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THE ELIXIR OF YOUTH: RETINOID REVELATION

Benadict Jeslina Roshni[*1], Yenugula Chenna Harshan Reddy[1], M. Jagadish Swamy[1], Monika Nijhawan[2], Sneha R Nawale[3]

[1]*Department of Pharmacology, Gokaraju Rangaraju College of Pharmacy, Bachupally, Hyderabad, Telangana, 500090 (Osmania University), India*
[2]*Department of Pharmaceutics, Gokaraju Rangaraju College of Pharmacy, Bachupally, Hyderabad, Telangana, 500090 (Osmania University), India*
[3]*Department of Pharmacognosy, Gokaraju Rangaraju College of Pharmacy, Bachupally, Hyderabad, Telangana, 500090 (Osmania University), India*

The integumentary system, mostly made up of skin tissue, is the most substantial system in the human skeleton, serving as an essential shield against a myriad of detrimental agents. These include but are not limited to, toxic chemicals, pervasive environmental pollutants, and the deleterious effects of ultraviolet radiation. The senescence of the dermis and epidermis is an inexorable biological phenomenon, subject to a multitude of contributing factors. Ultraviolet radiation, nutritional habits, aridity, tobacco consumption, hormonal fluctuations, and the force of gravity all play pivotal roles in this complex process. Dermatological aging manifests in two distinct forms: intrinsic aging, an unavoidable consequence of the passage of time that remains impervious to intervention; and extrinsic aging or photoaging, which owes its occurrence predominantly to environmental insults. As skin ages, it loses vital components such as elastin, collagen, and proteins that are essential for maintaining healthy skin. Currently, numerous skincare routines and methods are available to rejuvenate aged skin and prevent further aging. Antiaging strategies can be divided into preventive measures and secondary antiaging approaches. Tretinoin, in particular, is a topical retinoid that has been proven effective as an antiaging agent for treating conditions like acne, wrinkles, and melasma. However, the effectiveness of retinoids is often challenged by issues such as instability, low skin penetration, and potential irritation. To address these drawbacks associated with traditional retinoids like tretinoin and retinol, nanotechnology-based topical drug delivery systems have been developed. These advanced systems have demonstrated improved stability, better tolerability, and enhanced efficacy of retinoids

Keywords: *Retinod; UV rays; photoaging; inflammaging; Tretinoin; Matrix metalloproteinases*

INTRODUCTION

Aging is an inevitable part of life that necessitates physical and psychological changes in humans. As we age, cells and tissues deteriorate, causing visible signs on the skin such as wrinkles, gray hair, and changes in skin texture. These signs become more apparent later in animate life and are important for our social interactions and appearance[1,119]. The skin shields the body from the outside world, which acts as a protective barrier. Its primary function is to safeguard the body from dehydration and infection-causing micro-organisms. Additionally, the appearance of the skin plays an essential role in enhancing one's aesthetics. Having youthful and attractive skin can have a positive impact on an individual's social behavior and reproductive status[2,120]. The process of aging starts from the moment we are born and this includes our skin. Being the largest organ in the body, our skin begins to

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*Corresponding author: Benadict Jeslina Roshni, E-mail: sneha.nawale11@gmail.com or sneha8032@grcp.ac.in

display visible signs of aging. Therefore, people spend a lot of money on cosmetics and pharmaceuticals to slow down or reverse the process of skin aging. Ongoing research on skin aging and its treatment has been driven by the ever-increasing demand for cosmetics. This demand has necessitated a relentless pursuit for knowledge and innovation in the field of skincare.[3,4,5,120]. Our skin is our primary defense against various environmental threats such as exposure to solar ultraviolet (UV) radiation, physical and chemical injuries, and infections from pathogens. It also prevents water loss, which is critical to maintaining healthy skin. The human skin is composed of two essential layers, namely the epidermis that covers the skin's surface, and the dermis that lies beneath it. The outer layer of the skin, known as the epidermis, is primarily made up of keratinocytes. These cells produce keratins that are essential in forming the stratum corneum, which is the skin's protective layer. The dermis, unlike the epidermis, has a lesser number of cells. It is mainly composed of proteins such as collagen, elastin, fibronectin, and proteoglycans. These protein components work together to create the extracellular matrix (ECM). Collagen is the most abundant protein in the skin, it makes up around 90% of the skin's dry weight. It's an essential component that helps keep our skin healthy and youthful. Dermal fibroblasts are essential in the production, arrangement, and preservation of the collagen-enriched extracellular matrix (ECM) in the human skin[1]. Cutaneous aging is a consequence of both internal and external factors. Intrinsic ageing is a natural process that results in thin, dry skin, tiny wrinkles, and gradual dermal atrophy. On the other hand, extrinsic aging is brought on by outside environmental variables like smoking, air pollution, inadequate diet, and sun exposure. It causes rough-textured wrinkles, elasticity loss, laxity, and coarse wrinkles[4,5]. Extrinsic skin aging, or photoaging, is predominantly caused by long-term exposure to solar ultraviolet (UV) radiation[5]. Wrinkles, dermal atrophy, and decreased suppleness are clinical signs that can be caused by the natural ageing process. These alterations are the outcome of a variety of molecular-level processes caused by both intrinsic and external factors. Over time, these processes cause degenerative changes in the skin and a decrease in the number of functioning components, ultimately impacting the skin's general health and look[6,7,121]. In this comprehensive review, we will delve into the intricate details of skin aging, discussing the various changes that occur over time. We will also explore the latest research advances that shed light on the molecular mechanisms responsible for these changes. Finally, we will examine the various treatment strategies available to combat skin aging, providing valuable insights into how to improve the health and appearance of your skin.

Changes in skin aging

The Integumentary system, mainly the skin is immediately exposed to the environment, it is vulnerable to both intrinsic and extrinsic aging. The former transpires naturally over time, while the latter is hastened by exogenous factors, such as exposure to UV rays, tainting, and smoking. The aging processes culminate in cutaneous cell phenotypic changes as well as structural and functional changes to the extracellular matrix's collagen, elastin, and proteoglycan components. The latter is indispensable for giving the skin hydration, suppleness, and tensile strength[5,120]. Prolonged skin exposure to the sun's ultraviolet radiations about a gradual decline of skin elasticity. This phenomenon is caused by the destruction of fibrils and Collagen Type VII (Col-7), both of which contribute to strengthening the epidermis-dermis interconnection. Consequently, the skin becomes extrinsically aged, leading to sagging and other visible signs of aging[8,122]. Numerous theories were proposed to interpret the complex process of aging, including the Free radical theory, DNA or genetic theory, Mitochondrial decline theory, Neuroendocrine theory, Membrane theory, Hayflick limit theory, and Telomerase theory. Internal elements cause histological alterations in the basal cell layer, which causes the skin to thin and droop in intrinsically aged skin. On the other hand, aberrant elastic tissue accumulates in the mid and deep dermis of extrinsically aged skin that has been exposed to the sun; this condition is known as solar elastosis or UV irradiation. This rise in elastin promoter activity causes the elastin gene to become transcriptionally active and reduces fibrillin-1 production, which leads

to a significant buildup of dystrophic and shorter elastic fibres. If the cross-linked molecule formed from lysine rises, photoaged skin can be definitively established[9,10]. Skin aging can be classified into four types, one of which is intrinsic aging. Smooth, pale, unblemished, drier, and less elastic skin with fine wrinkles are the mark of Intrinsic aging.[11,12] and inside the tissue itself is a decrease in fibroblasts, cutaneous mast cells, collagen synthesis, and extrinsic aging. Pro-oxidant and antioxidant effects on cell turnover, as well as prolonged exposure to the sun—a condition known as photo-aging—can also contribute to this. These elements mainly affect the face and neck by acting through neuro-endocrine-immune biological response modifiers[13]. Photo-aging refers to the process of skin aging resulting from prolonged sun exposure. The main components of sunlight are ultraviolet (UV) radiation (3%), visible light (44%), and infrared radiation (52–55%), with the latter being more damaging to skin. The ozone layer, which protects the planet from harmful radiation, does not shield the skin from these rays, making it vulnerable to damage. As a result, the skin experiences significant damage due to the effects of UV radiation, resulting in wrinkles, dark spots, and other signs of aging. Considering the substantial effects of photoaging on the skin, it is imperative to take the necessary precautions to avoid it, such as proper sun protection and limiting exposure to intense sunlight[14]. The biological process of hormonal aging results ina decrease in the production of collagen, skin moisture, thickness, and epidermal barrier function. This can result in visible changes to the skin, such as wrinkles and dryness[15,16]. As individuals age, they become increasingly susceptible to a range of skin disorders that can result in altered skin appearance, heightened susceptibility to infections, and a higher likelihood of developing neurodegenerative disorders[17].

