

Retinoids — A unique ingredient for skin rejuvenation employing novel drug delivery systems

Sneha Jateen Pradhan , Ashwin Kuchekar* , Ashwini Gawade , Sushil Kore 

Department of Pharmaceutical Sciences, School of Health Sciences and Technology, Dr. Vishwanath Karad MIT World Peace University, Pune, India.

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ABSTRACT

Millions of people around the world fall within the age group of 35 and above; having fluctuating lifestyles, increased exposure to blue light, and a faster-depleting ozone layer that enhances entry of UVA and UVB rays in the skin which tends to age faster leading into collagen degradation that results in fine lines and decreased cell senescence. The goal of skin rejuvenation is to have healthy skin. Cosmeceuticals incorporating retinoids have been increasingly used over the past few years to promote collagen synthesis and rejuvenate the skin. Photo-induced and chronological aging processes are decelerated with retinoid application that endorses skin elasticity by free radical neutralization, new cell growth, and blood vessel promotion within the skin to help fight pigmentation and reduce fine lines. Retinoids are commercially available as creams and serums for topical application. Nanotechnology is used in the development of retinoids to counteract adverse reactions like skin irritation and purging to improve its stability, efficacy, and acceptability. Emerging studies on retinoids include formulating them within liposomes, solid lipid nanoparticles, nano-emulgels, and hydrogels. This review details understanding the aging process, the mechanism of action of retinoids to counterfeit aging, and the potential use of nanotechnological delivery in cosmeceuticals.

INTRODUCTION

Comprising many layers of epithelial cells, the human skin is the largest organ in the human body [1,2]. The epidermis, dermis, and hypodermis are its three primary layers [1]. The skin's outermost layer, or epidermis, is a complicated and multilayered structure system that is divided into several layers, or strata [1,3]. Starting from the most superficial layer, these include the stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum, and the stratum basale (the deepest portion of the epidermis) [1]. In addition to these layers, the epidermis comprises specialized cells which include keratinocytes, melanocytes, Langerhans' cells, and Merkel's cells [1]. The epidermal portion is followed by the dermis and the hypodermis (deepest layer of the skin) [1,3]. Owing to the

skin's structure it functions as the body's first line of defense, serving as a barrier to ward off infections, damaging UVA and UVB rays, trauma, and damage, and regulating sweating and water loss [1–4]. The skin microbiome, which is home to a range of microbial communities that preserve the balance within the skin and produce healthy, glowing skin, is another component of the skin's defensive system [5]. An appropriately functioning skin microbiota is one of the factors that affect optimal skin functioning [6]. It is involved in triggering the immune response and acts as an inflammatory mediator against viruses and infections [4,5]. The skin microbiome is composed of bacteria like *Staphylococcus aureus* and *Staphylococcus epidermidis*. Out of the 90% total microbial flora, Actinobacteria (52%), Firmicutes (24%), Proteobacteria (16%), and Bacteroidetes (6%) are the four classes of microbiota predominantly found in human skin [6,7]. The other species found in the skin microbiome are *Acinetobacter*, *Micrococcus*, *Streptococcus*, *Corynebacterium*, and *Propionibacterium acne* [6,7]. The human skin serves as the body's first line of defense, yet it is greatly impacted by multiple factors that contribute to its senescence across all age groups. These elements can be broadly

*Corresponding Author

Ashwin Kuchekar, Department of Pharmaceutical Sciences, School of Health Sciences and Technology, Dr. Vishwanath Karad MIT World Peace University, Pune, India.
E-mail: ashwin.kuchekar@mitwpu.edu.in

classified into two categories: intrinsic, or chronological factors and extrinsic, or environmental, factors. Phenotypical age-related data collection by preferred reporting item for systematic review and meta-analyses meta-analytical guidelines by Wong and Chew [8] revealed that increasing exposure to extrinsic factors like smoking [8], blue light from the screens [9], air pollution [10], and ultraviolet (UV) light are major contributors towards natural and premature skin aging [3,11]. In addition to these, age, gender, and ethnicity are fundamental intrinsic aging elements that cause pigmentation and skin aging [12]. In the recent and upcoming years, the worldwide population, including both developed and developing nations, will be experiencing increased premature skin aging because of their lifestyles and increased exposure to extrinsic aging factors [13]. Japan and South Korea have the oldest populations of all of them [14]. Particularly among the public, 90% of women are starting to learn more about anti-aging ingredients and skin-care routines and there is a projected market surge for anti-aging products in the next 10 years as shown in Figure 1 [13,14]. However, modern-day issues demand futuristic answers; merely adding active ingredients to your regular skincare regimen is not going to fix it. Instead, the latest developments in the skin-care sector; active substances like retinoids formulated within nano-formulations have shown to be the solution [15,16].

The term “retinoid” is broad and encompasses both synthetic and natural forms of vitamin A analogs, such as retinol [17]. In the skincare industry, a variety of retinoids and their derivatives, such as tretinoin, isotretinoin, adapalene, retinaldehyde, retinyl palmitate (RP), retinol esters, and retinoic acid esters, are used topically to treat acne and aging skin [18]. RP, which is found in eggs, chicken, and beef liver, as well as dairy products such as whole milk, yogurt, cheese, and butter, is a dietary source of vitamin A [19]. Vitamin A is produced by the body from absorbed beta-carotenoids found in squash, cantaloupe, sweet potatoes, pumpkins, carrots, and mangoes for people who are vegan or lactose intolerant [20]. As a naturally occurring endogenous photoprotector, β -carotene prevents the damaging effects of UV radiation on the skin [19]. Numerous

research and meta-analyses have also provided evidence for it [21,22]. The polar terminal end, conjugated side chain, and cyclohexenyl ring are the three components that make up the general structure of retinoid molecules [17]. These three fundamental components make up the majority of naturally occurring retinoids, including retinol, retinaldehyde, and retinoic acid as shown in Table 1 [17]. Retinol—a renowned derivative of vitamin A1 [23], is used as an over-the-counter (OTC) medication in the cosmeceutical industry as well as in the form of nutritional supplements [24]. It is a lipophilic molecule that exists as yellow or orange crystals [24]. In addition to its anti-aging properties, retinol supports brain development, growth, vision, hemopoiesis, wound healing, and epithelial cell differentiation [24,25]. Tretinoin—a prescription medicine has shown efficacious responses to improve wrinkling, hyperpigmentation, shallowness, and lentigines caused by photoaging within a period of a month and effects that lasted for 2 years [26]. Although vitamin A is a stable molecule, exposure to UV radiation renders it inactive [24,26]. The vulnerability of the skin to UV radiation without effective sun protection is a leading cause of early signs of skin senescence that can be controlled by appropriate usage of retinoids [27]. Retinoids are wonder drug molecules that find use in anti-aging therapy for the skin primarily in photoaging and sequential aging [28,29]. Retinoids are fat-soluble vitamins primarily used for acne vulgaris treatment and skin rejuvenation therapy, and their effect can be enhanced by the appropriate employment of nanotechnology and the use of nanoparticles in their formulations [30]. Retinoids or other vitamin A derivatives such as retinoic acid work against the aging process by reducing the presence of skin creasing, and crow’s feet and by increasing the epidermal thickness coupled with increasing the cell turnover rate [31,32]. Retinoids are formulated in a variety of topical preparations like serums, creams, and moisturizers, leave-on or rinse-off cosmetics as described in Table 2. They cause a tingling and a stinging feeling or irritancy after their application on the skin [29,33]. Very often, they also lead to the development of scales on the facial skin and lead to purging and desquamation [29].

