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A REVIEW ON SKIN AGING: MECHANISMS AND THERAPEUTIC STRATEGIES

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ABSTRACT
Background: Skin aging is a complex process driven by multiple factors. In addition to hereditary factors and cellular aging, exposure to sunlight, air pollution, and lifestyle factors are extrinsic factors that stress the skin. Skin aging involves multiple biological processes influenced by both internal factors (age, skin type, cellular aging) and external factors such as ultraviolet radiation, air pollution, and lifestyle. These cause various changes in appearance, function, and structure. **Methodology:** An extensive search of the published scientific literature on the mechanisms of skin aging and anti-aging treatments was conducted. Articles related to oxidative stress, inflammation, ECM degradation, melanogenesis, and signaling pathways, including MAPK, NF-κB, Nrf2, TGF-/Smad, and mTOR, were critically reviewed. **Results and Discussion:** The evidence indicates that skin aging is associated with the production of reactive oxygen species (ROS), DNA lesions, persistent inflammation, collagen lysis, and defective cellular regenerative processes. Current novel interventions, including antioxidants, senolytics, stem cell therapy, telomere-shifting, epigenetic-modifying approaches, and Mitochondrial therapy directed toward mitophagy, have shown noteworthy effects in reducing the progression of skin aging. Also, herbal topical preparations containing bioactive phytoconstituents have proven to be a safe and effective modality. **Conclusion:** Skin aging is a result of an intricate network of cross-interrelated intrinsic and extrinsic factors involving various molecular pathways. Novel, more effective, and safer therapeutic approaches and preparations of bioactive herbal formulations appear promising for treating skin aging.

INTRODUCTION

Humans have always been on a mission to achieve healthy, youthful skin, crossing cultures, traditions, and centuries. As the largest organ of the human body, the skin plays a vital role as an essential protective barrier against environmental trauma as well as a reflection of an individual's overall health and well-being. With increasing age and exposure to extrinsic stressors such as ultraviolet (UV) radiation, air pollution, and lifestyle factors, the skin slowly loses its structural framework and physiological function. These alterations are expressed as wrinkles, fine lines, sagging, loss of elasticity, and irregular pigmentation, together referred to as the visible signs of skin aging [1]. Over the last ten

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years, consumers have increasingly demanded natural and vegetable products for skincare and anti-aging. This behavior is driven not only by a heightened awareness of the potential side effects of chemical additives but also by a respect for ancient herbal remedies traditionally used for skin repair and maintenance. The plant materials explored for dermatological applications include polyphenols, flavonoids, ellagitannins, and vitamin C. These bioactive compounds have exhibited strong antioxidant, anti-inflammatory, and regenerative activities. "The quest for youthful, healthy skin is a timeless pursuit. Modern consumer behavior is driven not only by heightened awareness of the potential side effects of chemical additives, but also by a deep respect for ancient herbal remedies used for skin repair and maintenance. However, while the therapeutic potential of these botanical materials remains high, transforming them into safe, effective, and standardized topical products presents significant scientific and regulatory challenges. Plant products are inherently complex owing to raw material variability, extraction methods, and the stability of bioactive constituents. Maintaining product quality, batch-to-batch uniformity, and predictable efficacy for consumer application requires a scientifically rigorous process of standardization and detailed characterization. This includes the correct identification and quantitation of bioactive phytochemicals, evaluation of formulation performance, stability testing, and demonstration of anti-aging benefits by valid scientific means [2,3]. This review aims to comprehensively summarize the fundamental mechanisms underlying skin aging, including intrinsic and extrinsic factors, as well as the associated clinical signs and symptoms. It critically discusses key molecular and cellular pathways involved in the aging process and highlights current preventive and therapeutic strategies used in skin anti-aging management. Emphasis is placed on evidence-based approaches, including herbal and modern interventions, that target oxidative stress, inflammation, and extracellular matrix degradation. Overall, this review seeks to support the rational development of effective anti-aging skincare therapies [4,5].

STRUCTURE OF SKIN

Skin is mainly classified into three significant layers: epidermis, dermis, and hypodermis. The epidermis is the outermost layer and consists of keratinocytes, melanocytes, Langerhans cells, and Merkel cells. Its main functions are to act as a barrier to the external environment and to aid in skin color regulation through melanin synthesis. Located beneath the epidermis, the dermis is composed of a matrix of collagen and elastin fibers that provide resistance and elasticity to the skin. The dermis carries blood vessels, sensory endings, hair follicles, and sweat glands to perform its functions. The hypodermis is mainly composed of adipose cells, along with collagen and elastic fibers, which act as a cushion and insulating barrier. These three layers are required for regulating skin integrity, body temperature, and the skin's sensory functions. They also have unique immune defense and healing mechanisms that help develop healthy, firm skin.

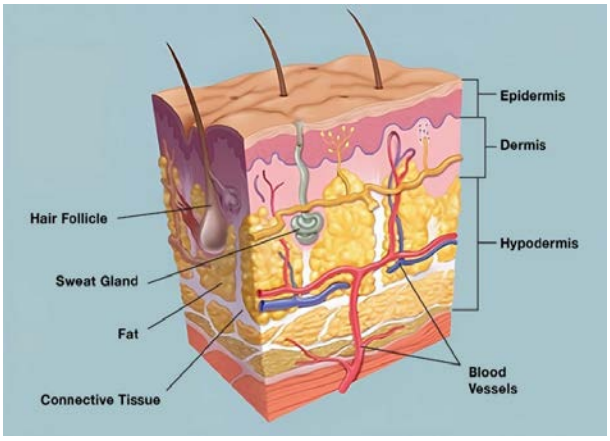

Figure 1: Structure of Skin

LAYERS OF THE SKIN

Facial skin is a specialized and complex structure composed of three fundamental layers: the epidermis, dermis, and subcutaneous (hypodermis) layer. Each layer helps preserve appearance, support sensation, and shield the face. The outermost layer, the epidermis, is visible to the naked eye. Keratinocytes, produced at the bottom and migrating upward, become flatter and finally die to create the strong, protective outer stratum corneum. The final layer is composed of corneocytes, dead cells that are always shed and replaced to preserve the skin's defensive barrier against pollutants and infections. Melanocytes, which produce melanin, the color responsible for skin and photoprotection, as well as Langerhans cells for immune surveillance, are also found in the epidermis. Particularly surrounding the eyelids, the facial epidermis is usually more sensitive to environmental elements than in other regions of the body. The epidermis lacks its own blood supply and depends on nutrients from the underlying dermis; it is avascular [7]. Under the epidermis, the dermis is a significantly thicker layer that provides the facial skin with both structural support and elasticity. Collagen and elastin fibers abound in the dermis, giving the skin strength and flexibility and housing blood vessels, nerve endings, hair follicles, sebaceous (oil) glands, and sweat glands. These structures are essential for sensory perception, temperature control, skin moisturization,

and protection against microbial invaders. Two areas make up the dermis: the deeper reticular dermis, which offers tensile strength, and the superficial papillary dermis, which provides nutrients and supports the structure of the epidermis. Furthermore, facial skin thickness varies: it is thinnest around the periorificial regions (eyes, mouth, nose) & thicker on the forehead & cheeks, which affects wrinkle development & mobility across the face. The epidermis is made of fat and loose connective tissue; the lowest level is the subcutaneous (hypodermis) layer. This layer serves as an insulator, helps to retain heat, provides cushioning from impacts, stores energy, and defines much of the facial shape. Due to the presence of larger fibrofatty tissue pads, subcutaneous tissue varies markedly across the face, being closer to the eyes and lips but more prominent in the cheeks and forehead. Together with connective tissue bands known as facial ligaments, these fat pads help define the face's three-dimensional shape and youthful plumpness. Together, the epidermis, dermis, and hypodermis create a dynamic framework that enables the facial skin to serve as a cushioning and protective barrier, a sensory interface, a regulator of temperature and humidity, and a crucial component of appearance and expression [8].