Pathophysiology of skin aging

The scholarly literature presents diverse molecular foundations that adequately justify mechanisms underlying skin pathophysiology, particularly skin aging. This makes the process explainable in terms of the theory of cellular senescence, which includes, among other things, oxidative stress, point mutations of extranuclear mitochondrial DNA, reduction in sugar, single-gene mutations, abnormalities in chromosomes, loss of telomeres, and chronic inflammation. Remarkably, studies indicate that extrinsic causes are typically responsible for the majority of skin aging, with internal factors accounting for only 3% of the aging factors[18,122].

Intrinsic Aging

The physiological alterations occurring naturally and chronologically within the skin over time are intrinsic skin aging[19]. Age-related alterations in the skin are distinguished by notable histological transformations that primarily manifest within the basal cell layer. Specifically, the process of cell proliferation within the basal layer decreases, leading to a reduction in epidermal thickness. Consequently, the area where the epidermis and dermis come into contact is turn, which results in a smaller exchange surface area for the provision of nutrients to the epidermis. Furthermore, this reduction in surface area weakens the potential of basal cells to escalate, leading to further deterioration of skin health[20,21]. The progressive reduction in ability of cells, including melanocytes, fibroblasts, and melanocytes to divide, which is usually termed as cellular senescence[22]. It is characterized by atrophy, which can lead to visible vasculature and reduced elasticity. Whereas the stratum corneum hangs around relatively stable, along with a weakening of the epidermis, the dermo-epidermal junction flattens, which increases the skin's susceptibility to damage[23]. Senescence marker β-galactosidase expression in dermal fibroblasts and epidermal keratinocytes was found to increase with age. This observation suggests that aged skin contains a higher number of senescent cells[22,120]. Furthermore, in photo-protected aged skin, the dermis exhibits scaling down in the number of mast cells and fibroblasts, in contrast to photo-protected young skin. Additionally, there exists a noticeable scarcity in collagen fibers and elastic fibers[23]. According to recent reports, naturally, aging human skin tends to produce less type I procollagen, most likely as a result of the TGF-b/Smad signaling pathway being downregulated. This signalling cascade also affects the connective tissue growth factor,

which is thought to be a crucial regulator of collagen expression[24]. The available evidence indicates that in skin that has aged intrinsically, there is a deterioration of the fibrous components in the extracellular matrix, including elastin, fibrillin, and collagens, as well as oligosaccharides. This degeneration has a negative influence on the skin's capacity to maintain bound water[25,26]. The aging process is also characterized by diminished immune responsiveness, which can be attributed to a down scale in the number of antigen-presenting cell and the existence of abnormal cellular morphology. The production of vitamin D3 is another important process that deteriorates with age, a process that is dependent on the availability of 7-dehydrocholesterol in the epidermal cells. This phenomenon can lead to a range of immunological and physiological impairments that can have a negative impact on overall health and well-being in older individuals[27,123].

Extrinsic Aging / Photoaging

In 1969, a proposal was put forward suggesting that in addition to intrinsic factors, overexposure to the sun is one of the factorsthat contribute to skin aging[28]. Exposure to ultraviolet (UV) radiation is the main cause of extrinsic skin aging, accounting for approximately 80% of facial aging[29]. The epidermis of skin exposed to UV radiation tends to thicken, in contrast to skin that is naturally aged[30]. Furthermore, it is discovered that the stratum corneum expresses more differentiation marker involucrin, which is consistent with the hampered differentiation process of epidermal keratinocytes during UV irradiation. Additionally, there is a noticeable decline in the expression of the cell-surface protein b1-integrin in basal cells, which is thought to be one of the markers for epidermal stem cells and interacts with extracellular matrix proteins. This suggests that over time basal keratinocyte proliferation is similarly hindered.[31,32]. In areas of skin exposed to UV radiation, keratinocytes exhibit the downregulation of type VII collagen. Because of the reduced link between the dermis and epidermis, wrinkles are primarily caused by diminished production of type VII collagen, which functions as anchoring fibrils at the dermal-epidermal junction[33]. According to recent studies, the levels of collagen type I in UV exposed skin tend to decrease over time[34,35] as a result of escalated collagen degradation[36]. Degradation is facilitated by a variety of enzymes, such as serine proteases, matrix metalloproteinases (MMPs), and other proteases[32,37,38]. The formation of aberrant elastic tissue in the dermal layers deep down is a prominent feature of photoaged skin[39]. Solar elastosis is a pathological condition characterized by the deposition of truncated elastic fibers resulting from elastolysis, which involves elastic fiber cleavage by proteases. Ultraviolet (UV) irradiation stimulates a 4-fold enhanced expression of elastin, which ultimately leads to elastolysis. This process is mediated by the aforementioned proteases[40]. MMP-2, MMP-3, MMP-7, MMP-9, MMP-12, cathepsin G, a neutrophil serine protease, and human leukocyte elastase are among the enzymes that are known to be involved in the breakdown of elastin. Recent studies reveal that photoaging accelerates the age-related degradation of elastin by aggravating the enzymatic cleavage of the N-terminal and central regions of tropoelastin molecules. Additionally, microvasculature capacity decreases with age, an outcome attributed to endothelial dysfunction, which includes reduced angiogenic potential, anomalous adhesion molecule expression, and impaired vasodilatory function[41,120]. The skin's pores, when subjected to chronic exposure, exhibit an enlargement and buildup of sticky substances that puts patients at risk for the nodular elastoidosis, cysts, and comedones associated with the Favre-Racouchot syndrome. This phenomena is linked to a higher frequency of benign tumours such ruby spots, fibroma, acrochordon, and seborrhoeic keratosis. Furthermore, the frequency of "premalignant" lesions, such as lentigo maligna and actinic keratosis, as well as malignant lesions, such as malignant melanomas and basal and squamous cell carcinomas, is increased[42,43].

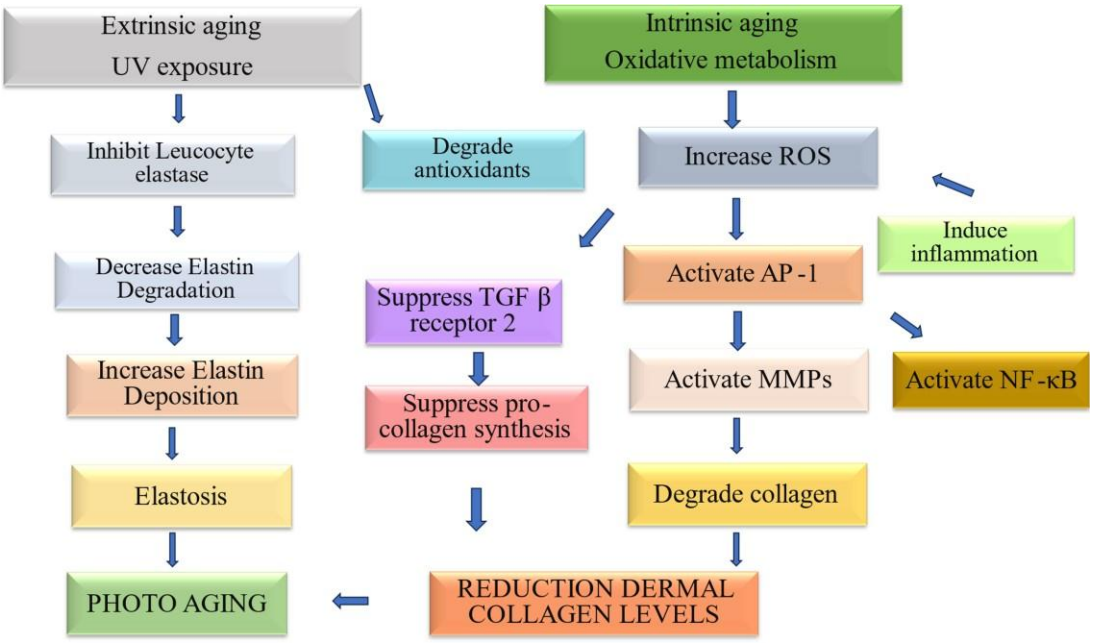

Fig. 1: Mechanism of Intrinsic and Extrinsic aging.