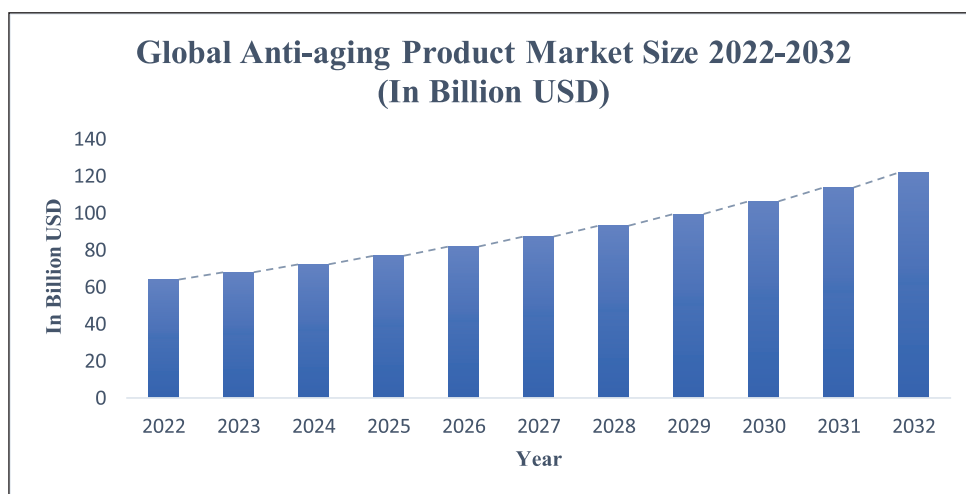
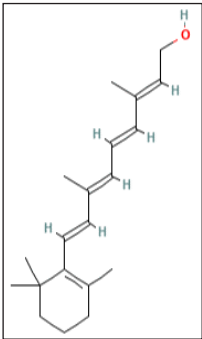
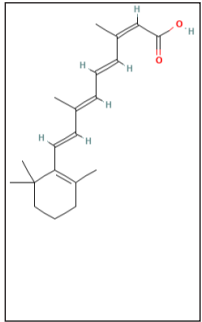
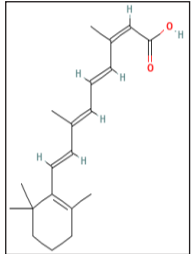
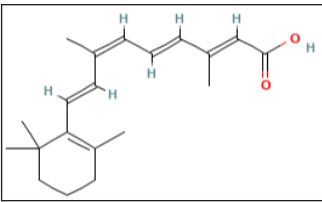
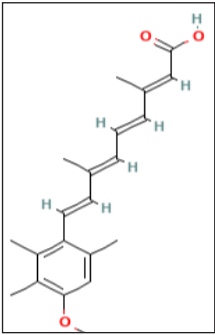
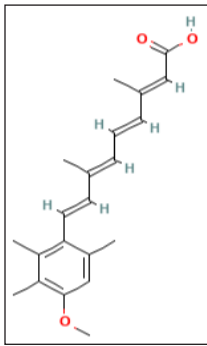
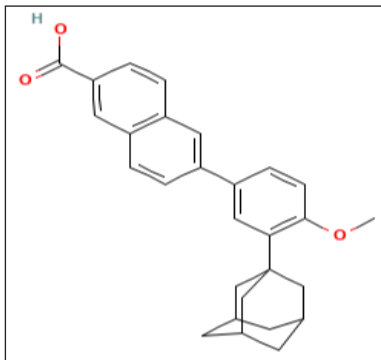
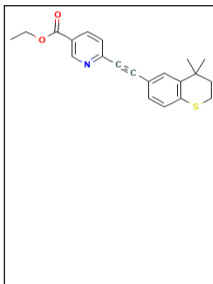
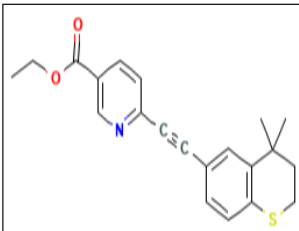
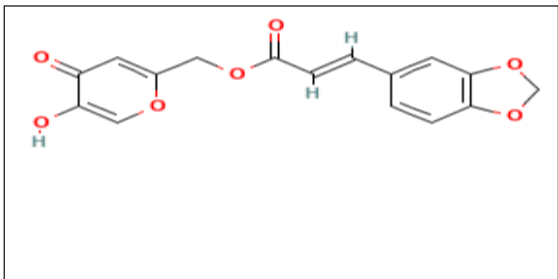


Figure 1. Graphical representation of projected surge in global anti-aging product market size from the year 2022 to 2032 in billion US dollars.

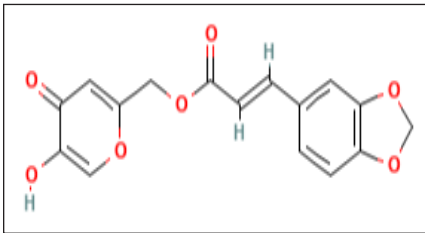
Table 1. Classification and concentration of retinoids.

Types of retinoids	% Strength range	Molecular structure
First generation		
Retinol	0.0015%–2%	
Tretinoin	0.025%, 0.05%, 0.1%	
Isotretinoin	0.1%, 0.05%	
Alitretinoin	0.1%	
Second generation		
Etretinate	Currently under investigation	

Continued

Types of retinoids	% Strength range	Molecular structure
Acitretin	Currently under investigation	 <p>Third generation</p>
Adapalene	0.1%, 0.3%	
Bexarotene	1%	
Tazarotene	0.05%, 0.1%	 <p>Fourth generation</p>
Trifarotene	0.005%	

Continued

Types of retinoids	% Strength range	Molecular structure
Seletinoid-G	0.25%, 0.5%, 0.1%, 1%	

These adverse effects of retinoids decrease patient compliance with them [33]. To overcome these problems, nanocarriers are employed for topical retinoid drug delivery in the form of liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), polymeric micelles, and microemulsions [34]. Nanoparticles exhibit controlled drug release, targeted drug delivery, and strong drug adhesion to the skin and are highly specific in their drug delivery [34].