Table 1: List of layers of the skin.

Layer	Key Features
Epidermis	Outermost layer; provides the initial barrier to the environment. Contains keratinocytes (secrete keratin), melanocytes (secrete pigment), Langerhans cells (immune protection) & Merkel cells (touch receptors). It is made up of a few sublayers: stratum corneum, lucidum (palms and soles), granulosum, spinosum, and Basale. It is of different thickness—thickest on eyelids and thinnest on cheeks and forehead [6].
Dermis	Middle, thicker layer consisting of connective tissue. Composed of collagen & elastin for strength & elasticity, blood vessels, nerves, lymphatics, hair follicles, along with sweat & sebaceous glands. Consists of 2 layers: papillary (superficial, vascular, forms fingerprints) & reticular (deeper, thicker, supportive).
Hypodermis (Subcutaneous Fat)	Deepest layer. Made primarily of adipose tissue along with connective tissue, acting as insulation, energy storage, and shock absorption. Anchors the skin to underlying facial muscles and bones

THE MECHANISM OF SKIN AGING

Skin aging is driven by cumulative DNA damage and oxidative stress primarily induced by ultraviolet radiation and environmental pollutants. Excessive generation of reactive oxygen species (ROS) leads to oxidative damage of cellular DNA, proteins, and lipids, impairing normal cellular functions. ROS activate multiple signal transduction pathways, including mitogen-activated protein kinases (MAPKs) and nuclear factor-κB (NF-κB), resulting in the upregulation of matrix metalloproteinases (MMPs). These enzymes degrade collagen and elastin in the extracellular matrix, leading to loss of skin elasticity, wrinkle formation, and structural deterioration associated with aging [2].

OXIDATIVE STRESS

Ultraviolet (UV) light triggers the formation of reactive oxygen species (ROS), which play a significant role in skin damage and speed up aging. ROS forms as a result of UV interacting with chromophores in the skin along with oxygen. The body helps prevent ROS-induced damage as long as ROS levels remain moderate and physiologically relevant. Still, if Reactive Oxygen Species (ROS) levels increase, it can result in DNA damage, protein damage, damage to the skin matrix, abnormal pigmentation, and inflammation. Ultraviolet A (UVA) generates singlet oxygen (1O2), and Ultraviolet B (UVB) generates superoxide anions ($\cdot O_2^-$). UVA can activate enzymes that generate superoxide and hydrogen peroxide (H_2O_2), which, in turn, can produce especially harmful hydroxyl radicals. Excessive (beyond moderate physiological) UV exposure can also promote the formation of nitric oxide (NO), which reacts with superoxide to form peroxynitrite and other deleterious ROS, or further react to activate inflammatory pathways that can contribute to photoaging [2].

DNA DAMAGE

UV radiation can damage DNA in two ways: directly and indirectly, with UVB being the main cause of direct damage. It mainly affects the telomeres and mitochondrial DNA (mtDNA) in particular. If telomeres are damaged, the cell activates DNA damage response proteins (such as p53), which induce programmed cell death (apoptosis). Unlike telomeres, mitochondrial DNA is located adjacent to the respiratory chain (a major source of reactive oxygen species [ROS]) and is particularly susceptible to damage. When mitochondrial DNA is damaged, excessive ROS production depletes mtDNA's ability to repair itself. As a result, more mutations associated with excessive ROS production emerge, which leads to further cellular damage [9,10].

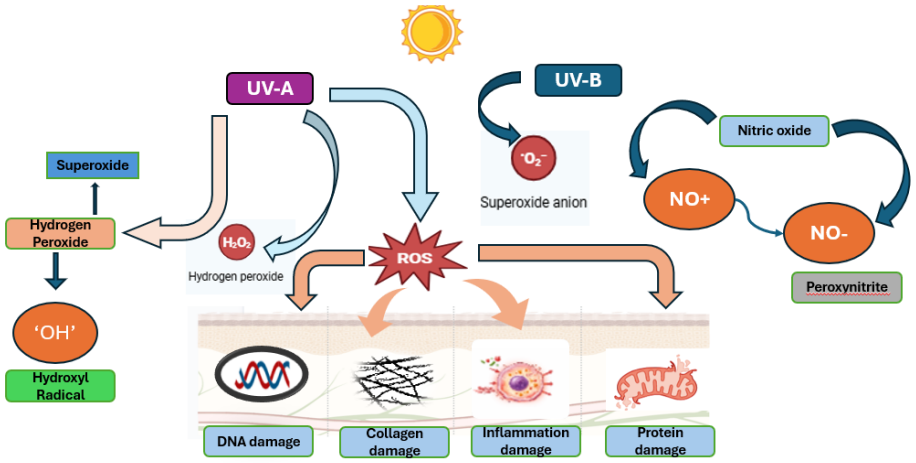

Figure 2: Oxidative Stress

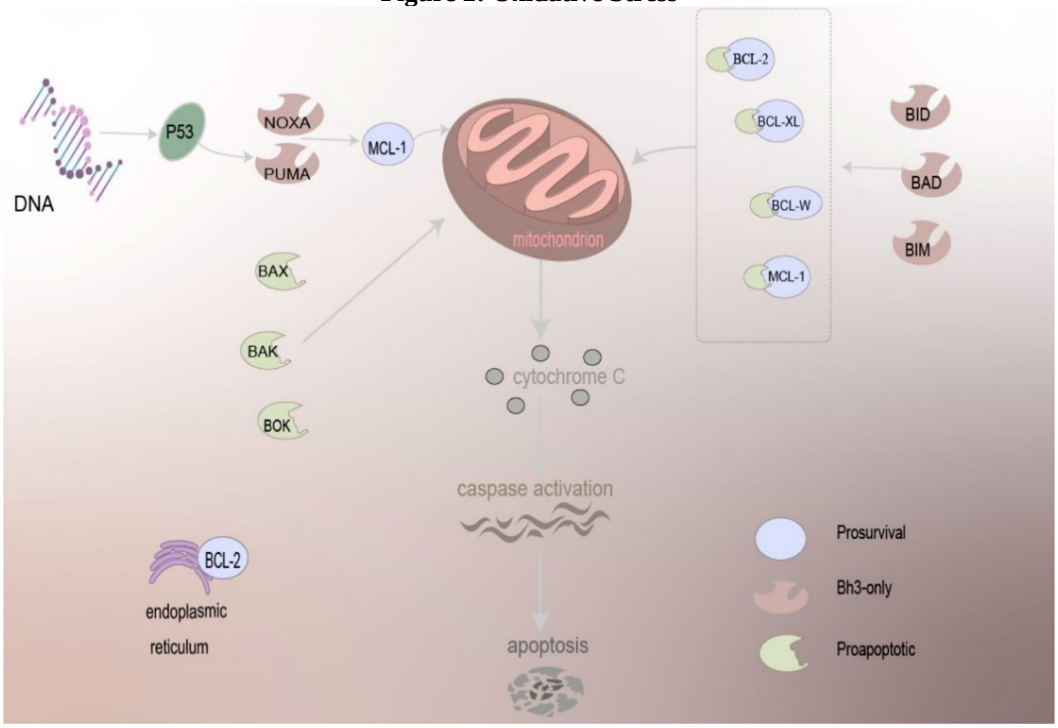

Figure 3: DNA Damage

SIGNAL TRANSDUCTION

Ultraviolet (UV) radiation activates multiple cytokine and growth factor receptors, including the epidermal growth factor receptor (EGF-R), tumor necrosis factor-α (TNF-α) receptor, platelet-activating factor (PAF) receptor, interleukin-1 (IL-1) receptor, and platelet-derived growth factor (PDGF) receptor. All of these receptors activate multiple signal transduction pathways [11]. Under photooxidative stress, some of the more relevant pathways affected include the mitogen-activated protein kinase (MAPK) pathway, nuclear factor kappa B (NF-κB/p65), and nuclear factor erythroid 2-related factor 2 (Nrf2). The MAPK family of proteins includes the extracellular signal-regulated kinases (ERK), c-Jun N-terminal kinase (JNK), and p38 MAPK, all of which, when activated, can phosphorylate the transcription factor activator protein-1 (AP-1) that drives expression of matrix metalloproteinases (MMPs). Nrf2 is a key regulator of many antioxidant defenses [12]. Under homeostasis, Nrf2 regulates endogenous antioxidant enzymes and mitochondrial bioenergetics. However, UV radiation suppresses Nrf2 expression and the expression of its downstream effector targets. Moreover, Nrf2 activation is associated with oxidative damage to cellular membranes, leading to the release of inflammatory cytokines, including IL-1, IL-6, vascular endothelial growth factor (VEGF), TNF-α, and TNF-β, particularly in fibroblasts, keratinocytes, leukocytes, and endothelial cells.

