Frontiers in Bioscience Landmark

Front. Biosci. (Landmark Ed) **2025**; 30(1): 25463
https://doi.org/10.31083/FBL25463

Review

Impact of Vitamin D on Skin Aging, and Age-Related Dermatological Conditions

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Academic Editor: Giuseppe Murdaca
Submitted: 1 July 2024 Revised: 1 September 2024 Accepted: 10 September 2024 Published: 20 January 2025

Abstract

Human skin is a physical and biochemical barrier that protects the internal body from the external environment. Throughout a person's life, the skin undergoes both intrinsic and extrinsic aging, leading to microscopic and macroscopic changes in its morphology. In addition, the repair processes slow with aging, making the older population more susceptible to skin diseases. Intrinsic factors associated with advanced age gradually degrade the dermal collagen matrix, resulting in fine wrinkles and reduced elasticity; this is accelerated in post-menopausal women due to estrogen deficiency. In contrast, extrinsic factors associated with advanced age, primarily caused by exposure to ultraviolet (UV) radiation, lead to coarse wrinkles, solar elastosis, hyperkeratosis, irregular pigmentation, and skin cancers. UVB radiation, while contributing to skin photo-aging, also induces the cutaneous synthesis of vitamin D. Vitamin D, in turn, protects the skin from oxidative stress, inflammation, and DNA damage, thereby delaying both chronological and photo-aging. Moreover, research has demonstrated an association between lower vitamin D levels and a higher prevalence of certain cutaneous diseases. This review explores and summarizes the critical role of vitamin D in skin aging and age-related skin diseases. The data presented highlight the importance of maintaining vitamin D adequacy throughout life.

Keywords: vitamin D; skin aging; age-related skin diseases

1. Introduction

The skin, the largest organ in the human body, acts as a physical barrier that safeguards internal structures from external threats. The skin comprises three layers: the epidermis, dermis, and hypodermis, with each layer exhibiting distinct anatomical features. The outermost layer, the epidermis, protects the skin from external damage and maintains hydration. It primarily consists of keratinocytes originating from the basal layer and moving upward toward the surface (Fig. 1).

As keratinocytes ascend, they become highly keratinized, mature, change shape, and join the stratum corneum, the dead surface layer of the skin [1–3]. The epidermis also includes melanocytes, Langerhans cells, and Merkel cells. Melanocytes produce melanin, a pigment that gives the skin its color. Antigen-presenting dendritic Langerhans cells act as the skin's first line of defense, and Merkel cells in the stratum basale function as mechanoreceptors for light touch [4]. The layer directly below the epidermis, the dermis, is comprised of fibroblasts, vasculature, nerve fibers, sensory receptors, and extracellular matrix (ECM). The ECM is composed of two major components: collagen and elastic fibers. Collagen is the major structural component that provides both structure and tensile strength. Elastic fibers maintain tissue elasticity and resilience to restrain stretching [5] and are composed of elastin and microfibrils. The deepest layer, the hypodermis, is located under the dermis and composed of loose connective tissue with larger blood vessels, subcutaneous fat, and areolar connective tissues that provide insulation, thermoregulation, and cushioning to the skin [6].

As the body's outermost layer, the skin is continuously subjected to external stressors such as solar radiation. Ultraviolet (UV) radiation from the sun can be categorized into three types based on wavelength: UVA (320–400 nm), UVB (280–320 nm), and UVC (100–280 nm) [7–10]. The impact of UVC is minimal since the ozone layer completely absorbs it. However, the ozone layer only absorbs some UVA and UVB rays. This incomplete absorption allows a portion of UVB and UVA rays to reach the skin and penetrate the epidermis. Prolonged exposure to UVB can cause erythema and DNA damage in both keratinocytes and melanocytes, as well as stimulate proteolytic enzyme production. UVA is 10–100 times more abundant near the Earth's surface than UVB and penetrates deeper, affecting both epidermal and dermal components (Fig. 2) [10,11].