This review focuses on the increasing demand for skin-care formulations that include retinoids as the primary active ingredient which is formulated into nanotechnological vesicles to maximize patient compliance and minimize side effects in the everyday skincare routine of individuals. For the generation exposed to a greater degree of extrinsic and intrinsic aging triggers, these nano-drug retinoid-loaded vesicles will help to prevent early indications of aging and pigmentation, rejuvenate the skin, and attain a healthy, glowing complexion. The general audience is yet unaware of nano-drug delivery that has promising long-term advantages above easily available marketed cosmetics. To raise public awareness about the advantages of nanotechnology and retinoids, and how their combination rejuvenates the skin without requiring invasive and expensive dermatological procedures, considering the growing market trends for anti-aging products is the central aim of this review.

METHODS AND LITERATURE SEARCH

To prepare this manuscript, literature review, data integration, and collecting processes were initiated in September 2022 and continued until December 2023. Finding novel cosmeceuticals that delay skin aging and promote skin rejuvenation by understanding their mechanism of action, pharmacokinetics, and formulation strategies was the key objective of the data-gathering process. The primary goal in preparing this manuscript was to emphasize the significance of skincare regimens that incorporate cutting-edge novel cosmeceuticals providing nano-drug delivery, resulting in a healthier and more balanced skin barrier that can adapt to changing environmental conditions rather than spending a lot of money on invasive dermatological treatments. ScienceDirect (<https://www.sciencedirect.com>), PubMed (<https://pubmed.ncbi.nlm.nih.gov>), and Google Scholar (<https://scholar.google.com/>) search engines were used to conduct the literature search. Keywords like “nano-drug delivery,” “nano-particles” and “Retinol” were used to obtain maximum data. PubChem (<https://pubchem.ncbi.nlm.nih.gov/>) was used to describe the structures of Retinoids and their derivatives in more detail and contributed to 13 references. A comprehensive search

was done to include the marketed preparations from the global as well as the Indian market and pharmacies. For this review paper, 120 publications were chosen after carefully weighing the data from the literature survey.

SKIN REJUVENATION

The art of skin rejuvenation involves using surgical and non-surgical methods to restore the skin’s most natural, healthy texture and tone by promoting collagen synthesis and reducing fine lines and wrinkles through a variety of mechanisms [15,35–38]. Chemical peeling, ablative [39] and non-ablative laser photo-rejuvenation [39,40], and injectable skin biostimulation and rejuvenation are examples of surgically invasive procedures [36,38,41]. Despite their promising outcomes, they come at a considerable cost [36,38,41]. Botox (*Botulinum toxin*) fillers [42], microdermabrasion [43], and laser hair removal [44] are the most favored non-invasive dermatological procedures [35,45]. In the last 10 years, most people have turned to at-home skin care to enhance their skin instead of intrusive and invasive procedures like aesthetic plastic surgeries that break the bank [35]. The cosmeceutical industry has witnessed a significant surge of 82% in the use of anti-aging active ingredients such as retinoids due to their ability to improve fine lines and wrinkles and reduce hyperpigmentation when formulated within nano-drug vesicles, in contrast to other active species that may only provide transient benefits [35].

Retinoid classification

An assortment of retinoids find usage for a wide range of skin concerns according to their varying concentrations. Based on the molecular structure retinoids can be classified into four generations [24,46–58]. The molecular structures and concentration strength of retinoids commonly employed in formulations are shown in Table 1.

The aging process

Aging is a natural phenomenon. However, the causes of aging can be natural or man-made. Aging is seen more predominantly on facial skin than in the other parts of the body [1]. The following Figure 2 depicts a young, healthy skin section depicting the presence of hyaluronic acid (HA) and collagen that supports and provides elasticity to the skin.

Aging is characterized by decreased collagen synthesis, fine lines, facial sagging, and depletion of antioxidants such as Vit A, Vit C, and Vit E. The two processes by which aging takes place are intrinsic or chronological aging and extrinsic or photoaging processes [59,61].

Table 2. Marketed preparations of retinoids available on a global market scale.