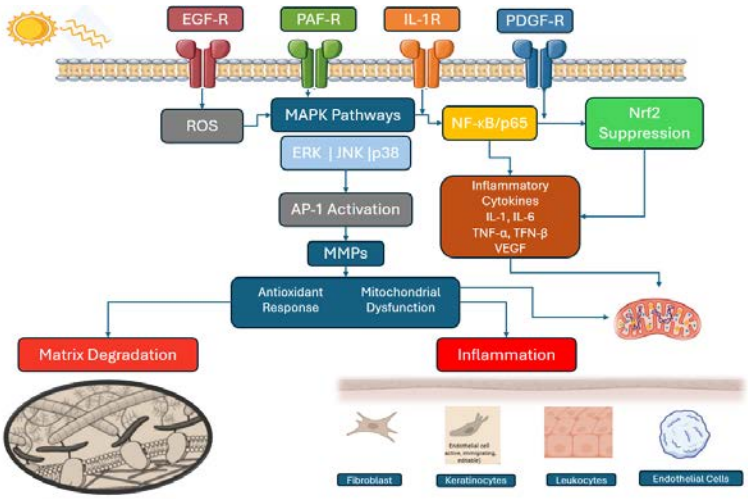

Figure 4: Signal Transduction

CHANGES IN THE EXTRACELLULAR MATRIX

The skin's extracellular matrix (ECM) consists predominantly of collagen, elastin, and glycosaminoglycans (GAGs), providing structural support. Collagen is the most abundant protein in the ECM and is responsible for its structural integrity and tensile strength. Elastin imparts elasticity to the skin, and GAGs are critical for hydration. ECM degradation occurs primarily via a group of zinc-dependent endopeptidases called matrix metalloproteinases (MMPs), which are largely transcriptionally regulated by activator protein-1 (AP-1) acting downstream of MAPK signaling.

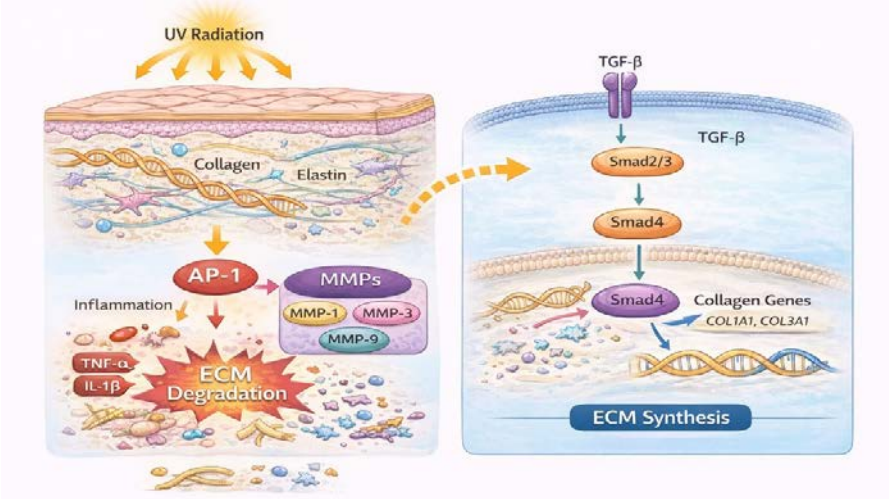

Figure 5: Changes in the Extracellular Matrix

Among the MMPs, MMP-1 breaks down collagen types I and III, MMP-9 continues to degrade the fragments of primary collagen, and MMP-3 acts specifically to degrade collagen type IV, a critical structure for the basement membrane. Following UV exposure, keratinocytes upregulate MMP-9, which continues to degrade collagen and further propagates inflammation via release of TNF-α & IL-1β. The TGF-β/Smad pathway is equally important for promoting ECM synthesis and fibroblast function. After binding to its receptor, TGF-β activates Smad2/3, which then associates with Smad4 to induce the expression of collagen genes such as COL1A1 & COL3A1. Smad7 prevents the activation of Smad2/3, which serves as a negative regulator. UV-induced AP-1 activation suppresses TGF-β receptor expression & thus inhibits TGF-β-Smad signaling [13].

INFLAMMATION AND IMMUNOSUPPRESSION

Many proinflammatory signaling pathways (such as NF-κB and the p38/MAPK, PI3K/Akt) are activated upon irradiation of ultraviolet light (UV), leading to the production and secretion of inflammatory cytokines and enzymes such as IL-1, IL-6, VEGF, TNF-α, TNF-β, and COX-2 by keratinocytes, fibroblasts, leukocytes, as well as endothelial cells. These cytokines further strengthen the inflammatory signaling and induce MMP-1

secretion, causing ECM degradation. Inflammatory cytokines modulate mitochondrial function and enhance ROS production [14,15].

MELANOGENESIS

Reactive oxygen species, cytokines, and hormones affect pigmentation. Microphthalmia-associated Transcription Factor (MITF) is the master regulator of their expression and also transcribes Tyrosinase (TYR) and Tyrosinase-Related Protein (TYRP) proteins. Melanin synthesis is regulated by MITF. UV irradiation of the skin activates signaling pathways, such as MAPK and cAMP/PKA, that are crucial for the transit stages of melanogenesis. Hyperactivation of the cAMP/PKA pathway is known to enhance MITF, which in turn leads to the expression and upregulation of genes associated with increased melanogenesis. In addition, increased ROS in melanocytes resulting from UV exposure activates the MAPK pathway, further enhancing the expression of MITF and TYR and increasing melanin transport and production. Paracrine cytokines secreted from UVB-irradiated keratinocytes and fibroblasts are also known to regulate melanogenesis. These cytokines in melanocytes have been reported to stimulate cAMP levels, thereby activating PKA, which could increase MITF expression and promote melanin synthesis [16,17]. In addition, there are paracrine cytokines induced by UVB-activated keratinocytes and fibroblasts that, in turn, regulate melanogenesis. These cytokines in melanocytes are also known to increase intracellular cAMP and activate PKA, further inducing MITF and promoting melanin production [18].

PHOTODAMAGED VASCULAR ENDOTHELIAL CELLS AND BLOOD VESSELS

The microvasculature of the skin is affected by ultraviolet rays & both destruction of these vessels and mosaic (abnormal) new blood vessel development occur. Vascular endothelial cells (VECs) undergo degeneration in aging. This is characterized by the absence of normal capillaries and irregular dilation of other vascular structures, especially in the upper dermis, where there is considerable breakdown of connective tissue. Elastin-rich vessels are further widened and cradled in abnormal, diseased VECs that promote disordered endothelial activity, which contains a large number of organelles and numerous pinocytic vesicles. Vascular changes, specifically decreased blood flow, lead to reduced skin temperature. These changes also result in the persistence of subcutaneous hematomas and a significant delay in wound healing [19,20].