Mechanisms of Aging

In an attempt to explain the molecular causes behind skin ageing, several models have been developed. These models include, among other things, the theory of cellular senescence, reduced sugar, single-gene mutations, oxidative stress, point mutations in extranuclear mitochondrial DNA, loss of telomeres and decreased ability for cellular DNA repair, and chronic inflammation. Each of these models has been supported by evidence from various studies, highlighting the complex and multifactorial nature of skin aging[44]. According to some scientific propositions, the majority of aging effects can be attributed to extrinsic factors, while only a mere 3% have intrinsic origins. It is suggested that such a small percentage of factors are inherent, while the remaining aspects of aging are externally influenced[45,120]. This line of reasoning is important because it emphasizes how environmental influences may play a part in the aging process and how important it is to take preventative actions to lessen their impacts. In this context, we aim to highlight crucial models and advancements in the realm of molecular mechanism research regarding skin aging.

Cellular Senescence

An eventual loss of the capacity to replicate and significant alterations in cellular phenotype are the results of a biological process known as cellular senescence. This phenomenon, which has been thoroughly researched concerning the ageing of human skin, where senescent cells are known to accumulate, is primarily driven by cell division. Senescence is seen as the hallmark of ageing and has important consequences for the emergence of age-related illnesses[46]. The phenomena wherein, at the completion of their replicative lifetime, the increase of cellular activity is stopped during the G1 phase. Consequently, senescent cells are unresponsive to physiological mitogens that aim to stimulate their entry into the S1 phase[47]. The reduction in growth associated with aging can be attributed, in part, involves the specific suppression of several growth regulatory genes essential to the advancement of G1 and DNA synthesis. The c-fos proto-oncogene, the helix-loop-helix genes Id-1 and Id-2, and the E2F transcription factor and its components are notably downregulated in senescent fibroblasts due to this suppression in fibroblasts. Furthermore, there is an overexpression of negative growth regulators, including as p21 and p16, which are inhibitors of cyclin-dependent protein kinases[48,49,50]. Alterations in senescent skin fibroblasts are characterized by an upregulation of IL-1 expression[51]. Senescent stromal cells are known to exhibit a growth arrest that is irreversible, and they require resistance to apoptotic death. These cells also release a

range of substances that affect the development and differentiation of epithelial cells. These factors include matrix metalloproteinases, which facilitate tissue remodeling, and Heregulin is an EGF-like cytokine that affects how breast and other epithelial cells develop and differentiate. Therefore, the equilibrium between the overlaying epithelial cells' development and differentiation may be impacted by the presence of senescent stromal cells[52]. It has been observed that they display modified differentiation capabilities[53]. It has been proposed that this process results in the build-up of senescent cells, which are non-proliferating cells displaying altered gene expression and behavioural alterations. This ultimately leads to a progressive deterioration in tissue integrity and function, which is a hallmark of the ageing process.[54]. Cellular differentiation changes are hypothesised to play a role in the changes observed in matrix and metalloproteinase expression in aged skin. Collagenase (MMP1) and stromelysin (MMP3), two important enzymes that break down the dermal extracellular matrix, are expressed at extremely low levels in presenescent dermal fibroblasts, and metalloproteinase activity is comparatively low in these cells. In contrast, there is a significant reduction in the degradative ability due to the high levels of matrix metalloproteinase inhibitors TIMP 1 and TIMP 3.[53]. Them expression levels of matrix metalloproteinases and tissue inhibitors of metalloproteinases are reversed in fibroblasts that have experienced senescence. Specifically, there's an upregulation of matrix metalloproteinase expression and a downregulation of tissue inhibitors of metalloproteinase expression[55,56,57]. Ageing is frequently associated with many changes in the skin, one of which is a reduction in the rate of collagen manufacture. This reduction in collagen expression levels is particularly significant in elderly individuals, in contrast to early postnatal years or foetal tissue[58]. A notable alteration is the transition from a matrix- producing to a matrix-degrading phenotype, which contributes to the disorganization and decrease of collagen, which is a common characteristic of deteriorated skin and comprehensive dermal atrophy. In addition, the expression of the elastin gene decreases significantly after the ages of 40 to 50, as demonstrated by steady-state mRNA levels in fibroblasts that have been grown, and the dermis gradually loses its elastic tissue[59, 60]. One prominent feature of ageing skin is the loss of oxytalan fibres in the papillary dermis, which are usually seen as finger-like extensions towards the foundation membrane. Another typical characteristic of aged skin is loss of recoil, which may be clinically manifested as a decline in the ability of aged cells to re- synthesize these fibres[61].

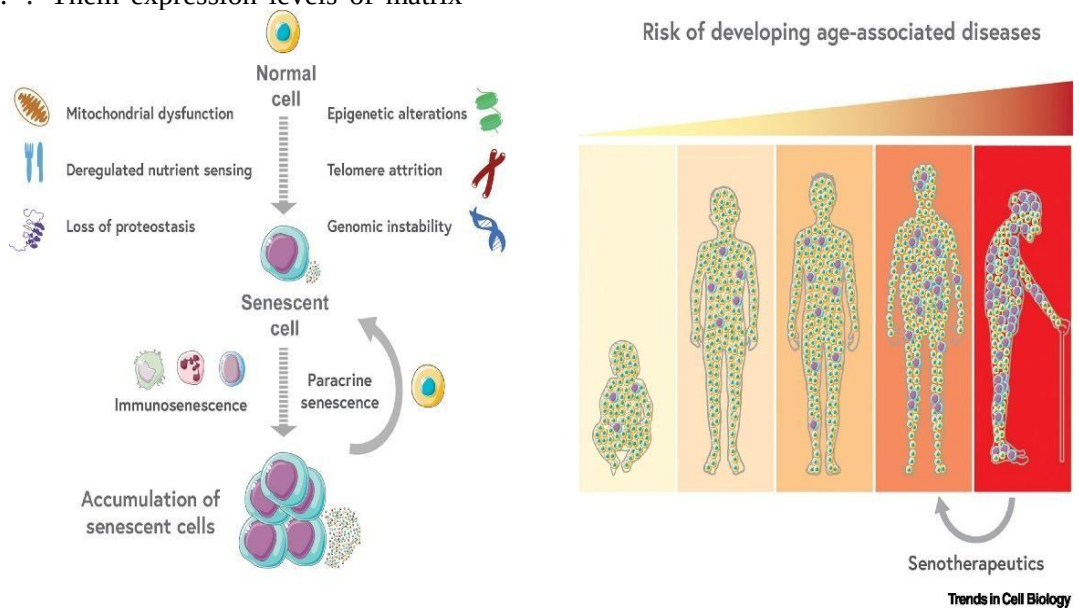

Fig. 2: Schematic representation of cellular senescence.

Oxidative Stress

When it comes to the changes in dermal extracellular matrix that are linked to intrinsic ageing and photoaging, reactive oxygen species (ROS) are thought to be a key player. The mitochondrial electron transport chain, peroxisomal and endoplasmic reticulum (ER) localised proteins, the Fenton reaction, and a number of enzymes, including cyclooxygenases, lipoxygenases, xanthine oxidases, and nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, are some of the sources that cause ROS to be produced[62]. A multitude of cellular functions are regulated by receptor tyrosine kinases (RTKs), which are essential parts of the cellular signalling apparatus. RTKs on the cell surface are normally controlled by receptor protein tyrosine phosphatases (RPTPs), which dephosphorylate RTKs. However, when exposed to ultraviolet (UV) radiation, cellular chromophores absorb the energy and get excited, which results in the production of reactive oxygen species (ROS) and oxidation products. It has been noted that ROS can bind to cysteine residues in the catalytic areas of RPTPs, interfering with their action and causing inhibition[63]. A surge in Receptor Tyrosine Kinases (RTKs) that are phosphorylated, which initiates downstream signalling cascades. One such route is the activation of Mitogen-Activated Protein Kinase (MAPK), which in turn activates transcription factor activator protein-1 (AP-1) and nuclear factor-kB (NF-kB). As consequence, photoaged skin loses collagen because activated NF-kB and AP-1 restrict collagen formation while upregulating the transcription of Matrix Metalloproteinase (MMP) genes[64]. Notably, the mammalian target of rapamycin complexes 2/Akt/IkB kinase a (mTORC2/Akt/IKKa) pathway has been connected in recent times to the activation of nuclear factor kappa B (NF-kB) in both intrinsic and photoaging[65].