Marketed preparations	Composition	Strength	Cost of product
Minimalist 0.3% retinol face serum for anti-ageing with coenzyme Q10 (30 ml)	Squalene, caprylic/capric triglyceride, coco-caprylate/caprates, bakuchiol, retinol, polysorbate 20, ubiquinone (coenzyme Q10), tocopheryl acetate, BHT	0.3% Retinol	INR 599/-
The ordinary retinol 0.5% in squalane (30 ml)	Squalene, caprylic/capric triglyceride, <i>Simmondsia chinensis</i> (jojoba) seed oil, retinol, <i>Solanum lycopersicum</i> (tomato) fruit extract, <i>Rosmarinus officinalis</i> (rosemary) leaf extract, hydroxymethoxyphenyl decanone, BHT.	0.5% Retinol	INR 800/-
Plum 1% retinol face serum with bakuchiol (30 ml)	Aqua, <i>Aloe barbadensis</i> leaf juice, sucrose, propanediol, squalene, isodecyl neo pentanoate, retinyl palmitate, <i>Malus domestica</i> fruit cell culture extract, hydrolyzed rice protein, hydrolyzed pea protein, glycine, proline, hydrolyzed sodium hyaluronate, <i>Psoralea corylifolia</i> (Bakuchi) oil, benzyl alcohol, hydroxy acetophenone, caprylyl glycol, xanthan gum, glycerin, lecithin, phenoxyethanol, sorbitol, cyclodextrin, hydroxyethyl acrylate/sodium acryloyl dimethyl taurate copolymer, isohexadecane, polysorbate 60, sodium gluconate, sodium polyacryloyldimethyl taurate, ammonium acryloyldimethyltaurate/VP copolymer	1% Retinol	INR 790/-
The derma co 2% granactive retinoid serum (30 ml)	Aqua, diethylhexyl carbonate, coco caprylate caprate, octyldodecanol, behenyl alcohol, cyclopentasiloxane (and phenyl trimethicone (and) dimethiconol (and C12-15 alkyl benzoate (and) dimethicone crosspolymer, methyl glucose sesquisteate, hydroxyethyl acrylate sodium acryloyldimethyl taurate copolymer, trisodium ethylenediamine disuccinate, glycerin, dimethyl isosorbide (and hydroxypinacolone retinoate, pentaerythrityl distearate, butyl hydroxy toluene, sodium metabisulfite, isohexadecane, <i>Caesalpinia spinosa</i> gum, polysorbate 60, ethylhexylglycerin, phenoxyethanol, fragrance.	2% Retinol	INR 699/-
Tretin 0.025% cream (30 g)	Tretinoin, cream base, sorbic acid, BHT	0.025% Tretinoin	INR 190/-
Retino A 0.5% cream (20 g)	Tretinoin USP, cream base	0.5% Tretinoin	INR 240/-
Sotret gel (30 g)	Isotretinoin, isopropyl alcohol, gel base	0.05% Isotretinoin	INR 238/-
Panretin gel (60 g)	Alitretinoin, dehydrated alcohol, polyethylene glycol 400, NF, hydroxypropyl cellulose, NF and butylated hydroxytoluene, NF	1 mg Alitretinoin	INR 509,887/-
Adaferin gel (15 g)	Adapalene (0.1%), methyl parahydroxybenzoate, phenoxyethanol, gel base	0.1% Adapalene	INR 284/-
Tazret gel	Tazarotene, aqueous gel base, benzyl alcohol	0.05% Tazarotene	INR 260/-
CeraVe skin renewing retinol serum (1 ounce)	Aqua/water/eau, glycerin, caprylic/capric triglyceride, potassium cetyl phosphate, hydrogenated palm glycerides, polysorbate 20, Peg-40 stearate, cyclopentasiloxane, hydroxyethylcellulose, potassium phosphate, ceramide Np, ceramide Ap, ceramide Eop, carbomer, niacinamide, isoceteth-10, dimethicone/vinyl dimethicone crosspolymer, triethanolamine, cetearyl alcohol, behentrimonium methosulfate, <i>Cichorium intybus</i> root extract/chicory root extract, lecithin, retinol, silica, sodium lauroyl lactylate, cholesterol, phenoxyethanol, tocopherol, alcohol, hydroxyacetophenone, citric acid, hydrolyzed HA, pentylene glycol, xanthan gum, phytosphingosine, <i>Butyrospermum parkii</i> butter/shear butter, ethylhexylglycerin.	Encapsulated retinol	INR 2,083/-
L'Oreal Paris Revitalift Triple power LZR retinol night serum for face, with 0.3% pure retinol (1 Fl. oz)	Aqua/water, glycerin, alcohol denat., glycine soja oil/soybean oil, isononyl isononanoate, pentylene glycol, dicaprylyl ether, propylene glycol, PEG-6 caprylic/capric glycerides, PPG-6-decyltetradeceth-30, dicaprylyl carbonate, glyceryl isostearate, sodium hyaluronate, retinol, ammonium polyacryloyldimethyl taurate, caprylyl glycol, citric acid, trisodium ethylenediamine disuccinate, xanthan gum, butylene glycol, tocopherol, pentaerythrityl tetra-Di-T-butyl hydroxyhydrocinnamate, phenoxyethanol.	0.3% Pure retinol	INR 1,876/-
Neutrogena rapid wrinkle repair retinol Pro+ .5% power facial serum (1 Fl. oz)	Isohexadecane, dicaprylyl carbonate, pentaerythrityl tetraethylhexanoate, PPG-15 stearyl ether, triethyl citrate, polysorbate 20, retinol, fragrance, tocopheryl acetate, bisabolol, BHT, pentaerythrityl tetra-di-t-butyl hydroxyhydrocinnamate.	0.5% Retinol	INR 1,460/-
Retinol 2.5% solution facial serum with vitamin E—facial crepe erase (1.01 Fl. oz)	<i>Aloe barbadensis</i> leaf extract, propanediol, retinol, sodium hyaluronate, niacinamide, 1,2-hexanediol, polysorbate 20, tocopheryl acetate (vitamin E), <i>*Rosa damascena</i> extract, <i>*Lavandula angustifolia</i> flower extract, <i>*Camellia sinensis</i> leaf extract, <i>*Melissa officinalis</i> leaf extract, <i>*Artemisia vulgaris</i> extract, disodium EDTA.	2.5% Retinol	INR 833/-
Nature's holistics 100% organic retinol serum	Organic herbal infusion*, organic <i>Aloe barbadensis</i> leaf* (Aloe), witch hazel*, pentylene glycol, phospholipids, retinol*, sodium benzoate, potassium sorbate, ethyl hexyl glycerin, polysorbate 20, potassium phosphate, vitamin C*, vitamin B5*, vitamin E*, shea butter*, jojoba oil*, HA*, green tea' *from certified organic source.	2.5% Retinol	INR 1,568/-

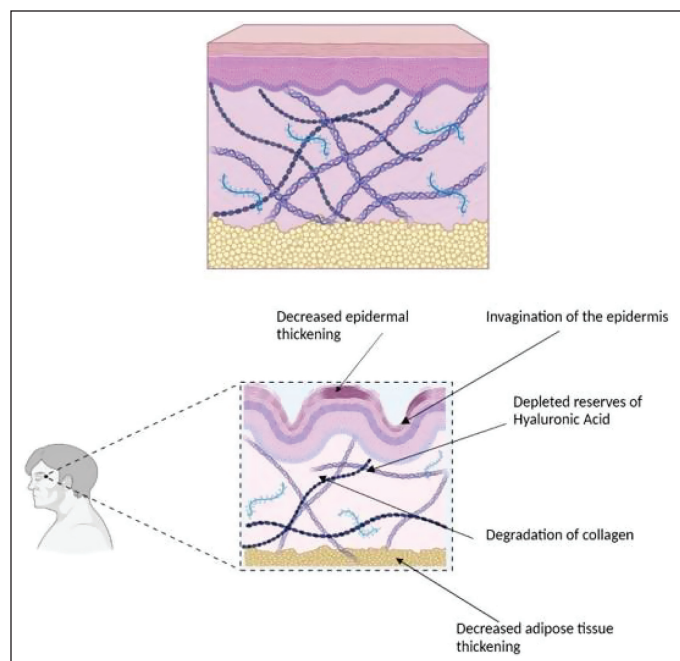


Figure 2. Healthy skin section with optimum collagen and HA deposition (above) and a skin snippet depicting decreased collagen and HA deposition because of intrinsic aging and photoaging (below).

Intrinsic aging

Chronological aging is referred to as intrinsic aging [2,62,63]. It accounts for 10% of skin damage leading to aging [6,62]. Constant generation of reactive oxygen species (ROS) is the cause of skin damage [64]. ROS is responsible for damage to vital cellular components like DNA, enzymes, cell, and plasma membranes [6,62,63,65]. The release of activator protein-1 (AP-1) is stimulated by the activation of the mitogen-activated protein kinases (MAPK) pathway, which is triggered by the generation of ROS [64,66]. The release of AP-1 causes matrix metalloproteinases (MMP) to activate [62], which in turn decreases the synthesis of collagen and elastin fibers and accelerates their breakdown in the skin [64]. Wrinkles and sagging are common indicators of aging skin caused due to decreased levels of collagen and elastin [62] as shown in Figure 3. Despite the presence of predisposing factors genetics contain a pivotal importance in the aging process accompanied by the depletion in the sex hormone levels [62]. The eukaryotic chromosome is made of distinct parts, the telomere being the last portion [62,67]. As we age, the cell divisions that take place also increase; the human telomere (TTAGGG) shortens with each increasing cell division [62,67]. Although a greater number of cells possess the potential of about 60–70 postnatal doublings, over the period, they do not proliferate but remain viable and become more susceptible to apoptosis [62,67]. This process is called the biological clock [8,12,62,63,68]. Along with this process, some signaling molecules increase while some decrease in number [62,63]. A decrease or increase in the number of signaling molecules like chemokines and cytokines leads to the damaging of several skin functions and results in fibroblast senescence [62,68]. All these factors decrease

the viability of the cells and hence aging occurs. Some of the prominent clinical features of aging are the appearance of benign cherry angiomas, fine lines, and wrinkles along with sloppiness of the skin [12,62]. A decreased volume of dermis and melanocytes is observed [62]. The number of blood vessels also decreases leading to a reduction in blood supply and nerve innervations to the epidermis and dermis [62]. A sparse number of melanocytes leads to greying of hair as well [62]. The age pigment “lipofuscin” marks cell damage and is responsible for the appearance of visible small brown spots on the skin [62,69]. The following Figure 2, depicts a young, healthy skin section depicting the presence of HA and collagen that supports and provides elasticity to the skin.