APOPTOSIS

UV-induced apoptosis occurs primarily by two pathways

1. The mitochondrial
2. The death receptor pathway.

In the mitochondria-mediated pathway, Cytochrome C (CytoC) is released from the mitochondria as a result of downregulation of B-cell lymphoma-2 (Bcl-2) and activation of Bax: bcl-2-associated X protein (Bax), a pro-apoptotic member of the Bcl-2 family. CytoC subsequently triggers caspase-9 by activating apoptotic-activating factor and deoxyadenosine triphosphate. Caspase-9 further downstream, together with activated caspase-3, drives irreversible cell death. The death receptor pathway includes Fas/FasL, TNFR, and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). The Fas/FasL couple, once activated, triggers apoptosis via caspase-8 activation, leading to Bcl-2 downregulation and the release of apoptotic factors from mitochondria. Furthermore, UV light, known to be harmful to the skin, can also induce the P53 tumor suppressor protein. P53 directly induces apoptosis in keratinocytes and fibroblasts [21].

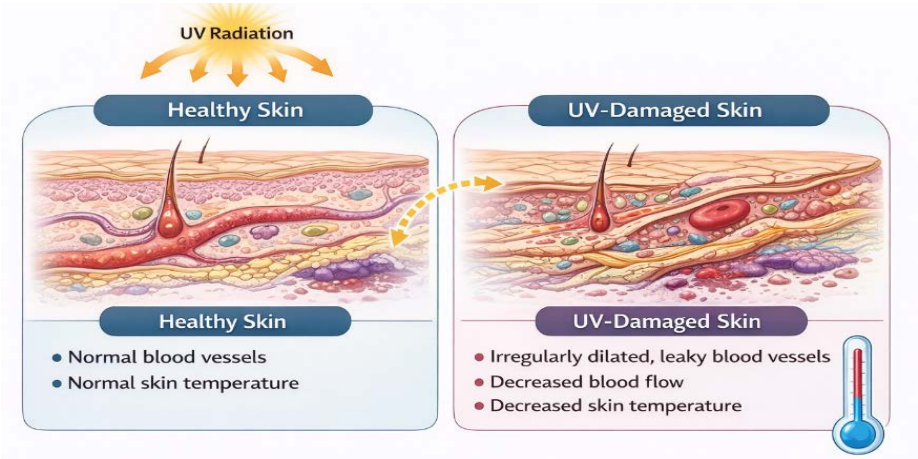

Figure 6: Photodamaged Vascular Endothelial Cells and Blood Vessels

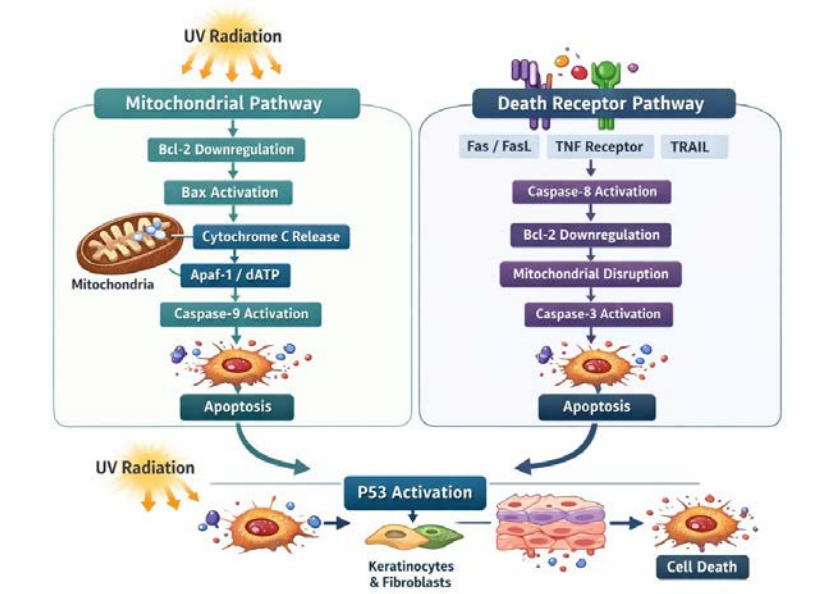

Figure 7: Apoptosis

Chronic exposure to ultraviolet (UV) radiation leads to elevated levels of reactive oxygen species (ROS) in cells; superoxide anion (O2-), hydrogen peroxide (H2O2), and hydroxyl radical play major roles as mediators of photoaging by contributing to cellular injury and activating three signal transduction pathways. Photoinduced ROS increased proteolytic deposition of oxidized collagen by activation of upstream redox-sensitive kinase; apoptosis signal-regulating kinase-1 (ASK1) and phosphorylation activity of mitogen-activated protein kinase (MAPK) signaling pathway responses; ERK, JNK, p38 MAPK. AP-1 enhanced the phosphorylation activity and transcription of MMPs. At the same time ROSs-mediated MAPK activation activates nuclear factor-kappa B NF-κB pathway by phosphorylation and degradation of inhibitor of B (I B) allowing nuclear translocation of NF-κB subunits with high expression of TNF-, IL-1, IL-6 and COX-2 leading to the continuous activation of NF-κB signalling pathway in inflammaging of human skin functionally, under normal physiological conditions, Nrf2 is an important regulator of antioxidant defence through induction of ARE-dependent cytoprotective enzymes, like heme oxygenase-1 (HO-1), superoxide dismutase (SOD), catalase, and glutathione peroxidase. Yet chronic UV-induced oxidative stress and long-term activation of MAPK and NF-κB signaling pathways compromise Nrf2 nuclear translocation and transcriptional activity, resulting in decreased levels of its cytoprotective genes and a fundamental imbalance between ROS-mediated chemokine production and equivalent decreases in cellular Nrf2-mediated antioxidant cytoprotection, signifying the onset of skin aging.

SIGNS AND SYMPTOMS OF SKIN AGING

Fine Lines and Wrinkles

Fine lines and wrinkles primarily result from aging, UV radiation, and gravity, which lead to dermal matrix breakdown and alterations in skin contours. These wrinkles can be either dynamic, like forehead lines that show muscle movement, or static, such as nasolabial folds, which are visible at rest. On the prevention side, there are antioxidants, broad-spectrum sunscreens, and innovative dermal fillers engineered to last longer and be easier to inject [22].

Age Spots

Age spots or solar lentigines are pigmented lesions resulting from chronic sun exposure. Age spots are caused by the accumulation of aged cells in the skin with lipofuscin bodies and altered keratinocyte proliferation. Melanocyte repair, accumulation of aging theory, and inhibition of lipofuscin formation are among the mechanisms underlying their development [4].

Sagging

Sagging skin can result from many factors, including aging, weight loss, and post-operative effects like liposuction. Some scientific findings emphasize the contribution of collagenous fibers in the retinacula cutis and the subcutaneous tissue to skin elasticity and the prevention of sagging. Some tackle loss of elasticity and sagging. Studies of sagging skin mechanisms emphasize the role of the subcutaneous collagenous fiber network, with greater density associated with improved elasticity and reduced sagging [23].

Skin Roughness

Skin roughness has many potential causes, including aging and environmental factors, as well as conditions like pellagra, a disease associated with high maize intake in places like Italy and the US, where rough skin is prominent. Physicians use skin roughness as a clinical sign to assist in the diagnosis of warts, psoriasis, and benign versus malignant lesions. Treatments also tend to include sodium chondroitin sulphate formulations that help moisturize your skin and decrease wrinkles. Correct identification of the causes along with targeted treatments can help you tame and prevent rough skin [24].

Dry Skin

Xerosis, or dry skin, is a very common disorder that can be affected by hydration, sebum, and environmental exposure. It can also delay wound healing and skin diseases. Both internal factors, such as aging, and external ones, such as sun exposure and chemicals, can cause dry skin. Effective prevention and treatment of dry skin depend on comprehensive emollient therapy, which helps healthcare professionals optimize skin health [23]. Understanding both the causes of dryness and the available remedies is a vital step toward improving skin's resilience.