DNA Damage

It has been demonstrated that prolonged and regular skin exposure to ultraviolet (UV) radiation damages DNA, causes mutations, and raises the risk of early ageing and cancer.

It is imperative to note that these negative outcomes may develop even with minimal sun exposure over time[66]. Upon absorption of photons from ultraviolet-B radiation, the nucleotides within DNA undergo structural rearrangement, leading to the manifestation of defects within the DNA strands. Such defects can have significant implications for the integrity of the genetic code and, consequently, the functioning of the organism at the cellular level[67]. Numerous investigations consistently demonstrate that topical sunscreen is an effective way to protect the skin against melanoma and squamous cell carcinoma as well as to prevent DNA damage in vivo. The evidence suggests that regular use of sunscreen is a simple yet effective strategy for mitigating the damaging effects of UV radiation on the skin. In light of these findings, it is recommended that individuals apply sunscreen regularly, particularly when exposed to sunlight for prolonged periods[68].

miRNA Regulation

A class of conserved noncoding RNAs known as microRNAs (miRNAs) is essential for controlling the expression of certain genes. To be more precise, miRNAs attach to target mRNAs' 3' untranslated region to either encourage or prevent translation. As mentioned, recent studies have demonstrated that miRNA dysregulation happens during organismal ageing and cellular senescence[69]. It has been documented that by specifically targeting hyaluronan synthase 2 (HAS2), miR-23a-3p contributes to the induction of cellular senescence. These conclusions have been examined, and the body of current research supports them even more[70]. One kind of polysaccharide present in the extracellular matrix is hyaluronan (HA). Research suggests that, in comparison to youthful, non-senescent fibroblasts, elderly and senescent fibroblasts both express higher levels of miR-23a-3p and release less HA. Moreover, miR-23a-3p introduced into non-senescent fibroblasts resulted in elevated senescence-associated markers, decreased proliferation, and decreased HAS2-mediated HA production. These results imply that miR-23a-3p may be essential for controlling fibroblast senescence and HA production[71].

Advanced Glycation End Products (AGE)

Glycation is a nonenzymatic process that forms advanced glycation end (AGE) products when sugar molecules, like fructose or glucose,

covalently attach to proteins, lipids, or nucleic acids. In contrast to regular glycosylation, which occurs at specific places under the guidance of enzymes and is necessary for target molecules to perform their tasks, this results in the suppression of the target molecules' normal function. Glycation plays a role in both extrinsic and intrinsic ageing. Glycation is particularly prone to short-lived proteins in the cytoskeleton and dermal matrix, which causes tissue stiffness and decreased elasticity[72]. Glycated elastin fibres within extracellular proteins in solar elastosis-affected skin undergo aberrant aggregation and show peculiar interactions with lysozyme, but not in sun- protected areas[73], and glycated collagen is very resistant to being broken down by macromolecule proteases[74]. Specifically, the implications of protein glycation have been found to include decreased collagen formation and increased breakdown of functional collagen. Notably, in elder human facial skin fibroblasts, vimentin - a major intracellular protein component - has been identified as the primary target for NE-(carboxymethyl) lysine glycation. Vimentin is redistributed into a perinuclear aggregate as a result of this alteration, which impairs the ability of the cellto contract[75].

Genetic mutation

Progeria is a type of premature ageing that frequently manifests as an accelerated skin ageing phenotype, caused by a genetic abnormality. Skin atrophy and sclerosis, poikiloderma, alopecia, and hair loss and greying are the characteristics of this phenotype[76]. Progerin, a mutant protein produced by a mutation of the LMNA gene, is known to disrupt several essential cellular functions, and is the cause of the rare hereditary disease known as Hutchinson-Gilford progeria syndrome (HGPS)[77,78].

Inflammaging

A renowned hallmark of the ageing process is low-grade, chronic inflammation, or "inflammaging." Age-related disorders such as type II diabetes, Alzheimer's disease, cardiovascular disease, frailty, sarcopenia, osteoporosis, and skin ageing are all influenced by inflammation in one way or another[79,80]. It is well known that ultraviolet (UV) radiation induces oxidative stress in epidermal cells, which results in oxidised lipid-induced cellular damage. When this damage occurs, the complement system recognises oxidation-specific epitopes on injured cells and oxidised lipids, which sets off an inflammatory response. This ultimately results in the invasion and activation of macrophages, which eliminate the oxidised lipids and damaged cells[81,82]. Matrix metalloproteinases (MMPs) are released by activated macrophages to break down the extracellular matrix. UV light exposure on a regular basis causes the complement system to become overactive, which damages the dermis-epidermis junction. When the activated complement system deposits on this junction, macrophages that carry oxidised lipids are subjected to an overwhelming burden. Reactive oxygen species (ROS) and proinflammatory cytokines are then expelled by fatigued macrophages. The latter results in oxidative stress-induced damage to the dermal extracellular matrix, whereas the former induces chronic inflammation and long-term damage to the dermis [81,83,84].

Biochemical events that set off activation of growth factor and cytokine receptors on cell surface

Multiple growth factors and cytokine receptors are activated in human skin cells in anticipation of ultraviolet (UV) light. A few instances of these receptors are the platelet-activating factor (PAF) receptors, insulin receptors, interleukin (IL)-1 receptors, platelet-derived growth factor, and epidermal growth factors receptors (EGF-R). Most research has focused on EGF-R activation among these receptors. EGF-R is a 180 kDa transmembrane protein that is composed of an extracellular domain that binds EGF and EGF-like ligands with high affinity, such as transforming growth factor (TGF)-α, amphiregulin, and EGF that binds to heparin. Tyrosine kinase activity is intrinsic in the intracellular domain. When EGF-R, sometimes referred to as ErbB1, homo- or heterodimerizes with ErbB2 or ErbB3, certain tyrosine residues are transphosphorylated. Following UV irradiation, EGF-R tyrosine phosphorylation takes place, which is a well-characterized hallmark for receptor activation. Interestingly, in cells harboring mutant EGF-R devoid of tyrosine kinase activity, UV is unable to cause EGF-R tyrosine phosphorylation.

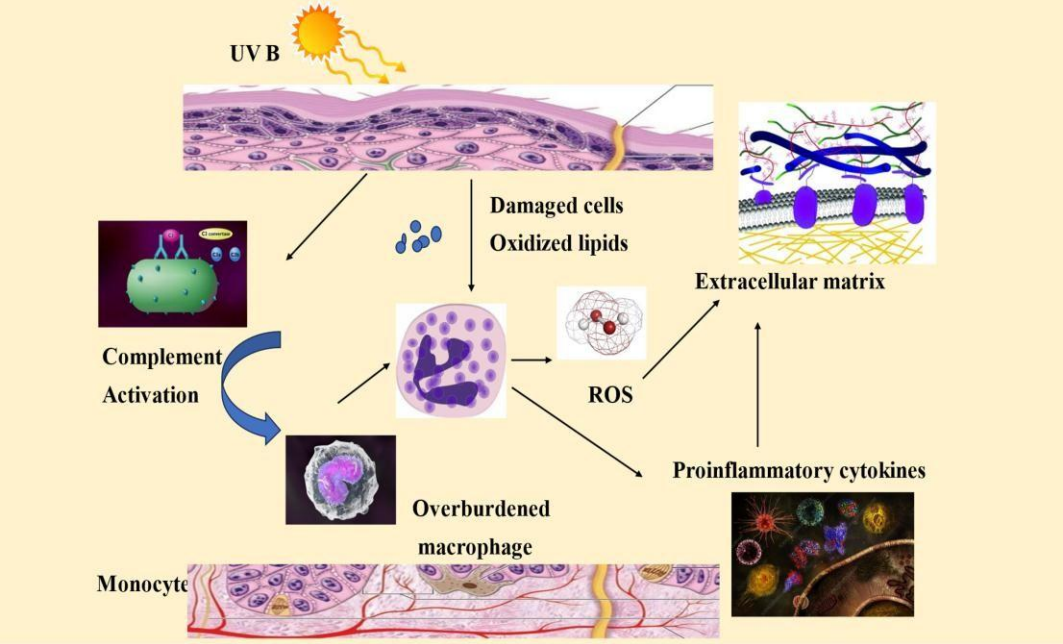

Fig. 3: Mechanism of inflammaging.