UVB radiation converts 7-dehydrocholesterol (7-DHC) into pre-vitamin D, which gets photo-converted to vitamin D_3 in the subcutaneous tissue (see Fig. 2). The cutaneous generation of vitamin D varies based on several factors, such as the amount of skin area exposed, intensity of sunlight, zenith angle of the sun, duration of exposure, skin

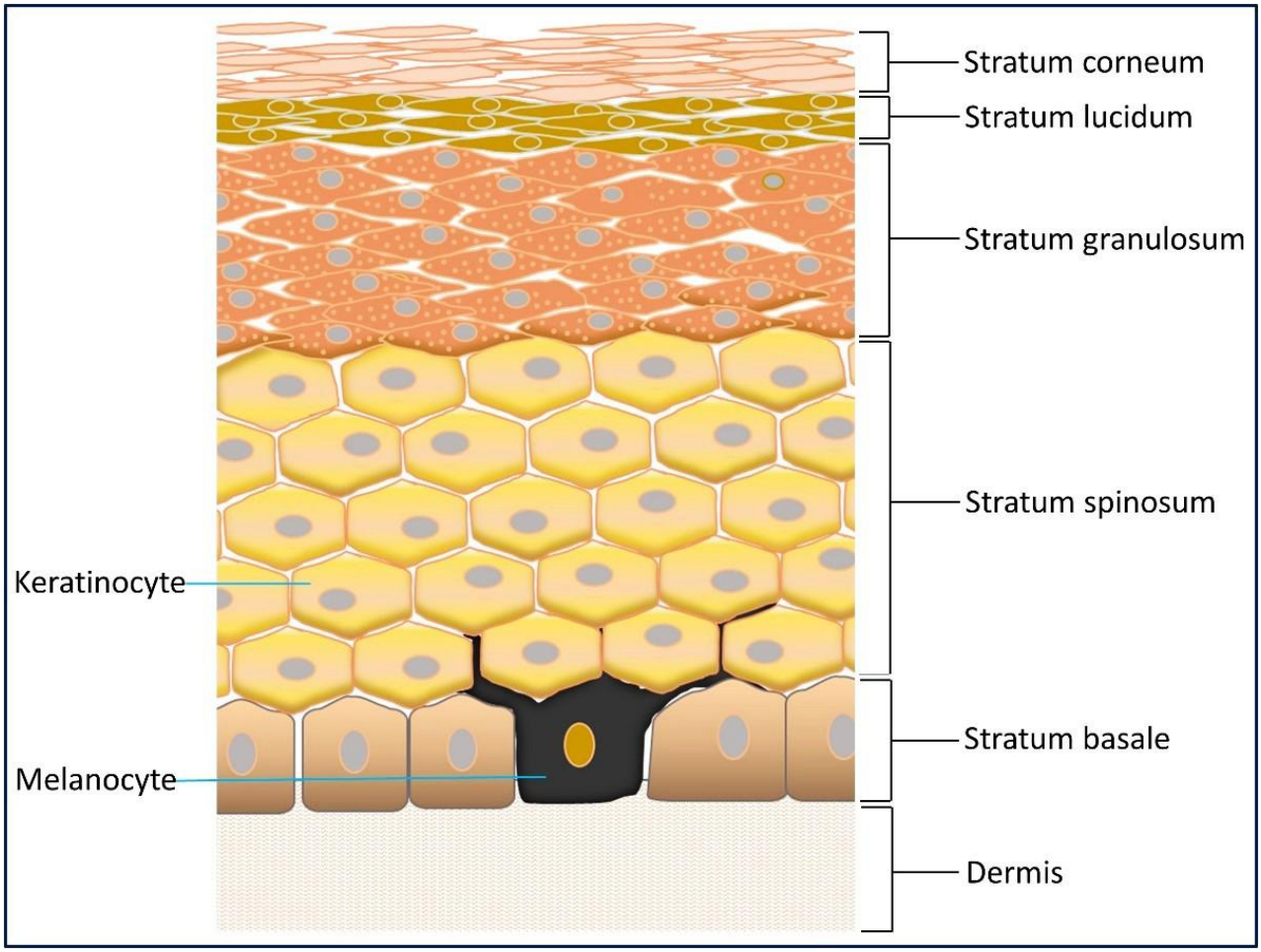

Fig. 1. The multilayer structure of the epidermis. The image shows multiple layers of the epidermis, the keratinocytes and melanocytes, and part of the dermis.

type & thickness, and the application of sun-blocking chemicals [12]. Due to enhanced UVB absorption by melanin, individuals with dark skin have a lower capacity to generate vitamin D than those with lighter skin [13].