TELANGIECTASIA, SKIN PIGMENTATION AND SKIN VOLUME LOSS

Telangiectasia is the appearance of small, widened blood vessels on the skin; it is caused by sun damage or inherited disorders such as hereditary hemorrhagic telangiectasia (HHT). Avoiding sun exposure helps mitigate its progression. Alterations in skin pigmentation occur for various reasons, including genetic predisposition, UV exposure, drugs, and skin disorders, resulting in conditions such as melasma, vitiligo, and post-inflammatory hyperpigmentation (PIH). PIH affects darker skin and manifests as dark brown, pigmentary patches following an inflammatory process, such as a pimple [25]. Facial aging is also characterized by age-related skin volume loss due to sun damage, genetics, and other factors, resulting in a sunken or sagging appearance. Volume can be replaced with soft tissue fillers, fat grafts, hyaluronic acid injections, collagen-stimulating procedures, etc. Both sun protection and antioxidants play key roles in slowing volume loss caused by environmental damage.

STRATEGIES OF SKIN AGING

Antiaging approaches using epigenetics

Chromatin, which packages DNA, has a twin role in aging. Chromatin remodeling can also accelerate aging. On the other hand, the chromatin itself changes drastically with age. These changes are largely due to decreases in histone protein levels and histone chemical modifications. Research in yeast and human cells has found that changes in chromatin organization directly influence aging. For instance, aging associated with loss of histone proteins, increased histone modifications (e.g., acetylation of H4K16 and at the H3 N-terminus), or inhibition of HDAC Rpd3 and H3K4 methylase resulted in lifespan extension and rejuvenation of young cellular functions [26]. Chromatin changes are strongly influenced by Extrinsic factors like diet, lifestyle, and environmental stress, which can accelerate or slow cellular erosion caused by aging. Moreover, epigenetic regulation by DNA methylation is also subject to age-related changes. Despite a general decline in global DNA methylation, certain loci (e.g., CpG islands and polycomb-regulated loci) result in hypermethylation, whereas gene-poor regions and tissue-specific promoters lose methylation. These dynamic patterns are known as epigenetic clocks, dependable predictors of biological age that strongly correlate with cellular aging [27].

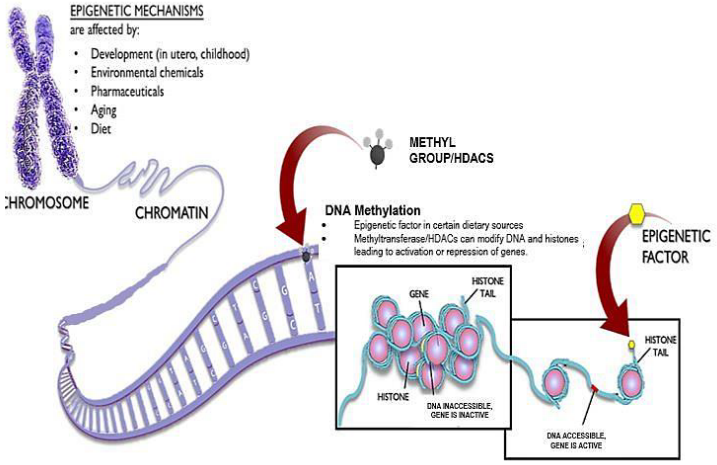

Figure 8: Antiaging approaches using epigenetics

Moreover, good diets and healthy living, environmental moderation, and epigenetic enzyme-targeting agents can postpone aging and extend longevity. Natural bioactives like spermidine and resveratrol have been shown to affect chromatin state in ways that could extend lifespan. Likewise, pharmacological interventions such as HDAC inhibitors are being investigated as anti-aging therapies, with the potential to slow or partially reverse certain hallmarks of aging, thereby promoting healthier aging [28].

Clearance of Senescent Cells

Cellular senescence is a fundamental aging mechanism, characterized by stable cell-cycle arrest in damaged cells, which helps inhibit the expansion of dysfunctional tissue. With aging, senescent cells accumulate and contribute to aging and age-related diseases. Removing or reducing these cells has become a way to extend lifespan, primarily via senolytics. Several compounds have been shown to induce apoptosis in senescent cells and selectively reduce senescence markers. These include dasatinib plus quercetin and BCL2 (B-cell lymphoma-2 is a key anti-apoptotic protein that regulates cell survival by controlling the mitochondrial pathway of apoptosis). SCAPs (Senescence-Associated Cell-Penetrating Peptides) are senolytic peptides that selectively penetrate senescent cells and eliminate them, thereby reducing inflammation and slowing skin aging. FOXO4 (Forkhead Box O4 FOXO4 peptides are senolytic agents that selectively induce apoptosis in senescent cells by disrupting the FOXO4–p53 interaction, thereby reducing inflammation and tissue degeneration associated with skin), family inhibitors, SCAPs, FOXO4 peptides, and natural compounds such as piperlongumine [29,30]. More recently, HSP90 inhibitors have been identified as new senolytics that can induce apoptosis in senescent cells and improve healthspan.

Stem Cell-Based Therapies

Stem cell exhaustion, the gradual loss of stem cell quantity and quality, is characteristic of aging in many tissues and organs. Adult stem cells typically maintain tissue repair and regeneration during life, but this ability is compromised with aging Hematopoietic stem cells (HPSCs), are specially impacted, their decline having been associated with stress responses, differentiation demands, mTORC1 hyperactivation (mechanistic Target Of Rapamycin Complex 1) is a key cellular signalling complex that regulates cell growth, protein synthesis, and metabolism, and its overactivation contributes to cellular senescence and skin aging) and disruption of AMPK signaling. Furthermore, the accumulation of DNA damage and expression is tightly associated with age-related stem cell exhaustion [31,32].

Stem cell attrition interventions focus on rejuvenation strategies that reinstate youthful phenotypes. Reprogramming old HPSCs to a pluripotent state or creating induced pluripotent stem cells (iPSCs) from old fibroblasts and differentiating them into NSCs are promising alternatives. Pharmacological interventions also hold promise: metformin, an FDA-approved antidiabetic drug, was shown to induce adult stem cell rejuvenation. AMPK activators such as 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR), metformin, and oxidized nicotinamide adenine dinucleotide (NAD+) have been suggested as adjuncts to stem cell–based transplantation therapies to enhance outcomes [33].

Telomere Reactivation

Telomeres are specialized, conserved TTAGGG repeat DNA sequences at the ends of chromosomes. They serve as protective caps, blocking chromosome ends from being misidentified as DNA breaks and thus avoiding undesired end-to-end joining, recombination, or repair. Because of the "end-replication problem," DNA polymerases cannot completely replicate linear chromosomes, causing telomeres to shorten during each cell division in somatic cells. The enzyme telomerase can offset this loss, but in most somatic and adult stem cells, its activity is insufficient to sustain telomere length fully, eventually pushing cells into replicative senescence and sometimes apoptotic death. Telomere shortening is an intrinsic feature of aging and a well-established biomarker of aging and longevity, with its effects modulated by genetic, epigenetic, and environmental factors. Significantly, shorter telomere length is associated with a variety of age-related diseases such as osteoarthritis, atherosclerosis, coronary artery disease, and atrial fibrillation. Experiments indicate that lifespan can be extended by telomerase overexpression, but chronic telomerase activation is associated with an increased risk of tumor formation. Over the last few years, various telomerase-focused therapies such as activators, transcription enhancers, and gene therapy have been investigated [34]. One of the most studied compounds is TA-65, an extract from Astragalus membranaceus. TA-65 lengthens telomeres without heightening cancer risk, and improves metabolic function, skeletal health, and skin condition in aging models. Other telomerase activators—including TERT transcription enhancers and some sex hormones—have also been shown to

prevent telomere erosion and extend lifespan. Gene therapy–based strategies that reactivate telomerase expression in experimental models, particularly in mice, have provided encouraging evidence of both life extension and delayed aging without tumorigenesis. In general, telomerase regulation is a two-edged sword in human health – its activation in benign cells might help us live longer and healthier lives. Still, its suppression in cancers presents a promising treatment path.