Extrinsic/photo aging

Environmental factors such as prolonged subjection of the skin to the sun, air pollution like dust and aerosols, blue light [32], tobacco inhalation, alcoholism, smoking, inadequate hydration, stress, poor sleep schedules, and having a diet devoid of essential nutrients contribute to the extrinsic aging process [9,62,70,71]. It accounts for 90% of skin damage leading to aging [62]. About 80% of extrinsic aging occurs from the vulnerability of the skin to UV radiation and is a common cause of early signs of skin senescence that leads to the generation of ROS [62,64,71,72]. The UV radiations can be categorized into UVA and UVB radiations [62]. Both UV radiations exert different effects on the skin. The UVA radiations can percolate into the subcutaneous layers of the skin involving the epidermis and dermis [62]. UVA radiations are held accountable for photoaging and premature aging. The UVA rays can also pass through the glasses of the windows. These radiations cause damage to the dermal layer leading to alterations along with a rise in the collagen-degrading enzymes and xeroderma pigmentosum factor (XPF) primarily found in the epidermis [62]. The beginning of the presence of fine creases on the skin is a result of XPF since it causes invagination of the epidermal layer [62]. On the contrary, UVB radiations do not perforate into the subcutaneous skin layers and get absorbed into the superficial layer of the skin—the epidermis [62,72]. The epidermis consists of specialized cells called keratinocytes and melanocytes [62]. The keratinocytes are responsible for keratin production which provides firmness and elasticity to the skin [62]. The melanocytes are concerned with the production of a pigment called melanin that imparts color to the skin [62]. The UVB radiations attack the DNA of keratinocytes and melanocytes present in the epidermis which results in the production of specific proteolytic enzymes upon being exposed to the UV rays [62,72]. Such affected cells appear sunburnt after 8–12 hours of sun exposure due to the occurrence of UV fingerprints which are characterized by the formation of thymidine dimers [62]. With increasing age, the lysis of thymidine bonds ceases leading to irreversible mutations [62]. Extrinsic aging owes to the lowered expression of type VII collagen in keratinocytes which leads to skin creasing and decreased levels of collagen type I [73]. In contrast, to the healthy skin section, the aged skin tends to show drastically different properties like invagination of the epidermis coupled with decreased collagen and HA deposition as depicted in Figure 2.

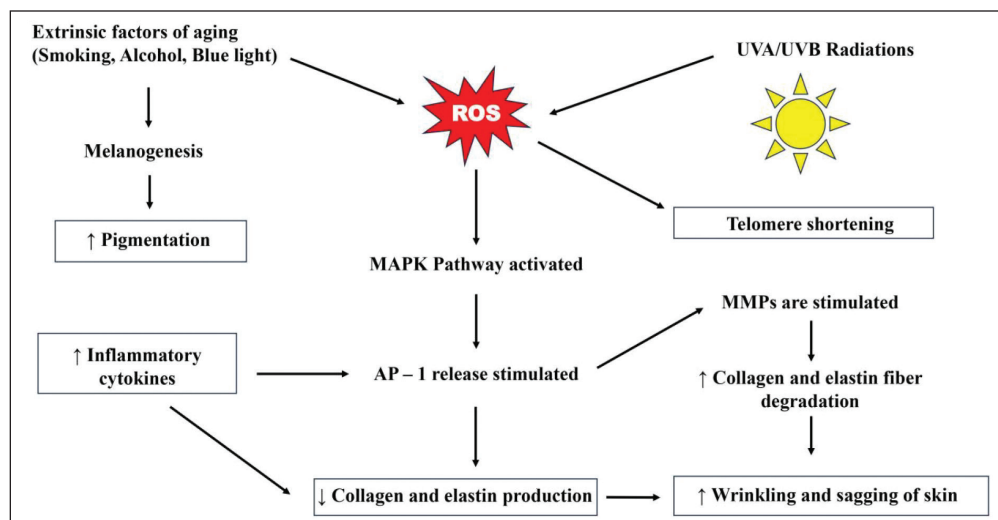


Figure 3. Mechanism of generation of ROS and its effect on the skin aging process.

Mechanism of action of topical retinoids in the anti-aging process

Post-absorption retinoids bind to different nucleic acid and cytosolic receptors at the molecular level to exert their action that initiates immune variations, inflammatory responses, and different cell programs such as cell differentiation and proliferation for epidermal thickening [27,47,74]. Cytosolic retinol binding proteins (CRBP I and II) and cytosolic retinoic acid binding proteins (CRABP I and II) are protein transporters essential to activate the receptors so that subsequent binding to nuclear receptors occurs [47]. Retinoids bind to nuclear receptors like retinoic acid receptors (RAR) and retinoid X receptors (RXR) present within the nucleus of skin cells [27,47,74]. These receptors are ligand-dependent transcription factors, wherein retinoic acid is the natural ligand for the RAR superfamily while 9-*cis*-retinoic acid is the natural ligand for the RXR superfamily [47]. The nuclear RAR family has three types of isotypes namely RAR α , RAR β , and RAR γ [47,75]. Human skin predominantly contains heterodimers of RXR α and RAR γ [27,75]. Post binding, RAR, and RXR form dimers [47]. Dimers formed can be homodimers (RAR/RAR) or heterodimers (RAR/RXR) [74]. These dimers bind to the suitable retinoid responsive elements (RAREs and RXREs) that induce successive gene expression which leads to cell differentiation [27,47,74]. The mechanism of action of retinoids to repair photodamaged skin can be sought from both the RARs and RXRs as shown in Figure 4 [27]. RARE elements are located near the gene promoter sequences to which retinoid binding occurs [47]. The absence of retinoid-responsive elements leads to competitive inhibition and inhibited gene expression [47,74]. Other transcription factors like AP-1 that regulate gene expression and cytokine proliferation are desensitized thus impacting cell differentiation [47,74]. Topical retinoids act by inducing different cell programs like cell differentiation and proliferation that pave the way for epidermal thickening which helps in skin rejuvenation [27,74,76]. Retinoid derivatives like retinol, or all-*trans* retinol are extremely lipophilic due to the polarity of the terminal group [45]. A chemical with excellent

lipophilicity readily passes through the phospholipid bilayer membrane of the cell and has good absorbability [45]. Retinoic acid has a highly polar group at the terminal position hence greater absorption in contrast to retinaldehyde which has a weak polar group at the terminal position and hence has poor absorption rates [45]. These structural benefits confer upon retinoids several avenues for skin rejuvenation at a much lower cost and pain than invasive dermal procedures for skin rejuvenation [45].