Vitamin D (calciferol) is a secosteroid molecule produced in the skin upon UVB exposure (Fig. 2). Following sufficient UVB exposure, 7-DHC is converted to pre-vitamin D_3 in the epidermal basal and spinous cell layers. This pre-vitamin D_3 gets converted to vitamin D_3 (cholecalciferol) by thermal isomerization. The photosynthesized vitamin D_3 and vitamin D_2 (ergocalciferol) absorbed from the diet are fat-soluble compounds. They bind to the vitamin D binding protein (DBP) and are transported to the liver and other tissues via circulation [14]. In the hepatocytes, vitamin D_2 and D_3 are hydroxylated by the 25-hydroxylase enzyme (transcribed from *CYP2R1*), generating 25-hydroxycalciferol [25(OH)D], also known as calcifediol or calcidiol [15,16]. Calcidiol is the predominant vitamin D metabolite in the bloodstream and the most accurate indicator of vitamin D nutritional status.

The DBP-bound vitamin D and 25(OH)D re-enter the circulation and are transported to proximal renal tubular cells in the kidney and peripheral target cells [16]. In the kidney, 25(OH)D undergoes additional hydroxylation by the enzyme 1α-hydroxylase (transcribed from *CYP27B1*), resulting in the formation of the most active secosteroid, $1,25(OH)_2D$ (calcitriol). In addition to hepatocytes, peripheral target cells have both *CYP2R1* and *CYP27B1* genes. Therefore, peripheral cells contain the enzyme 25-hydroxylase, promoting the endogenous synthesis of calcitriol [13,17–19]. The intracellular synthesis depends on the sufficient diffusion of vitamin D and 25(OH)D from the bloodstream into target cells [13,20]. Cell membranes of the target cells can also endocytose DBP-bound D_3 and 25(OH)D. Still, this endocytosis occurs to a lesser extent than the quantities entering via diffusion from circulation [21]. The cholecalciferol (D3) synthesized in the skin indirectly regulates its own catabolic enzyme, 24-hydroxylase (transcribed from *CYP24A1*), through a negative feedback mechanism [22–24]. This catabolizes excess vitamin D into the inactive form, 24(OH)D [25], preventing high levels of vitamin D from entering the circulation and causing adverse effects.