Loss of Proteostasis

Loss of proteostasis, a hallmark of aging, leads to protein misfolding, oxidative damage, aberrant modifications, and impaired protein turnover, all of which impair cellular function. The chief proteostasis-maintaining systems are the ubiquitin–proteasome system (UPS), the autophagy–lysosome system (ALS), and molecular chaperones. With age, these processes become compromised, resulting in protein aggregation, cell stress, and senescence. Increasing chaperone activity, for example, Heat Shock Protein 104 (Hsp104) in yeast or other Heat Shock Proteins in worms and flies, prolongs lifespan. UPS or ALS are essential for degrading broken-down or misfolded proteins. In old cells, their breakdown causes a collapse of proteostasis and aging. Experimental overexpression of proteasome subunits (e.g., in C. elegans, flies, or human cells) has improved lifespan and stress resistance. Some compounds, such as glycyrrhetinic acid or IGF signaling mutants, upregulate UPS and extend life in worms, while spermidine, metformin, rapamycin, and resveratrol are autophagy activators. Other agents, including minocycline and monorden, also boost lifespan in C. elegans through direct molecular targets. Breaking proteostasis is connected to neurodegeneration. Several pharmacological and phytochemical approaches that manipulate proteostasis-modulating pathways possess promising anti-aging properties through mechanistically distinct cellular effects. In particular, senolytic mixtures including dasatinib and quercetin (Dasatinib + Quercetin), which induce selective removal of senescent cells transiently by inhibition of senescent cell anti-apoptotic pathways (SCAPs) e.g. PI3 K/AKT, BCL-2/BCL-xL, ephrin-dependent signalling and tyrosine kinase survival pathways, have garnered interest given their potential to alleviate persistent accumulation of senescent cells during chronic aging and implement beneficial effects on several cell signalling cascades including reductions in pro-inflammatory senescence-associated secretory phenotype (SASP) factors IL-6, IL-1b TNFa MMPs and other proinflammatory cytokines, damaging effects on extracellular matrix and oxidative stress, and the generation of regenerative signals across tissues. In several aging models, treatment with (Dasatinib + Quercetin) significantly reduced cell senescence, suppressed SASP-related inflammatory signals, normalized mitochondrial function, and improved tissue regeneration8; approaches that relied more heavily on senescence removal achieved more profound effects than classic antioxidant approaches.

Then again, naturally derived phytochemicals like resveratrol, widely known for their geroprotective and cytoprotective activities, are less likely to display senolytic effects due to their mainly intrinsic mode of action within stress-adaptation pathways mediated by multiple intracellular signaling processes. Resveratrol has been mainly elucidated to exert resveratrol-controlled SIRT1-dependent signaling pathways, AMP-activated protein kinase activation, cellular mitochondrial biogenesis by peroxisome proliferator-activated receptor coactivator-1 phase stimulation, and, because of this, SIRT1-dependent deacetylation, abolishment of nuclear factor-B inflammation signal, induction of autophagic flux, which collectively enhances proteostasis maintenance and cellular stress resistance. Similar to resveratrol, phytochemical and pharmacological autophagy inducers such as spermidine, metformin, and rapamycin have been reported to alleviate dysfunctional proteostasis by modulating mTOR-related metabolic pathways.

Yet, despite their well-known antioxidant, anti-inflammatory, and mitochondrial-safing activities, the anti-aging potential of these phytochemicals and pharmacological autophagy inducers has not been directly verified to date. Notwithstanding emerging preclinical data, several translational hurdles remain, including suboptimal bioavailability owing to rapid first-pass hepatic metabolism, limited water solubility, and pharmacokinetic instability of resveratrol, which may limit its translational ease; and Dose-dependent toxicity, potential off-target effects, thrombocytopenia, and long-term safety specific to (Dasatinib + Quercetin) senolytic therapy. All in all, the current literature suggests that senolytics and phytochemical-based therapeutics exert protective effects against age-related proteostasis dysfunction by acting on overlapping yet distinct molecular pathways. Future trials will need to center on robust head-to-head mechanistic and efficacy studies (enabled by emerging biomarkers), as well as large-scale RCTs assessing safety, efficacy, and translational viability in age-related dermatoses and degenerative diseases.

MITOPHAGY ACTIVATORS AS AN ANTIAGING APPROACH (MITOCHONDRIAL DAMAGE)

Mitochondrial dysfunction is an identity of aging and is strongly associated with the development of multiple neurodegenerative diseases. Mitophagy defects, which normally remove injured mitochondria, contribute not only to aging but also to pathologies including cancer, metabolic disease, chronic inflammation, senescence, and genomic instability. Maintaining mitochondrial health is thus key for healthy aging and an important therapeutic target for longevity. But in the case of excess oxidative stress, mitophagy can become a runaway destructive pathway, hastening cellular aging. Drosophila models have demonstrated that Parkin, a key mitophagy regulator, can reduce lifespan when overexpressed. In addition, inflammation and mitochondrial function are intimately linked, as numerous inflammatory diseases originate from mitochondrial dysfunction. Recent studies emphasize the promise of natural compounds and bioactive molecules for anti-aging interventions. Agents, including Sirtuin-Activating Compounds (STACs), Nicotinamide Adenine Dinucleotide (NAD) precursors such as Nicotinamide Mononucleotide (NMN) and Nicotinamide Riboside (NR), and resveratrol, have been shown to enhance mitophagy and mitochondrial function, thereby promoting healthy aging.

Mitophagy plays a central role in mitochondrial health, and its disruption contributes to aging through processes such as impaired fusion and fission, reduced biogenesis, metabolic imbalance, and mitochondrial dysfunction linked to diseases like Alzheimer's and Parkinson's. Compounds such as sirtuin-activating molecules (STACs), nicotinamide mononucleotide (NMN), nicotinamide riboside (NR), and resveratrol help counteract these effects by regulating mitophagy and protecting functional mitochondria [35].

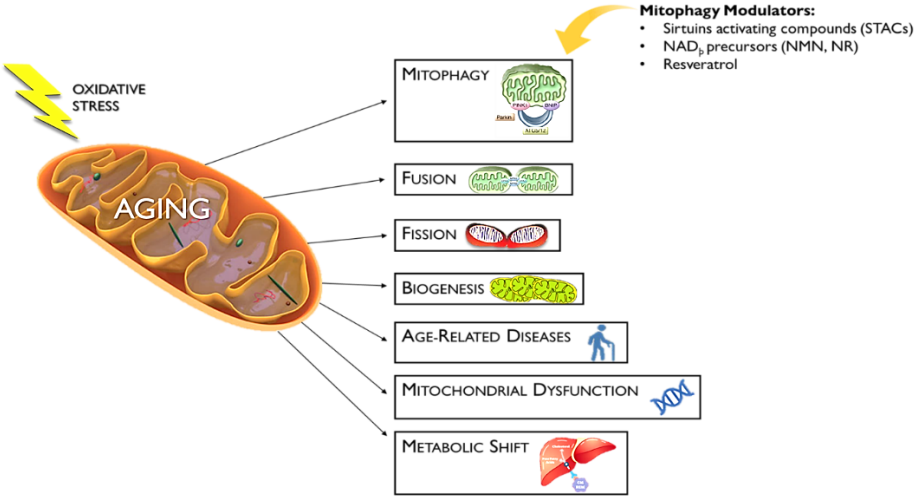

Figure 9: Mitophagy Activators as an Antiaging Approach

INHIBITION OF MTOR AND INSULIN/IGF-1 SIGNALING (IIS) AS AN ANTIAGING APPROACH (NUTRIENT SIGNALING).