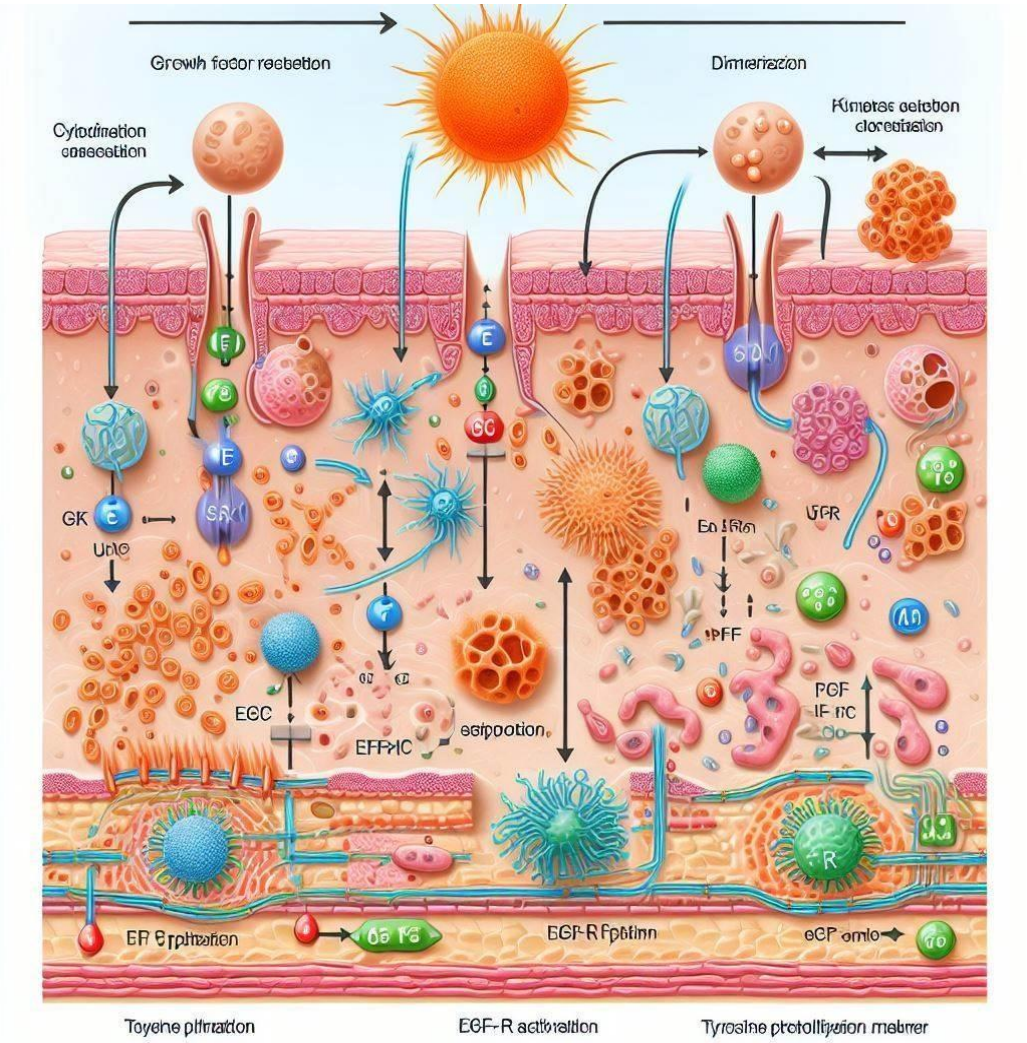

Fig. 4: Schematic representation of biochemical pathways involved in UV-activated receptors.

Owing to certain hypotheses, the inactivation of protein tyrosine phosphatases (PTPs), which keep EGF-R in a dephosphorylated basal state, is the cause of the tyrosine phosphorylation of the epidermal growth factor receptor (EGF-R) brought on by UV light. Tyrosine kinases that are specifically inhibited cause EGF-R to dephosphorylate quickly. Phosphorylated EGF-R tyrosinases have been demonstrated to live much longer when exposed to UV light, indicating that UV light inhibits PTP activity. It has been demonstrated that N-acetyl cysteine, a scavenger of reactive oxygen intermediates, can mimic the inhibitory action of UV radiation on cells. A crucial cysteine residue found in the catalytic active site of all PTPs is thought to be oxidised to sulfenic acid, which is the cause of UV radiation-induced PTP activity inactivation. Exposure to reactive oxygen species produced by UV radiation within cells causes this oxidation. PTPs can be rendered inactive, which can then activate other cell surface receptors including cytokine receptors. This can then activate small GTP-binding protein families like Rac, Ras, and Cdc42. Mitogen-activated protein kinases (MAPKs) are either directly or indirectly upstream regulated by these proteins.

Matrix metalloproteinases (MMPs) are a diverse set of zinc-dependent endoproteases that can break down any protein in the extracellular matrix (ECM), with a broad range of specificities. MMPs are first produced as proenzymes, or zymogens, which must undergo proteolytic cleavage in order to become active. Tissue inhibitors of metalloproteinases (TIMPs) control the activity of MMPs. MMP-1, also known as interstitial collagenase, is one of the AP-1 transcription factor-responsive MMPs that starts the breakdown of types I and III fibrillar collagens. Collagenases produce collagen fragments (gelatin), which are broken down by MMP-9, or 92-kDa gelatinase (gelatinase B). Meanwhile, MMP-3, or stromelysin 1, breaks down collagen type IV of the basement membrane and initiates proMMP-

1. MMP-1, MMP-3, and MMP-9 transcripts are all expressed within 8 hours of UV irradiation, indicating the importance of AP-1 transcriptional activity in controlling MMP- mediated ECM breakdown. Therefore, by inducing AP-1, MMPs as a group are able to totally breakdown mature fibrillar collagen in the skin 24 hours after UV exposure

UV radiation is the culprit in the deterioration of collagen and the disruption of collagen fibril production and organization in vivo. The transcriptional down-regulation of genes encoding for type I procollagenthe mediates the down-regulation of type I collagen. Type I procollagen mRNA and protein expression levels decline after in vivo UV irradiation and almost disappear in the upper dermis after 24 hours, which is consistent with prolonged c-Jun induction and subsequent AP-1 activation. One of the main profibrotic cytokines, transforming growth factor-beta (TGF-β), controls a variety of cellular processes, including differentiation, proliferation, and the manufacture of important extracellular matrix (ECM) proteins including collagen and elastin. TGF-β promotes the proliferation of dermal fibroblasts and suppresses the growth of epidermal keratinocytes in human skin. TGF-β promotes the proliferation of dermal fibroblasts and suppresses the growth of epidermal keratinocytes in human skin. By interacting to particular cell surface receptor complexes (TGF-β receptor proteins: TβR I/II/III), TGF-β also inhibits the expression of MMP-1 and MMP-3, inhibiting the breakdown of collagens. It has been demonstrated that UV irradiation inhibits the TGF-β signalling pathway by downregulating the expression of TβRII and, to a lesser degree, the inhibitory Smad 7. Furthermore, following UV irradiation, connective tissue growth factor is downregulated[85].

Treatments of Skin Ageing

Dermatologists possess an array of anti-aging treatments and preventive measures at their disposal. These measures include cosmetological procedures, systemic and topical therapeutic agents, and invasive techniques. There are numerous alternatives to therapy available to combat skin aging[86].