Studies conducted on tretinoin

Retinoids are widely known for their anti-aging benefits for the skin which help in skin firming, inducing elasticity, decreasing shallowness of skin increasing the epidermal thickness, and minimizing the fine creasing and wrinkling of the skin. Some of the retinoids that exert effective benefits are tretinoin, isotretinoin, adapalene, accutane, and retinols [77]. Tretinoin is mostly used for treatment against chronological or intrinsic aging [27,78]. Weiss *et al.* [79] demonstrated the efficacy of tretinoin by conducting randomized, double-blind studies on an assembly of 30 subjects for a short period of 4 months by using 0.1% tretinoin versus a vehicle [79]. The results exhibited a noticeable increase in glycosamine glycans, a depletion in shallowness, fine lines and wrinkles, compaction of stratum corneum, and an enhancement in perceptible roughness [79,80]. Leyden *et al.* [81] have proved the efficacy of tretinoin by conducting randomized, double-blind studies on a group of 30 subjects for an extended period of 6 months by using 0.05% tretinoin versus a vehicle. The results showed a reduction in shallowness, fine lines, and wrinkles, and an enhancement in hyperpigmentation [81]. Tretinoin proved to be an effective treatment for clinical signs of photoaging [27]. High strength tretinoin has disadvantages like irritation and dermatitis therefore low strength tretinoin comes to the rescue for patients who are allergic to typically higher concentrations of tretinoin (0.05%) [27]. The US Food and Drug Administration has recognized 0.02% tretinoin as the standard treatment for all skin types [27]. In conclusion, tretinoin primarily acts by amplifying

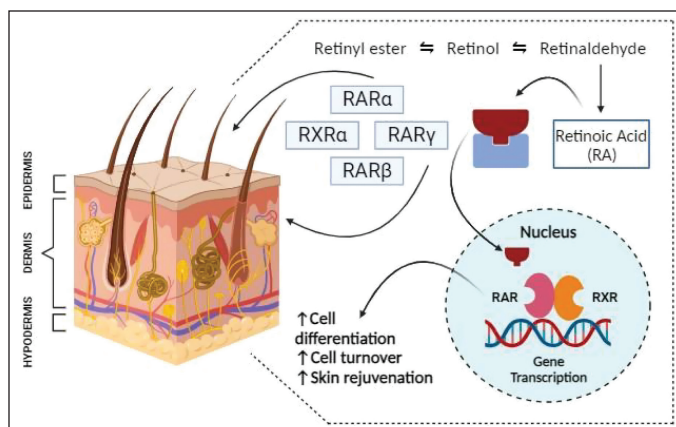


Figure 4. Mechanism of action and gene transcription of natural and synthetic retinoids in skin rejuvenation.

the epidermal thickness, improving fine lines and wrinkles, compaction of stratum corneum, and reducing the laxity of photoaged skin [27]. Along with the anti-aging benefits, tretinoin exerts severe side effects such as irritation, scaling, redness, dermatitis, and dryness. A first-generation retinoid—retinol provides an equal anti-aging benefit but with fewer side effects and reactions. Retinol is chemically known as all-*trans*-retinol or vitamin A alcohol [27,81]. It comes from the family of endogenous natural retinoids and is a precursor required to produce retinoic acid and retinal [27,81].

In comparison with tretinoin; retinol exhibited lesser signs of erythema and irritation [34,82]. But Fisher *et al.* [83], demonstrated that tretinoin is 20 times more effective than retinol. Nonetheless, retinol has effective anti-aging benefits such as epidermal thickening, keratinocyte proliferation, and a fundamental improvement in fine lines and wrinkles but with fewer side effects and aggravation [34].

Studies conducted on retinol

A cream tested by Oddos *et al.* [84], containing retinol with HA and dihydroxymethylchromone (DMC) demonstrates the retained anti-aging and skin rejuvenating benefits of retinol when paired with key ingredients like HA and DMC on the facial skin. The study was conducted for a period of 8 weeks with a dermal application of the cream [84]. A low concentration of retinol—0.1% when formulated into a cream using HA and DMC in the formulation exhibits a long-term anti-aging benefit on the facial skin [84]. HA is a mucopolysaccharide that helps to hold water molecules in the skin and supports collagen development [73]. Likewise, HA increases keratinocyte expansion through the stimulation of the CD44 receptor in the skin [84]. UV light exposure decreases the CD44 expression which is regressed by the presence of retinol [84]. Furthermore, the addition of DMC in the formulation provides a synergistic action to that of retinol [84]. Kaufman *et al.* [85], conducted a study by using an eye cream formulated with retinoids and alpha hydroxy acid (AHA, lactic acid) [85]. AHAs are alcoholic carboxylic acids procured from natural substances like fruits and fermented milk products which help in increasing skin hydration and enhancing the rate of keratinocyte proliferation and increased

thickening of the dermis [86]. An effective combination of retinoid and AHA-based eye cream was studied with a regular nighttime application for 12 weeks which revealed remarkable advancement in the reduction of darkness and puffiness of the eyes along with reduced lines and wrinkles in the under-eye region [85]. Farris *et al.* [87], tested a topical cream containing 0.5% retinol along with 4.4% niacinamide, 1% resveratrol, and 1.1% hexylresorcinol all put together in a nourishing moisturizer base [88]. This study was carried out over a period of 10 weeks with 25 subjects who had a moderate number of fine lines, wrinkles, and cutaneous hyperpigmentation [87]. The usage of antioxidants in retinol-based creams provides a synergistic effect in anti-aging therapy. Topically used 5% niacinamide (vitamin B3) is an antioxidant that exhibits anti-aging and skin brightening benefits as elucidated in results of studies conducted by Bissett *et al.* [89], with 50 female Caucasians for 4-week intervals. Reduced levels of hyperpigmentation were observed in the [89]. Resveratrol is a potent antioxidant that has effective anti-aging benefits and is extensively used in skin care formulations [90]. Furthermore, it is very helpful in reducing signs of photoaging [90] as it possesses the unique capacity to perforate into the subcutaneous layers of the skin and stimulate the increase of collagen III concentrations [91]. Schlessinger *et al.* [92], stated that hexylresorcinol is an efficient ingredient in anti-aging therapy for the skin. In conclusion, a combination topical cream evaluated by Farris *et al.* [87], demonstrates efficient anti-aging activity and helps in reducing hyperpigmentation and cohesively increasing the evenness of the skin. Piérard-Franchimont *et al.* [93], carried out controlled clinical trials with retinol formulations which demonstrated a significant depletion in fine lines after 12 weeks of application with reduced levels of MMP. In conclusion, retinol is an efficient treatment for aging skin, but its efficacy entirely depends on the vehicle being used for its delivery as it is highly unstable and gets degraded easily upon exposure to UV radiation [27].