The mTOR (mechanistic Target of Rapamycin Complex 1) is a key cellular signaling complex that regulates cell growth, protein synthesis, and metabolism, and its overactivation contributes to cellular senescence and skin aging. The pathway promotes growth by stimulating protein synthesis and suppressing autophagy and is closely associated with senescence phenotypes. As a nutrient sensor, mTOR affects mitochondrial biogenesis, mitophagy, the secretory phenotype of senescent cells, and stem cell functionality. Reduced mTOR signaling consistently correlates with lifespan extension across multiple organisms, including *C. elegans*, Drosophila, *S. cerevisiae*, and mice. Pharmacological inhibition of mTOR with rapamycin slows aging and delays age-associated diseases in yeast, flies, worms, mice, and humans. mTORC1 mainly phosphorylates S6 kinase, and 4E-BP1 (Eukaryotic Translation Initiation Factor 4E-Binding Protein 1) is a downstream effector of mTORC1 that regulates protein synthesis by inhibiting cap-dependent mRNA translation, thereby influencing cell growth and aging.) 4E-BP1, which is linked to longevity, and reduced S6 kinase activity powerfully drive lifespan extension [36]. The insulin/IGF-1 signaling (IIS) pathway is another nutrient-sensing pathway that controls aging in nematodes, flies, and mice. Inhibition of IIS/mTOR signaling not only increases lifespan but also postpones age-associated diseases in multiple model organisms, from yeast to monkeys. Recent findings suggest that certain

compounds such as celecoxib, recombinant BTI, and extracts of Ribes fasciculatum can downregulate the IIS pathway & extend lifespan in C. elegans. In addition, hypo-taurine, a natural antioxidant, extended nematode lifespan by impacting IIS signaling.

STEM CELL-BASED THERAPIES (STEM CELL EXHAUSTION)

Stem cell exhaustion, a loss of stem cell quantity and function, promotes aging across tissues and organs. Adult stem cells — including HSPCs — that support tissue repair and regeneration succumb to phenomena such as mTORC1 hyperactivation and dysfunctional AMPK signaling [37]. Accumulation of DNA damage and increased p16^INK4a levels strongly correlate with decreased stem cell pools in aging. Rejuvenation strategies, such as reprogramming aged HSPCs to a pluripotent state or generating neural stem cells from aged fibroblasts, also hold potential as anti-aging therapies [38]. Metformin, an FDA-approved drug, drives stem cell renewal and is featured in adult stem cell therapies. Because AMPK is a key regulator of HSCs, AMPK activators such as AICAR, A769662, metformin, and NAD+ could improve the outcomes of stem cell transplantation. Besides that, resveratrol activates SIRT1, which maintains self-renewal in human embryonic stem cells. Caloric restriction has also recently been shown to boost stem cell proliferation by affecting niche cells and energy metabolism, thereby delaying stem cell aging [39].

METHODOLOGY

An inclusive literature review was conducted to gather and assess published scientific evidence on the mechanisms of skin aging and anti-aging therapeutic approaches. Electronic databases, including PubMed, Google Scholar, Scopus, and ScienceDirect, were searched systematically for relevant articles and trends in skin aging and aging-related research published between 2010 and 2005. The literature review aimed to identify reports on intrinsic and extrinsic aging, molecules responding to photo-aging, and anti-aging therapeutic products [40]. The search strategy used various search terms/keywords linked with Boolean operators ("skin aging", "photoaging", "oxidative stress", "reactive oxygen species", "cellular senescence", "anti-aging therapy", "herbal preparations", "matrix metalloproteinases", "mitophagy", "stem cell therapy", "telomere reactivation", "epigenetic strategies", "natural bioactive compounds", "molecular signalling pathways") and further related articles were found by manually scanning the reference list from the searched articles [41]. Selection criteria include: original and review articles, as well as experimental studies in the English language, on mechanisms of skin aging, molecular signalling pathways, herbal and synthetic anti-aging compounds, nanocarrier based formulations and treatments for skin rejuvenation can also be works on oxidative stress inflammation breakdown of the extracellular matrix melanogenesis mitochondrial dysfunction and the signalling pathways of MAPK, NF-B Nrf2 TGF-/Smad, mTOR and IIS pathways. Articles were also excluded if they were duplicates, reports, or abstracts from a scientific conference, an unpublished article, not in English, or if the study was not directly related to the aging process of the skin or anti-aging treatment modalities. Further articles that were not sufficiently scientific to be concise or lacked clarity of approach were excluded from the literature review, which was later critically analyzed and categorized according to the principles of skin aging, specific clinical signs, and current prevention and treatment options. Database searching led to the initial identification of about 94 articles, with nearly 75 shortlisted after preliminary screening. In addition, 68 articles that met the inclusion criteria were ultimately selected for the current review.

FORMULATION STRATEGIES FOR HERBAL-BASED TOPICAL DOSAGE FORMS

The activity of anti-aging agents may be reflected in pharmacological activity, but other contributing factors include the suitability and elegance of the formulation [42]. Preparations for topical application, such as creams, gels, lotions, and ointments, serve as carriers for delivering active ingredients to the skin. The choice of base (oil-in-water or water-in-oil emulsion), gelling agents (e.g., carbomers, natural gums), emulsifiers (e.g., lecithin, polysorbates), and preservatives (ideally natural but occasionally synthetic) is important for stability and effective function [43,44]. These platforms deliver bioactive compounds, also known as actives, which must be integrated into the vehicles at the right time and temperature to preserve bioactivity and prevent degradation. Stability in the formulation, including resistance to phase separation, microbial spoilage, and physical changes under varying environmental conditions, is integral to product quality.

The commercialization of novel delivery systems for herbs, such as nanoemulsions and liposomes, further enhances the skin penetration and stability of herbal actives and is an emerging approach to increase efficacy [45,46].

ROLE OF INTRINSIC AND EXTRINSIC FACTORS IN SKIN AGING

Skin aging is caused by a complex interaction between intrinsic and extrinsic factors that induce both clinical and functional degradation over time. Intrinsic aging causes fine wrinkles, loss of elasticity, and changes in the fundamental structural proteins, collagen and elastin, that give skin its integrity. Extrinsic factors, particularly UV radiation, accelerate photoaging, resulting in deeper wrinkles, laxity, and a rougher texture. Age-related flattening of the dermal-epidermal junction renders skin more vulnerable to injury, and a decrease in water content and aquaporin levels results in dryness [54,55]. Aging also decreases skin's biomechanical strength, an effect exacerbated by photoaging. Accumulation of Advanced Glycation End-products (AGEs) compromises elasticity and blood flow, making them hallmarks of skin aging. Superior microcirculatory quality correlates with a youthful appearance, and skin thinning may be systemically related to bone loss. In general, skin aging results from genetic and environmental factors that affect its structure, function, and appearance [56].