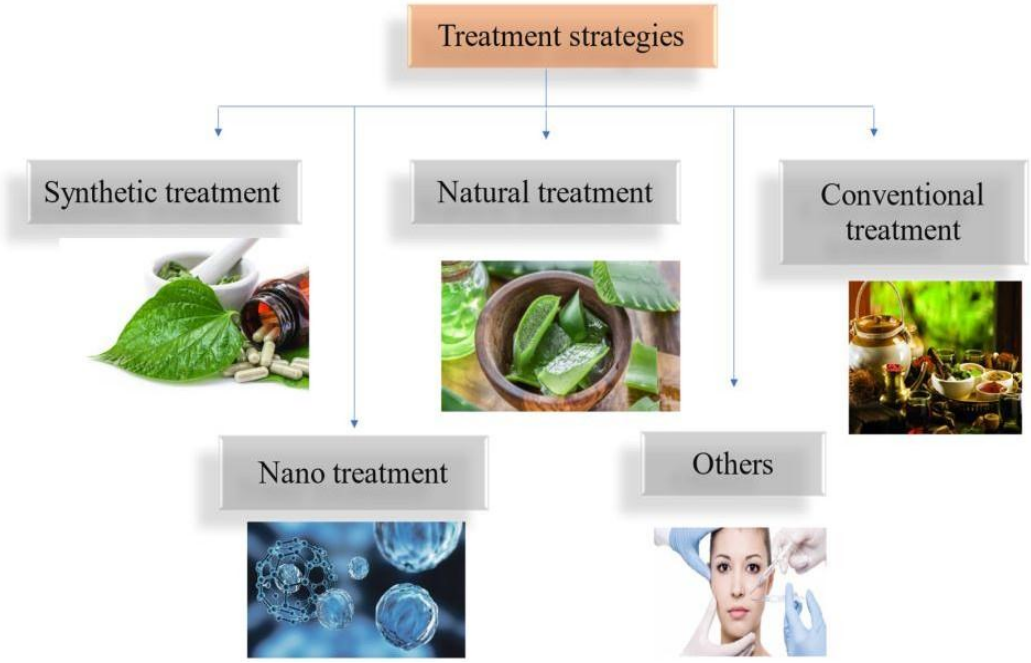

Fig. 5: Treatment strategies involved in skin aging

Cosmeceuticals

A wide variety of over-the-counter topical medications, known as "cosmeceuticals," are made with non-prescription components such vitamins, antioxidants, hydroxy acids, and plant extracts. These products were designed in such a way to improve appearance and overall health of the skin, and are often used in broad array of medicinal and cosmetic uses[87]. Cosmeceuticals constitute a necessity for sustaining the skin's hydration levels, promoting skin homeostasis, and are frequently combined with topical retinol to enhance their anti-aging properties. These products contain active ingredients that are intended to pierce the skin's outer layer and provide therapeutic benefits[88].

Evidence Behind Retinoid-Based Cosmeceuticals

Numerous studies and research suggest that tretinoin is a highly effective treatment for photoaging. Furthermore, extensive research backs up the usage of over-the-counter retinoids, which are frequently included in cosmeceuticals. These retinoids have been extensively researched and have been found to be highly effective in treating photoaging[89,124]. A class of chemicals known as retinoidoids is derived from vitamin A or has structural or functional similarities with vitamin A[90]. Retinaldehyde/retinal and retinoic acid are two of the metabolites of vitamin A, which is also known as retinol[91]. This chemical substance, which is soluble in fat and its metabolites, is crucial for the control of the immune system, healthy reproduction, vision, intercellular communication, and cell differentiation, among other physiological processes[92]. Preformed vitamin A, sometimes referred to as retinol, and provitamin A, which is present in carotenoids, are the two main forms of vitamin A that humans can receive through diet. Vitamin A is an essential nutrient. The bulk of retinyl esters are stored and processed by keratinocytes in the epidermis, whereas both forms of vitamin A are kept in the liver. Retinol and its more potent metabolite, retinaldehyde, are two common topical retinoids used for both medicinal and cosmetic purposes[93,125].

The group of compounds known as the retinoid family includes both naturally occurring and artificial retinol (vitamin A) derivatives. Topically applied retinoid-containing formulations provide anti-wrinkle benefits by promoting keratinocyte proliferation and collagen synthesis. They lessen transdermal water loss (TEWL), strengthen the epidermal barrier, stop collagen deterioration, and stop metalloproteinase activity[94,95,121]. Retinol, referred to as all-trans-retinol, is a 20-carbon molecule having a cyclohexenyl ring, four trans-configured double bonds in its side chain, and an alcohol

terminal group. The alcohol group in retinol oxidises to generate an aldehyde called all-trans retinaldehyde or retinal. This aldehyde can then be further oxidised to form a carboxylic acid called all-trans retinoic acid or tretinoin. Vitamin A needs to be received through diet because the human body is unable to synthesise it. Naturally, beta-carotene and retinyl esters are forms of it. Before being absorbed from the gut, retinyl esters are changed into retinol and then re-esterified for liver storage. Retinol attaches itself to plasma-retinol binding proteins in plasma. Four important byproducts of retinoic acid metabolism are retinyl esters, 14-hydroxy-4,14-retro-retinol, all-trans 3,4-didehydroretinol, and all-trans retinoic acid. Numerous biological functions, such as embryogenesis, reproduction, vision, growth, inflammation, differentiation, proliferation, and apoptosis, depend on retinaoids. One essential part of the rhodopsin pigment required for vision is the retina[96].

Mechanism of topical retinoids

Retinoids are recognized as controlling an array of cellular functions, involving immune-mediated responses, cell development, differentiation, and membrane remodelling. Many of these physiological effects are caused by interactions between retinoids and specific cellular and nucleic acid receptors. The Cellular Retinoic Acid Binding Proteins (CRABP) types I and II and the Cellular Retinol-Binding Protein are the main protagonists in these interactions"[97]. The identification of a transcription factor specific to tretinoin signifies a pivotal advancement in understanding its role as a hormone. This transcription factor is related to the vitamin D, thyroid hormone, and steroid receptor class of nuclear DNA transcription factors. There aretwo separate clans within this superfamily, and each of them is represented by three genes.

The clan of receptors for nuclear retinoic acid, or RARs, was the initial ones to be identified. There are three forms available: RAR-α, RAR-β, and RAR-γ. All-trans-retinoic acid specific to RARs, or tretinoin, is what activates them. The RARs operate in tandem resulting in either heterodimers, or pairs of distinct receptors, or homodimers, or pairs of identical receptors. Each RAR has a distinct DNA and retinoid-binding domain. In human skin, the retinoid X receptors (RXRs) and RARs pair up to form heterodimers. This collaboration is essential for the control of retinoid-influenced gene expression and has significant effects on dermatological research and therapy[98,99,100,101]. A unique class of nuclear receptors designated as retinoid X receptors (RXRs) binds to 9-cis retinoic acid. Normal skin contains both RXRs and retinoic acid receptors (RARs), which are necessary for the retinoid-mediated healing pathway in photodamaged skin. Generally speaking, RAR-γ makes up around 90% of RARs in the human epidermis, whereas RXR-α makes up over 90% of RXRs. Consequently, RAR-γ and RXR-α coupled heterodimers govern most aspects of normal human skin. These heterodimer complexes bind to particular DNA sequences called retinoic acid response elements (RARE), which are found in the promoter regions of genes that are regulated by particular retinoids. This modulates the transcriptional activity of the gene. Remarkably, the incorporation of an RXR-binding retinoid (9-cis retinoic acid) does not increase trans-activation by the RAR retinoid; rather, the heterodimer only needs a RAR-specific retinoid (tretinoin) to bind to RARE and start transcription. However, because it has to bind with the RAR protein, the RXR protein's physical existence is necessary for heterodimer functioning. The mechanism by which topical retinoids reduce photoaging is probably due to this interaction, which modifies cellular differentiation processes. These processes include thickening the epidermis by causing increased epidermal proliferation, compaction of the stratum corneum, and stimulation of glycosaminoglycan biosynthesis and deposition[102]. New chemical entities with selectivity for certain retinoic acid receptors (RARs) have been made available as a result of current developments in retinoid research. Adapalene, a third-generation retinoid, is renowned for its specificity towards RAR-β. Likewise, the newest class of retinoids has strong anti-inflammatory actions and operates as an antagonist. Because of these qualities, they are attractive options for topical psoriasis treatment[103,123].