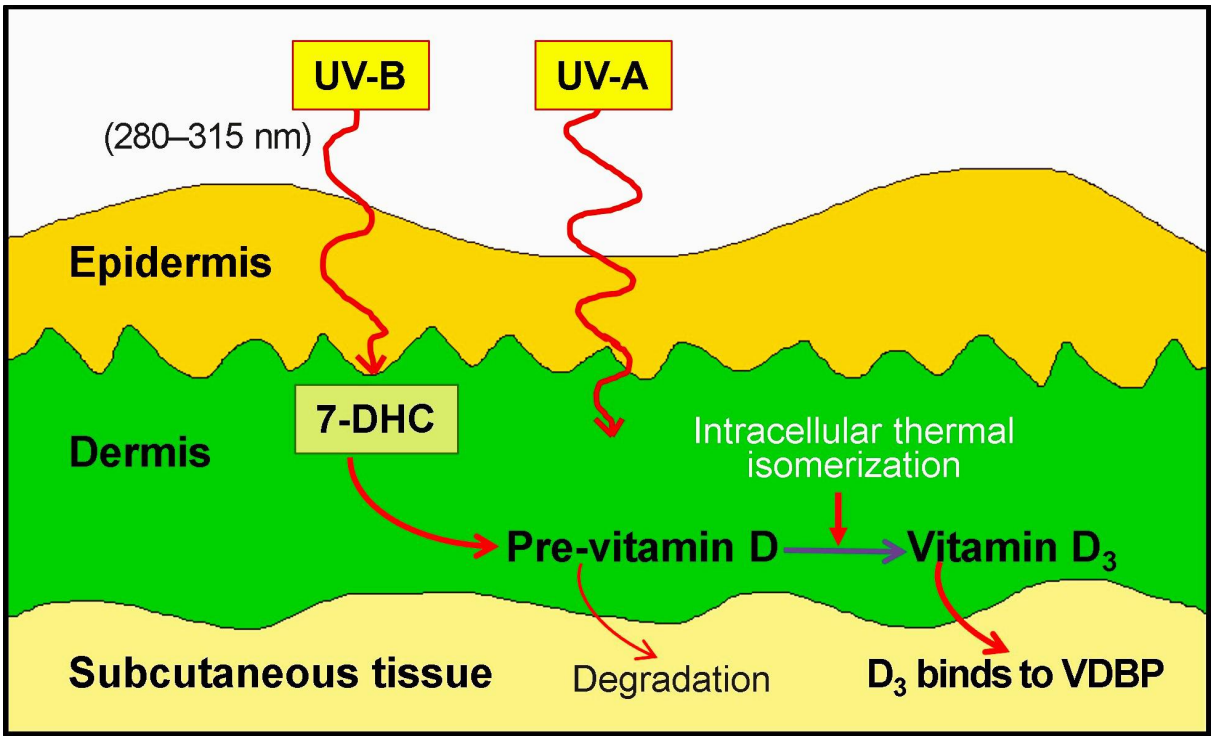

Fig. 2. Wave-length-dependent ultraviolet (UV) radiation penetrates human skin and activates the production of vitamin D_3 from the precursor 7-dehydrocholesterol (7-DHC).

Vitamin D Signaling and Target Genes in the Skin

The skin is the only organ capable of producing vitamin D, converting it to biologically active $1,25(OH)_2D$, and responding to it in a cell-specific manner [23,26]. The metabolite $1,25(OH)_2D$ is the high-affinity ligand of the transcription factor calcitriol receptor (used to known as vitamin D receptor, VDR). VDR regulates the expression of hundreds of target genes by binding to the vitamin D response elements on the chromosome [13,14,27,28]. Under the direct influence of vitamin D, these target genes perform various skeletal and extraskeletal functions. A review by Carlberg C. [29] comprehensively covers the general overview of vitamin D signaling and VDR target genes.

In the skin, keratinocytes are the cells that respond to $1,25(OH)_2D$. VDR is most active in keratinocytes during cellular differentiation and proliferation [23], with the highest levels of VDR and *CYP27B1* expression found in the stratum basale (basal layer) of the skin [30,31]. Epidermal stem cells within the stratum basale produce transient amplifying cells, which begin the differentiation process as they ascend into the stratum spinosum. Once in the stratum spinosum, $1,25(OH)_2D$ promotes the production of involucrin, keratin 1, and transglutaminase, which helps maintain proper barrier function [23].

The cells in the stratum granulosum contain profilaggrin, which is cleaved proteolytically to release filaggrin. In response to $1,25(OH)_2D$, cells in the stratum granulosum produce filaggrin and loricrin proteins, which together form the cornified envelope [23,32]. Proteins play a crucial role in maintaining the integrity and function of the skin barrier [33].

The activation of genes by VDR and $1,25(OH)_2D$ in the skin depends on the level of cellular differentiation. Coregulators such as the Mediator complex (MED, previously known as DRIP) and Steroid Receptor Coactivator (SRC) complex (SRC2 and SRC3) modulate the transcriptional activity of VDR in a cell-specific manner [34]. In undifferentiated cells, MED directly interacts with VDR to inhibit its activity. In differentiated cell layers within the stratum granulosum, the coactivators SRC2 and SRC3 enhance VDR activity [35]. Calcium also influences the effects of $1,25(OH)_2D$ and VDR indirectly by acting through the multifunctional protein β-catenin and the calcium-sensing receptor (CaSR) [23,36]. The close proximity of VDR and β-catenin response elements in many genes suggests a dual regulation. As an example of this duality, VDR and $1,25(OH)_2D_3$ have been shown to repress the oncogenic actions of β-catenin, thus protecting against skin cancer [37]. Recent evidence also indicates that VDR regulates the highly conserved Grainyhead-like (*GRHL*) family genes. These genes code for transcription factors necessary for the maintenance and development of different types of epithelia [28]. Understanding the regulatory pathways and molecular mechanisms by which vitamin D influences the skin remains incomplete, highlighting the need for further research.