Table 2: List of herbs used for treating aging

Herbal Intervention	Clinical Trial Quantitative Data Related to Skin Aging	Outcome	Specific SPF Value Reported
Aloe vera	In a clinical study involving 30 women aged >45 years, oral aloe vera supplementation at 1200 mg/day and 3600 mg/day for 90 days significantly improved facial wrinkles and skin elasticity. Collagen production increased in both dose groups [47].	Significant reduction in wrinkle depth and improved skin elasticity.	4
Green tea	A randomized, placebo-controlled clinical trial in 40 women with moderate photoaging used a 10% green tea cream and 300 mg of oral green tea twice daily for 8 weeks. Histological analysis showed a significant increase in elastic tissue content ($p < 0.05$) [48].	Improved dermal elastic tissue and reduced photoaging damage.	4
Sesame oil	Clinical evidence mainly demonstrates barrier repair and antioxidant effects. In a randomized study involving 40 bedridden patients, sesame oil application significantly improved skin integrity and prevented oxidative skin damage ($p = 0.04$) [49].	Improved skin barrier protection and reduced oxidative injury associated with aging skin.	8
Coconut oil	Virgin coconut oil has shown significant improvement in skin hydration and elasticity in topical clinical evaluations. Studies reported enhanced skin moisture and reduced transepidermal water loss after regular topical application for 4–8 weeks [50].	Improved skin hydration and maintenance of skin barrier function associated with anti-aging benefits.	4
Pomegranate	In a randomized double-blind placebo-controlled clinical trial involving 28 healthy adults aged 25–55 years, supplementation with 250 mg pomegranate extract daily for 4 weeks reduced facial wrinkle severity by $6.2 \pm 1.6\%$ ($p = 0.004$), whereas the placebo group showed a $1 \pm 1.4\%$ increase in wrinkles [51].	Significant reduction in wrinkle severity and improved skin barrier function [52].	21
turmeric	In a 2-year double-blind trial, 56 women aged 25–75 years received 250 mg turmeric polyphenols twice daily. Improvements in photoaging parameters, including roughness, elasticity, and solar elastosis, were observed during treatment [53].	Reduced photodamage and improved skin texture.	6

LIMITATIONS OF CHRONOLOGICAL AGE AS A PREDICTOR OF SKIN AGING.

Chronological age alone is a flawed predictor of skin aging because of the complex interplay among genetics, environment, and lifestyle. Although intrinsic aging and photoaging occur at the molecular level and share common pathways, these pathways are modified by individual differences in sun exposure and skin pigmentation, which account for patterns of aging [57]. Evidence suggests that a genetic predisposition for longevity does not necessarily translate to delayed cutaneous aging [58]. This was demonstrated in studies comparing the middle-aged offspring of long-lived siblings with their respective partners, in which no significant differences in skin aging were observed. Biological skin age, which includes skin appearance and function, can vary significantly from chronological age and is influenced by factors such as body mass index and hormones [59,60]. Methods, including photometric scales for specific populations and advanced imaging with machine learning, provide ways to measure skin aging beyond chronological age

objectively. Interventions such as retinoids also show that targeted biological interventions can modulate signs of aging, underscoring the importance of multi-dimensional rather than single-axis measures, such as chronological age [61].

LIMITATIONS OF HERBS USED FOR TREATING AGING

While this review offers readers good insight into the mechanisms of skin aging and available anti-aging treatment options, some limitations need to be noted. For instance, many of the studies cited focused on herbal formulations and cosmetic applications. They were published in journals with low or moderate impact factors, which are not representative of high-quality evidence [62]. In addition, most herbal anti-aging approaches discussed in this review have been supported primarily by in vitro studies, animal models, and basic formulation research. In contrast, clinical studies in humans and safety evaluations for long-term treatment remain scarce. Differences in plant provenance, extraction techniques, preparation methods, and parameters used to assess effectiveness among studies may hinder comparisons [63, 64]. It is also worth noting publication bias, as positive findings are much more likely to be published than those with negative or inconclusive results. Since this article is a narrative rather than a systematic review or meta-analysis, treatment efficacy was not quantitatively assessed. Further well-designed, controlled, and blinded clinical research on these anti-aging strategies is required to substantiate their long-term efficacy [65].

Table 3: List of key findings

Literature	Study type/system	Intervention or focus	Key result/ relevance to review
Fernández-Varela -Gómez F., 2024	Review (clinical signs)	Signs and clinical classification of skin aging	Summarised clinical manifestations (wrinkles, laxity, pigmentation) and role of photoaging; supports clinical phenotype sections
Lei X., 2025	Review / mechanistic	Medicinal plants in photoaging	Describes antioxidant/anti-inflammatory roles of plant polyphenols and supports inclusion of herbal extracts as protective agents against photoageing
Mishra SK et al., 2022	Review (mechanistic/therapeutic)	Anti-aging strategies (senolytics, autophagy)	Summarised senolytics, autophagy inducers and systemic anti-aging agents; supports discussion on senolytics and proteostasis approaches.
Shin SH et al., 2023	Review (dermal aging)	Dermal ECM degradation and interventions	Highlighted MMPs, TGF-β/Smad dysregulation and therapies that target dermal matrix — referenced in ECM and formulation strategy sections
Costa EF et al., 2022	Review /compendium	Herbal-derived products and cosmetics	Provided data on botanical actives and formulation trends (nanoformulations); supports claims about nano-carriers improving penetration/stability of phytochemicals.
Wang J & Gu H., 2021	Experimental / bioinformatics	Biological processes in aging skin	Identified candidate targets/pathways (MMPs, oxidative stress markers) for inhibition — cited for pathway targeting rationale.
Yang F. et al., 2022	Clinical / formulation study	Alpha-ketoglutarate anti-wrinkle cream	Reported improvement in hydration and wrinkle metrics in treated subjects — used to illustrate measurable clinical endpoints for topical actives
Shailendra K. Mishra et al., 2022 (cited within)	Mechanistic review	mTOR/IIS, mitophagy, resveratrol, NMN	Supported inclusion of nutrient-sensing and mitophagy interventions such as STACs, NR/NMN, and mTOR inhibitors as promising strategies
Selim Ali S. et al., 2025 (and similar)	Formulation studies	Polyherbal creams/gels	Reported formulation stability and some in vitro/in vivo antioxidant effects; used as examples but noted low-level evidence and need for RCTs

CONCLUSION

Skin aging is a highly complex and multifunctional biological process caused by the imbalance of an intrinsic endogenous genetic program and a complex of our exogenous environmental factors like UV light, air pollution, oxidative stress, and stress-related factors, etc., leading to inevitable progress as well as structural, functional, and aesthetic declines in the skin. In this review, we have summarized the major molecular and cellular pathways involved in the process of cutaneous aging: reactive oxygen species, inflammation, collagenase, elastase, mitochondrial dysfunction, DNA damage, dysregulation of melanogenesis, and cell transformation pathways of MAPKs, NF-B, Nrf2, TGF-/Smad, and mTOR signaling [66]. Therapeutic and preventive interventions targeting these

pathways were critically discussed. Formulations containing herbal ingredients and bioactive phytoconstituents are highly effective for skin aging due to their antioxidant, anti-inflammatory, photoprotective, collagen-preserving, and regenerative effects. Novel formulation techniques such as nanoemulsions, liposomal formulations, phytosomes, and other nanocarrier-based approaches help overcome inherent limitations, including poor dermal penetration, formulation stability, and low bioavailability of herbal actives [67].

However, optimizing and validating herbal anti-aging products requires addressing not only preclinical and formulation issues but also the availability of large, well-designed, placebo-controlled, robust randomized controlled clinical trials and systematic analyses of long-term safety, safety-related issues, and the reproducibility of efficacy. Because of this, further studies should focus on mechanistically oriented and clinically validated research approaches, such as large-scale clinical trials, randomized controlled trials exploring polyherbal nanocarrier system(s) based formulations, detailed stability profiling, pharmacokinetic, dermal permeation, and biomarker monitoring studies for efficacy. Finally, refinement of the standardization of phytochemicals, formulation characteristics, and clinical evaluation protocols is necessary to transition from experimental and cosmetic trials of herbal anti-aging formulations to evidence-based dermal therapies [68].

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NIL

CONFLICT OF INTEREST
The authors declare no conflict of interest.

AUTHOR CONTRIBUTION
The authors contributed significantly to the preparation of this review manuscript. Parwati, Mallikarjun, and Dattatreya were responsible for data collection and extensive literature review. Pratiksha carried out the critical review and analysis of the compiled data. Revati contributed to manuscript correction and overall supervision.

DECLARATION OF USE OF AI TOOLS
The authors have used ChatGPT as an AI tool for language editing, Grammar corrections, and improving readability. All content, analysis, and conclusions were reviewed and verified by the authors. The authors take full responsibility for the originality, accuracy, and integrity of the work.

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