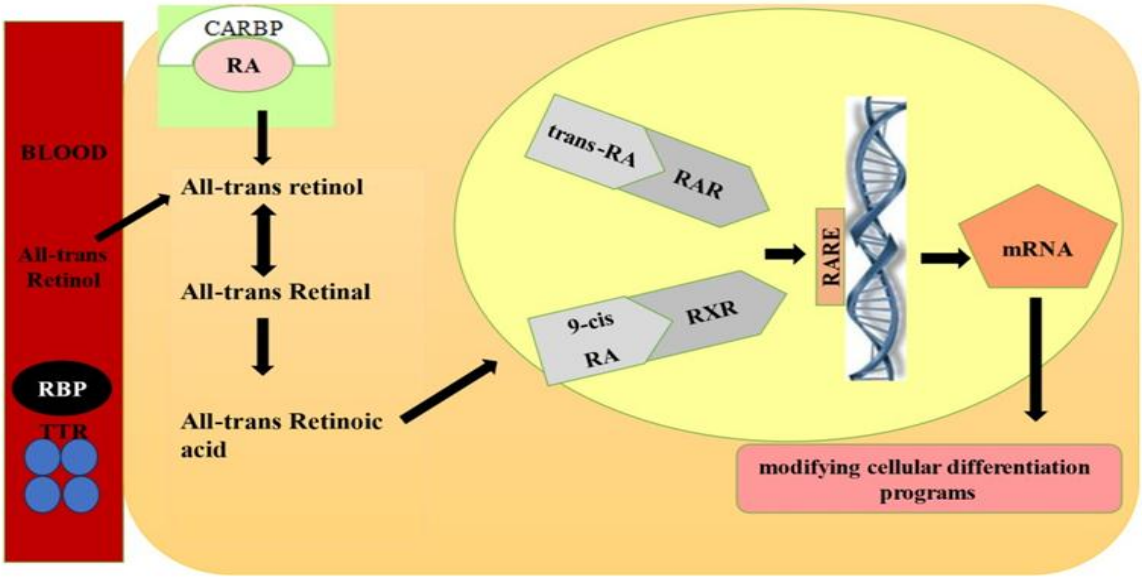

Fig. 6: Mechanism of topical (retionoids)

Application in cosmetologyTretinoin

Tretinoin, or all-trans-retinoic acid, stands out as the most potent retinoid for topical application on the skin. Its efficacy is attributed to its ability to expedite epidermal cell renewal and disperse melanin granules, thereby enhancing skin texture and tone. Notably, Tretinoin impedes matrix metalloproteinases (MMPs) by hindering the activator protein-1 (AP-1), rather than elevating the levels of the tissue inhibitor of metalloproteinases (TIMP1). In the realm of acne remedies, Tretinoin concentrations typically range from 0.01% to 0.4%, available in both gel and cream formulations for topical use" [104,105,126].

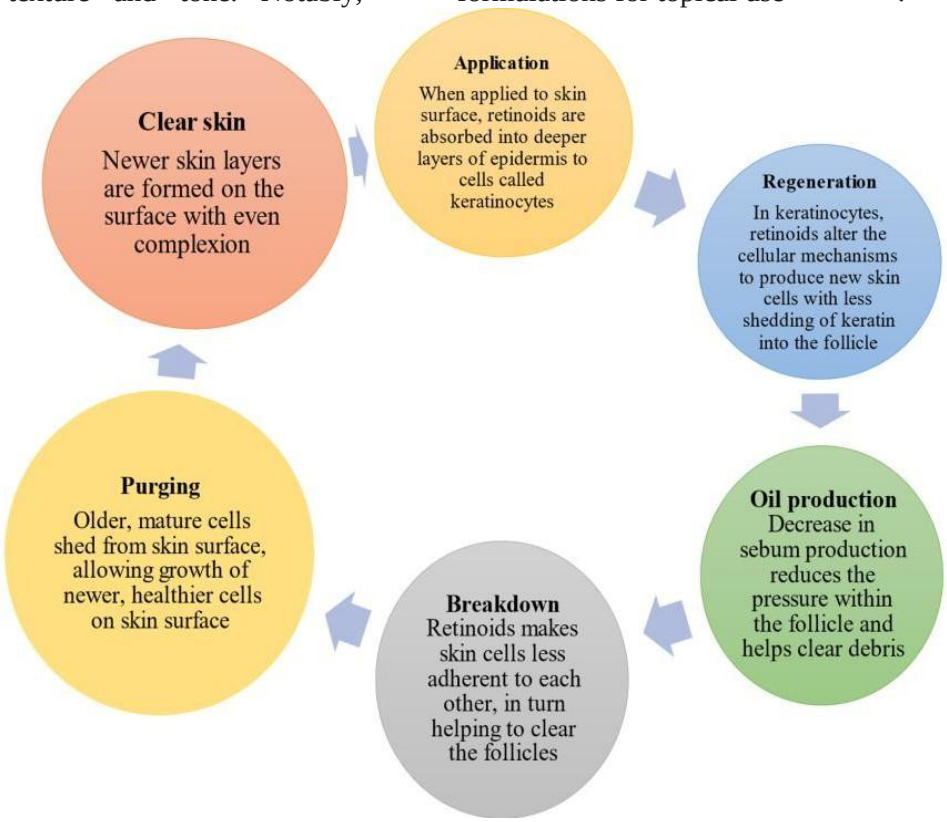

Fig. 7: Schematic representation of Anti-aging activity of Tretinoin.

Retinol

Vitamin A alcohol, referred to as all-trans-retinol, is a kind of retinoid found naturally in the human body. It functions as an important precursor in the manufacture of endogenous retinal and retinoic acid[106]. Retinol, commonly incorporated in cosmeceutical therapies, exhibits remarkable stability within product compositions and is generally well-received. When compared to retinoic acid, it delivers superior outcomes in analogous quantities[107].

The administration of all-trans-retinol to the typical human epidermis resulted in a considerable increase in skin thickness. This action is accompanied by an increase in Cellular Retinoic Acid Binding Protein II (CRABP II) and Cellular Retinol Binding Protein (CRBP) at both the mRNA and protein levels, similar to the effect seen with retinoic acid administration. Notably, retinol usage is associated with relatively minor symptoms of erythema and irritation, which presents a stark contrast to the effects often attributed to tretinoin[108].

Retinoic acid is known for its high potency, being roughly 20 times more effective than retinol. The oxidation of retinol to retinoic acid is a two-step process. Because of its binding capabilities, retinol first interacts with the retinoic acid receptors. The conversion commences when retinol merges with a specific cytoplasmic protein adept at retinol binding. This combination generates a compound that acts as a substrate for the enzyme retinol dehydrogenase, which helps convert retinol to retinaldehyde. Next, retinaldehyde is oxidised by retinaldehyde oxidase[107], culminating in the formation of retinoic acid. Renowned for its skin-enhancing properties, retinol is instrumental in refining the texture of the skin, mitigating pigmentation, alleviating scaly skin, and Softening facial wrinkles. However, The optimal concentration for maximizing effectiveness while minimizing skin irritation remains undetermined. Typically, cosmetic products incorporate retinol concentrations ranging from 0.0015% to 0.3%[109].

Retinol Derivatives

Derivatives of retinol have been synthesized to enhance retinol's chemical robustness. Compounds such as retinyl palmitate, propionate, and acetate are typically incorporated into skincare products as alternatives to retinol. These derivatives have garnered attention in what they can do to treat aging, evidenced by studies manifesting that retinyl propionate can thicken the epidermis in murine tails and boost collagen production in UV-exposed mice[110].

Combinations if Retinol

The integration of combination therapiesis becoming increasingly pivotal in the therapy of dermatological diseases including acne vulgaris and psoriasis, with superior therapeutic outcomes being observed when compared to monotherapies. In this context, the synergy of retinol with other anti-aging agents is being explored[111].

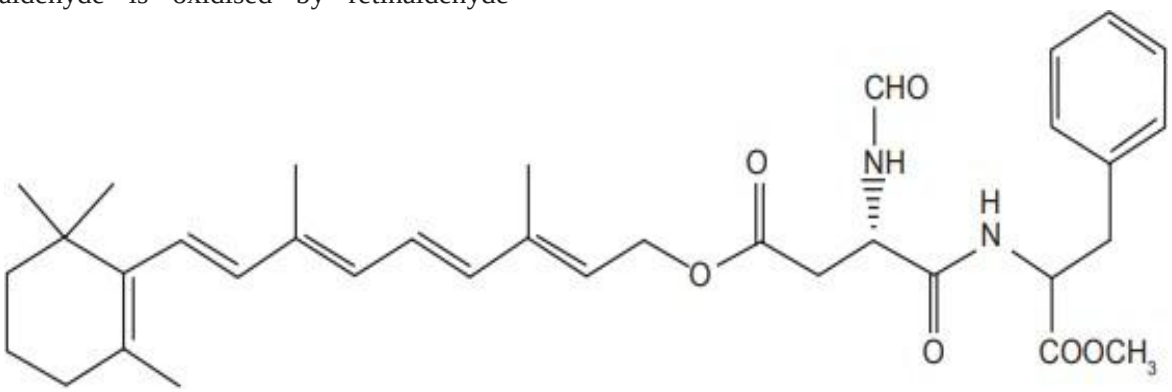

Fig. 8: Retinol derivative- N-formyl aspartame.