Adverse effects of retinoids

Antithetical to the good benefits that retinoids have to offer they come with their own set of side effects commonly called the “retinoid reaction.” Retinoids tend to cause a tingling and a stinging feeling after their application on the skin [29]. Very often, they also lead to the development of redness, dryness, and scales on the facial skin [29]. Retinoids are a potent form of vitamin A which is primarily used for targeting skin concerns like acne, hyperpigmentation, fine lines, and wrinkles. Studies suggest that continual usage of retinoids by oral or topical dosage forms leads to a rise in serum vitamin A levels. Increased Vit A levels are harmful to the growing fetus. Therefore, oral, and topical usage of retinoids is not recommended for pregnant women and lactating mothers [94]. Studies have shown that retinoids like isotretinoin and accutane should be avoided during pregnancy as it leads to fetal retinoid syndrome and the risk of developing this syndrome stands high at 35% if pregnant females use retinoids [72,95]. Fetal retinoid syndrome is a rare case of birth defect that involves congenital malformations and teratogenic effects which results in cardiovascular and central nervous system abnormalities [95].

Marketed preparations of retinoids

Retinoids are formulated in a variety of topical preparations like serums, creams, and moisturizers, leave-on or rinse-off cosmetics. The various preparations commonly used are described in Table 2 along with the ingredients used in the formulation.

Nanotechnological approach in retinoid-based cosmeceuticals

Nanotechnology refers to the improved absorption or penetration of the active ingredient species into the body because of the highly reduced size of the drugs [34]. It focuses on nano-drug delivery at specific targets in the body and is a very useful method of topical and dermatological nano-drug delivery [34,96]. Nanotechnology in cosmeceuticals is implied through “nanocarriers” that target specific skin concerns and provide sustained release of drugs [97]. The skin has several factors that influence the rate of absorption and penetration of active ingredients like intermolecular drug interactions and the physicochemical properties of the nanoparticles like particle size and partition coefficient [34]. Moreover, the skin is in continual contact with the environment making it more vulnerable to wear and tear. At the cellular level, epidermal cell cohesion and the presence of lipids in the stratum corneum impose a barrier to the effective absorption of the drugs [98]. Considering these barriers, nanotechnology is an efficient method for better absorption and penetration of active ingredients [34]. The nanoparticles or nanocarriers used in skincare formulations help in adhering the active ingredient to the skin for a prolonged time without much degradation or spoilage and do not disturb the normal functions of the skin [97]. Furthermore, better absorption and penetration of drugs in the skin are observed owing to the small size of the active pharmaceutical ingredient (API) [34]. Nanocarriers are colloidal particles with a size range of 10–1,000 nm. The skin penetration mechanism is influenced by the rigidity, hydrophobic nature, particle size, and particle charge of the nanoparticles [34,99]. These small nanocarriers are available as liposomes, SLNs, NLCs, polymeric micelles, and hydrogels [34]. Nanoparticles exhibit controlled drug release, targeted drug delivery, and strong drug adhesion to the skin [34,99,100]. They are highly specific in their drug delivery thus leading to a reduced percentage of active ingredients used in the formulations and fewer side effects are observed [34,99]. A sunscreen formulation tested against its non-nanosized formulation not having TiO₂ and ZnO nanoparticles had lower penetration than their nanosized counterparts [34,97].

Nanotechnological delivery for retinoids

Retinoids are linked with an extensive number of side effects post-application while some adverse reactions take place due to the route of administration. To overcome these side effects, Nano formulations have been developed that help in effective drug delivery, improved penetration mechanisms, and a significant reduction of retinoid reactions post-dermal application [49,101]. Retinoids especially retinol a highly popular OTC anti-aging treatment are formulated either within serums, creams, or nano gels for their increased therapeutic action. Nano formulations are favorable as they have low toxicity and lower biodegradation levels [34]. It consists of

various delivery systems for efficient drug penetration and increased skin bioavailability, the formulations widely used are lipid-based, polymer-based, and metal-based [34,97]. Retinoids are typically formulated using lipid-based nanosystems which include liposomes, niosomes, SLNs, NLCs, and nanoemulsions. These nanoparticles help in the effective drug delivery of poorly soluble substances across the skin barrier along with the addition of excipients that aid the absorption of drugs through the skin. Among these nano-drug delivery systems, liposomes hold immense importance and are by far the highest used materials for Retinoid formulations.

Liposomes

Liposomes are small, spherical vesicles that are prepared from phospholipids and cholesterol and they deliver both lipophilic and hydrophilic drugs [102]. Due to their small size, they have a higher penetration rate through the superstratum [74]. Based on their size liposomes are classified into three types:

- Multilamellar vesicles (300–5,000 nm) [74].
- Large unilamellar vesicles (100–300 nm) [74].
- Small unilamellar vesicles (20–100 nm) [74].

Due to their size and penetration powers, liposomes hold immense importance and are by far the highest-used material for retinoid formulations. Studies conducted by the Korean Society [30,103] have shown that retinol when incorporated into lamellar liposomes exhibits a slower degradation and an increased shelf life as compared to its non-liposomal counterparts. Studies conducted by [104] use multi-layered liposomal delivery technology which incorporates 0.5% retinol coupled with niacinamide and *Terminalia chebula* [104]. Retinol is an OTC drug that is spontaneously converted to retinoic acid for exerting its therapeutic action. A 12-week *in-vivo* study involved topical application of this formulation which had positive outcomes such as patient compliance mitigation of irritation and reduced fine lines [104]. Transferosomes, flexible liposomal counterparts, were loaded with RP to assess its penetration in the skin [105]. The development of RP-loaded transferosome cream was assessed in three distinct systems [105]. In the first investigation, only 7.64% of the RP was able to pass the membrane throughout 30 hours *in vitro* over a synthetic membrane [105]. The RP-containing transferosomes were effective in breaking through the membrane and releasing the RP [105]. Franz-cells were used for full-thickness pig skin penetration testing, wherein 63% RP was effectively released in the second research than with its plain RP counterparts [105]. *In-vivo* topical application of transferosome RP cream was performed on six healthy volunteers but the results showed no difference between the transferosome RP cream and its non-transferosome counterpart in terms of compatibility [105]. Overall, this study developed a transferosome RP-loaded cream that is a good candidate for achieving targeted drug delivery [105].

