion and then incorporated into a hydrogel system. After topical application, the retinyl palmitate-loaded nanoemulgel delivery system significantly improved ($p<0.05$) skin permeability. The development of a retinyl palmitate topical administration system using the nano-encapsulation method, followed by hydrogel dispersion improved both the system's UV and storage stability **[114]**.

The ginsenoside metabolite, 20(S)-Protopanaxadiol (20S-PPD) shows strong skin antiaging properties. However, its large molecular weight and limited aqueous solubility limit its skin deposition. Accordingly, a suitable formulation method was used to raise its solubility and skin permeability. A Carbopol-based microemulsion hydrogel system of 20S-PPD with a mean droplet size of 110 nm and a restricted size distribution was successfully developed for a practical topical administration approach **[115]**.

4.5. Solid Lipid Nanoparticles

In contrast to nano-emulsions, solid lipid nanoparticles (SLN) contain lipids in a solid phase. The physiological lipids in these sub-micron colloidal nanocarriers, which range in

size from 50 to 1,000 nm, are distributed either in aqueous surfactant solutions or in water. SLN is created using high-energy techniques including ultrasonication, high-pressure homogenization, or micro-fluidization **[116]**.

Such NPs have the advantages of small size, large surface area, superior drug loading efficiency, and phase interaction at the interface. This class of nanocarriers was created to alleviate the drawbacks of colloidal nanocarriers including polymeric NPs, liposomes, and emulsions because they can be advantageous like tailored favorable release profiles and effective medication delivery. Such NPs can be loaded with therapeutic drugs in one of two ways: either by integrating them into the core matrix or by attaching them to the surface. The ability to fabricate stable particles that can entrap lipophilic compounds without the need for organic solvents is one of the major benefits of SLN. Due to their distinct size-dependent characteristics and ability to integrate medicines, these NPs provide a variety of therapeutic benefits. These benefits include the suitability for large-scale production, the ability to combine hydrophilic and lipophilic pharmaceuticals, and low toxicity **[117]**.

Innumerable medicinal substances can be applied topically using SLNs. Three natural substances-naringenin, nordihydroguaiaretic acid (NDGA), and kaempferol-were combined in a nanostructured lipid carrier (NLC) a lipidic carrier that integrates liquid lipids within its structure in addition to the solid ones- to create a topical formulation with antioxidant properties **[118, 119]**. Another study found that Idebenone-loaded NLC had lower antioxidant activity than Idebenone-loaded SLN, possibly as a result of Idebenone's stronger interaction with NLC's lipidic matrix, this diminished the NPs' Idebenone release, and consequently the colloidal system's antioxidant efficacy **[120]**.

4.6. Nanocrystals

Nanocrystals are pure (carrier-free) drug NP colloidal dispersion systems that are sub-micron in size (often between 10 and 800 nm). They can be made using mechanical or chemical processes **[121]**. The primary benefit of such nano-systems is particle size reduction to the nanoscale range, thus increasing the surface area of the particle in contact with the dissolution media. In comparison to pharmaceutical formulations that are currently in use, nanocrystal formulations possess potential therapeutic benefits including higher drug loading and increased saturation solubility and dissolution rate **[122]**.

A polyphenolic flavonoid with an intriguingly broad therapeutic range is rutin. However, due to its weak water solubility and low absorption, its clinical benefits are constrained. Rutin nanocrystals were created utilizing a variety of stabilizers, such as nonionic surfactants and nonionic polymers, to get around these restrictions. It has been noted that rutin nanocrystals enhance its saturation solubility and enhance diffusion to the deeper stratum corneum layers. It should be made clear that water readily dissolves rutin nanocrystals, To increase the skin absorption of antioxidants like rutin, nanocrystals are a potential approach **[123]**. Antioxidant-rich nanomaterials have promise for treating disorders brought on by ROS **[124]**. It has been discovered that cerium oxide nanocrystals have antioxidant qualities and can be used repeatedly over the course of weeks **[125]**. Antioxidant qualities of starch nanocrystals have also been discovered **[126]**.

Conclusion

Skin aging is a multisystem degenerative natural process that typically begins in the mid-20s and is influenced by a combination of exogenous or extrinsic elements including chemicals, ionizing radiation, pollution, and prolonged exposure to light, smoking, gravity, repetitive facial expressions, sleeping positions,

and toxins, where the skin becomes thinner and more porous. Skin thinness, altered barrier function, the appearance of spots, alteration in surface line isotropy, decrease in skin thickness, loss of collagen, and finally wrinkles are symptoms of aging. Other symptoms include skin drying out, loss of elasticity, texture, and substances needed to preserve smooth skin. The following strategies can be used to categorize the skin anti-aging techniques used to reverse the epidermal and dermal indications of photo- and chronological aging: cosmetological care, topical agents or topical medicine agents, intrusive techniques such as visual lighting apparatus and fractional laser, avoiding exogenous factors of aging, correction of lifestyle and habits, and preventive medicine. A Healthy and effective skin barrier is an important defense against radiation, reactive oxygen species, dehydration, and penetration of numerous pathogens. Different categories of antioxidants are employed to treat skin aging with different mechanisms of action but unfortunately, there are a lot of barriers they face for penetrating the skin. This can be overcome by their loading into nanocarriers such as; liposomes, polymeric NPs, metallic NPs, nanoemulsions, nanocrystals as well as SLN to aid in overcoming the barriers.

Declarations

Consent to publish

All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Availability of data and material

All data generated or analyzed during this study are included in this published article in the main manuscript.

Competing interests

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