Retinaldehyde

Retinaldehyde, a precursor of retinoic acid, operates as a precursor metabolite during the conversion of retinol to retinoic acid in human keratinocytes. Within the dermal layers, retinaldehyde is converted to retinoic acid, which is known for its anti-aging qualities, before reverting to retinol and retinyl esters. The latter is typically diminished due to photoaging, underscoring the potential application of retinaldehyde in addressing the signs of photoaged skin[112]. Furthermore, the conversion of retinaldehyde into retinoic acid is exclusively conducted by keratinocytes when they reach an appropriate level of differentiation. This process ensures a regulated release of retinoic acid, resulting in diminished retinoid-related side effects in comparison to tretinoin and other artificial retinoids[113,114,115]. Topical retinaldehyde is well tolerated on human skin. It has been linked to the upregulation of CRABP type 2 mRNA and protein. Furthermore, it contributes to a surge in epidermis thickness, improves keratin-14 expression, and elevates its proliferation. It is important to note, however, that these biological activities are attributed to retinaldehyde's conversion to retinoic acid[115].

Adapalene

A derivative of naphthalene carboxylic acid, exhibits retinoid-like properties. It engages with nuclear retinoic acid receptors at the intracellular level, leading to modifications in the expression of genes and transcript production. Notably, the compound is a strong activator of hair follicle cell keratin formation and changes keratinocyte metabolism. This action stimulates proliferation and has keratolytic consequences[116].

TAZAROTENE, licenced by the US FDA, represents a chemically produced retinoid in the form of prodrugs. Its primary application is in the topical treatment of plaque psoriasis and acne vulgaris. Additionally, it serves as an adjunctive therapy for certain clinical signs of chronic photodamage to the skin, which includes alterations in pigmentation and textural irregularities such as fine lines and benign facial lentigines[117,126].

SELETINOID G, a novel fourth-generation retinoid, has shown promising potential in addressing intrinsic/photoaging. Unlike other synthetic retinoids, it has receptor specificity for RAR-gamma, which is largely found in the epidermal layer. A study conducted by Kim et al. in 2005 assessed Seletinoid G's safety and effectiveness relative to tretinoin. This evaluation involved topical applications on 23 patients across various age groups, providing valuable insights into its therapeutic benefits for skin aging. Notably, upon topical application of seletinoid G, MMP-1 levels decreased whereas type I procollagen, tropoelastin, and fibrillin-1 expressions increased in aged skin, mirroring the effects observed with tretinoin, thereby underscoring its potential utility in addressing intrinsic aging. Furthermore, when applied to UV-exposed youthful skin, seletinoid G thwarted the UV-triggered Down regulation in type I procollagen and elevated MMP-1 and c-Jun proteins, similar to the results obtained with tretinoin. It is worth noting that the superficial application of the drug, even under impingement, did not elicit skin irritation, in sharp contrast to tretinoin, which generated substantial erythema. Consequently, this drug perhaps equally efficacious like that of tretinoin for treating intrinsic/photo aging, while also offering the notable benefit of not causing skin irritation. Nonetheless, to substantiate the application and ascertain the pros and cons of this particular chemical entity in treating photoaging, more thorough, blinded, and controlled trials are requisite[118].

Conclusion

Aging research encompasses two primary areas: the study of the pathophysiological and molecular processes that contribute to aging, and the investigation of potential anti-aging compounds. Despite extensive research into the mechanisms of aging, efforts will persist until a complete understanding of the molecular sequence leading to aging are achieved. Among numerous rejuvenating chemicals, retinoids appear as an especially efficient bunch in treating ageing signs. Tretinoin stands out as the most potent and extensively researched retinoid. Nevertheless, due to its potential for irritation, dermatologists are increasingly opting for less irritating yet similarly effective

retinoids such as Adapalene, and limited degree, retinol and its derivatives, receptor-specific retinoids such as seletinoid G have been crafted with this objective in mind and have shown promise in preliminary studies.

Current literature indicates that retinol could play a significant role in cosmeceuticals, but additional research is needed to confirm their effectiveness at the concentrations found in over-the-counter products. Regarding acne treatment, the data on retinol is notably sparse; more human trials are necessary to ascertain the practical benefits of encouraging in vitro findings.

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إكسير الشباب: اكتشاف الريتينويد

بنديكت جيسلينا روشني*[1] – ينوجولا تشينا هارشان ريدي[1] – م. جاغاديش سوامي[1] – مونيكا نيجاوان[2] – سنيها آر نوالي[3]

[1] قسم علم الأدوية ، كلية جوكاراجو رانجاراجو للصيدلة ، باشوبالي، حيدر أباد، تيلانجانا، ٥٠٠٠٩٠ (الجامعة العثمانية)، الهند

[2] قسم الصيدلانيات ، كلية جوكاراجو رانجاراجو للصيدلة ، باشوبالي، حيدر أباد، تيلانجانا، ٥٠٠٠٩٠ (الجامعة العثمانية)، الهند

[3] قسم العقاقير ، كلية جوكاراجو رانجاراجو للصيدلة ، باشوبالي، حيدر أباد، تيلانجانا، ٥٠٠٠٩٠ (الجامعة العثمانية)، الهند

يعد النظام الواقى ، الذي يتكون من أنسجة الجلد، هو النظام الأكثر أهمية في الهيكل البشري، ويعمل كدرع أساسي ضد عدد لا يحصى من العوامل الضارة.وتشمل هذه، على سبيل المثال لا الحصر، المواد الكيميائية السامة والملوثات البيئية المنتشرة والآثار الضارة للأشعة فوق البنفسجية.وتعد شيخوخة البشرة هي ظاهرة بيولوجية لا هوادة فيها، وتخضع للعديد من العوامل المساهمة. و تلعب الأشعة فوق البنفسجية، والعادات الغذائية، والجفاف، واستهلاك التبغ، والتقلبات الهرمونية، وقوة الجاذبية، أدوارًا محورية في هذه العملية المعقدة.وتتجلى الشيخوخة الجلدية في شكلين متميزين: الشيخوخة الجوهرية، وهي نتيجة لا مفر منها لمرور الوقت الذي يظل منيعًا للتدخل؛ و الشيخوخة الضوئية، والتي ترجع في الغالب إلى العوامل البيئية. ومع تقدم العمر، تفقد البشرة مكونات حيوية مثل الإيلاستين والكولاجين والبروتينات الضرورية للحفاظ على صحة البشرة. وتتوفر حاليًا العديد من إجراءات وطرق العناية بالبشرة لتجديد شباب البشرة المتقدمة في السن ومنع المزيد من الشيخوخة.ويمكن تقسيم استراتيجيات مكافحة الشيخوخة إلى إجراءات وقائية وأساليب ثانوية لمكافحة الشيخوخة. ويعتبر التريتينوين، على وجه الخصوص، هو ريتينويد موضعي والذى أثبت فعاليته كعامل مضاد للشيخوخة لعلاج حالات مثل حب الشباب والتجاعيد والكلف.وغالبًا ما تواجه فعالية الرتينوئيدات تحديات كثيرة بسبب مشكلات عديدة مثل قلة الثبات، وانخفاض اختراق الجلد، والتهيج المحتمل. ولمعالجة هذه العيوب المرتبطة بالريتينويدات التقليدية مثل تريتينوين والريتينول، تم تطوير أنظمة توصيل الأدوية الموضعية القائمة على تكنولوجيا النانو.ولقد أثبتت هذه الأنظمة المتقدمة ثباتًا أفضل وتحملا أفضل وفعالية معززة للريتينويدات.