Solid-lipid nanoparticles

SLNs are comprised of a solid lipid core enclosed within a layer of surfactants [74,106]. SLNs deliver both hydrophilic and lipophilic drugs and their size ranges between 40 and 1,000 nm [107]. It has been introduced to induce enhanced dermal

absorption [108] and to overcome the drawbacks of liposome-based delivery systems [108,109] SLNs exhibit a sustained drug release and extended fortification of active compounds and a reduction in chemical degradation [97,103,108–110] when the core is filled with the drug and burst release when the shell is loaded with API [74]. A comparable *in-vitro* study conducted by [111] reported prolonged release of vitamin A palmitate for up to 24 hours, which was used as the primary API embedded in the core of SLN [111,112]. The developed gel had twice higher drug retention in the superstratum with enhanced hydration and no skin irritancy in contrast to the traditional gel prepared [111]. Jun *et al.* [113], developed a cream containing, 0.1% retinol-loaded solid lipid nanocarriers employing the vacuum emulsification method (VLN-ROL) to maintain the stability of retinol in the formulation. This prepared cream was evaluated on porcine skin and a 3D human skin model [113]. Application of this VLN-ROL-containing cream to the porcine skin demonstrated better retinol retention as compared to other commercial products procured from BASF [113]. Similarly, the 3D human skin model exhibited increased thickness of the superstrata, a boost in collagen levels, and lessened irritation in contrast to other formulations tested [113]. NLCs are the next generation of SLNs developed to counterfeit the drawbacks of SLNs in terms of their core loading capacity [74] NLCs contain both solid and liquid lipids in their cores in contrast to SLNs [112].

Microemulsion

Microemulsions are colloidal nanosystems that exist as transparent, monophasic systems which are thermodynamically stable. They contain an organic phase and aqueous phase dispersed in a solution which is stabilized by the addition of a mixture of surface-active agents coupled with co-surfactants [113,114]. Microemulsions are of potential use in targeted delivery for dermal applications, lessened skin irritancy, and improved bioavailability of drugs [115] Tretinoin lacks water solubility and is a chemically unstable, photo-unstable ingredient that is it undergoes degradation upon exposure to light [116]. Topical application of tretinoin leads to redness and skin irritation [27]. The incorporation of efficient carriers for the drug helps to transport the drug through an aqueous vehicle and has also shown increased rates of drug stability and drug retention [116]. As per the studies conducted by Špaglová *et al.* [117], the potential of a new microemulsion was studied and prepared using carbopol as a wetting agent incorporating tretinoin (TRE) as the active ingredient which was later dispersed in a hydrogel for effortless application purposes [116,117]. This study was conducted in comparison with a hydrogel formulated with xanthan gum as a wetting agent with a similar procedure [116,117]. A comparison of permeation enhancers used in the microemulsion proved that the tretinoin penetration rates were 2.5 times higher with increased drug retention and improved skin bioavailability of tretinoin-after-dermal-application-of carbopol-based hydrogel [116,117]. Algahtani *et al.* [118], prepared a nano-emulgel system containing RP as the API for increasing the drug transport across the skin and overcoming the side effects caused by the application of retinoid derivative—RP. This study assessed the stability of RP and its hydrophobicity

[118]. Stability evaluation studies of the nano-emulgel suggest increased UVA stability upon exposure to direct UVA rays as compared to that of pure RP exposed [118]. This increased UV stability is obtained by the virtue of encapsulation of RA within the nano-emulgel [118].

Niosomes

Niosomes are second-generation nanotechnological vesicles enclosed by an admixture of non-ionic surface-active agents like cetyl alcohol, polysorbates, and cholesterol instead of phospholipids [74]. It overcomes the drawbacks posed by liposomes and provides better penetration mechanisms through the superstrata, decreased skin irritancy, and enhanced stability [74]. Niosomes can deliver both hydrophilic and lipophilic drugs. Studies conducted by Manconi *et al.* [119], compare the *in vitro* delivery of trans retinoic acid (TRA) or tretinoin-loaded niosomes and liposomes. After evaluating the incorporation of vesicles *in-vitro* by Franz cells on newborn pig skin and the high-performance liquid chromatography method it was concluded that formulations containing niosomes had a greater skin bioavailability as compared to other formulations evaluated in this study [119]. Surfactants also play a crucial role in deciding the absorption and retention of the TRA niosomes and liposomes. TRA niosomes were formulated using two non-ionic surfactants, ORAMIX CG110 and ORAMIX NS 10. The former showed more targeted (trans) dermal delivery than the latter, which showed improved TRA retention within the skin [119].

CONCLUSION AND OUTLOOK

Skin aging is an intricate and complex process that is being comprehended from its mechanism of action and is a field that is very much sought for treatment via topical and ingestible modes of action. Primarily skin ages due to intrinsic and extrinsic predisposing factors, which may differ according to different parts of the world. Signs of skin aging are shown in people above the age of 35. Premature aging has become a common concern due to several predisposing factors, such as those that accelerate the aging process of the skin. However, society at large, especially women over the age of 35, has begun to become more conscious of their appearance. Fluctuating work schedules, and disturbed sleep patterns make it even more difficult to maintain healthy, youthful-looking skin without the use of cutting-edge novel cosmeceuticals. The ability to rejuvenate and restore the natural glow of skin has been made possible by the development of innovative anti-aging cosmeceutical solutions that incorporate nanotechnological vesicle-loaded drug delivery techniques. Although intrinsic factors are beyond one's control, the rate of extrinsic or photo-induced aging can be restrained with the appropriate usage of anti-aging molecules like retinoids in the form of tretinoin, isotretinoin, retinol, and adapalene formulated within the topical route of administration and seldom via an oral route. The key function of retinoids is to mitigate the signs of aging and help achieve healthy and well-maintained skin even in older adults. However, retinoids are accompanied by a lot of adverse reactions that lead to a decline in patient compliance. To overcome these adverse effects, retinoids are formulated within nanotechnological vesicles and

other potential delivery systems to reap the benefit without the adverse effects. Polymeric micelles, liposomes, SLNs, and microemulsion-based hydrogels have opened a new era of targeted drug delivery systems with little to no side effects. SLNs are potential nanotechnological delivery systems, their presence in sunscreens as TiO₂ (titanium dioxide) and ZnO (zinc dioxide) loaded SLNs helps prevent sun damage due to UV radiations and can benefit in photodamage of the skin preventing fine lines and wrinkles. Before SLNs; Liposomes were used extensively in cosmeceuticals but owing to their side effects now SLNs are used further. Considerable research is being carried out to minimize the chemical, particle-particle, and particle-skin interactions that contribute to the instability of nanoparticles. Evaluation of patient health and safety post-exposure to nanoparticles is still under evaluation. Emerging studies for skin rejuvenating cosmeceuticals focus on developing newer derivatives of retinol possessing fewer side effects, but due to the developmental cost involved the process is slowed down. Research is now being carried out to find retinol-mimetic ancient medicines like PADMA-28 that stimulate procollagen synthesis and help fight the signs of aging. Overall evolving research will focus on the development of innovative retinoid derivatives like N-formyl aspartate, drugs having receptor selectivity like seletinoid-G, combination therapy of API having synergistic effects, retinyl ascorbate co-drug for better acceptability and ancient medicines having therapeutic benefits. In conclusion, continued help and support of dermatologists is required for the endorsement of newer drug delivery technologies and their potential benefits.

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All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the committee of medical journal editors (ICMJE) guidelines.

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USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declares that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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