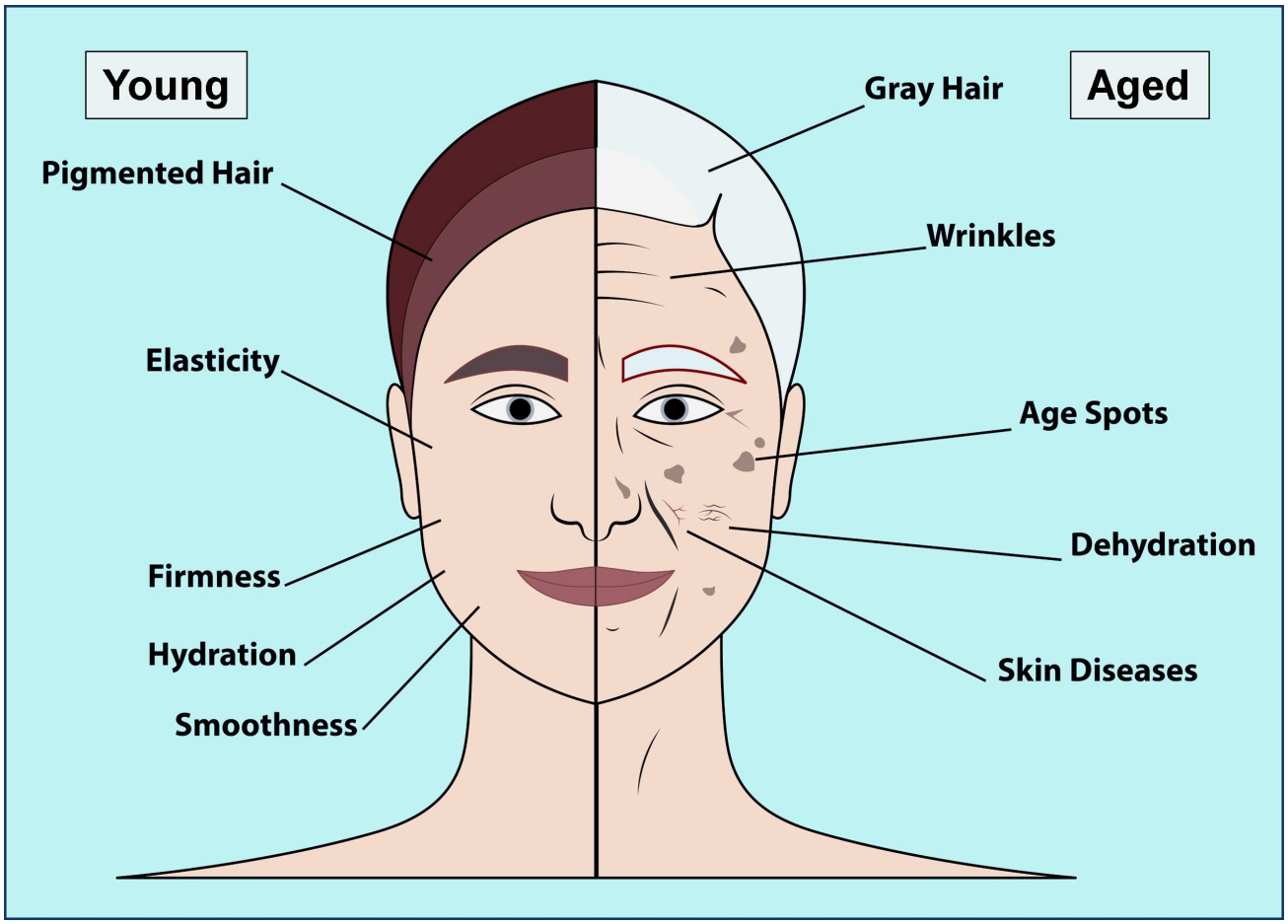

Fig. 3. The characteristics of young and aged skin as visible to the naked eye (left side: young; right side: aged). Adapted from [44].

2. Skin Aging—Structural, Physiochemical, and Functional Changes

The skin undergoes genetic, molecular, cellular, and organ-specific changes throughout a human's lifetime [3, 38]. Intrinsic aging refers to the natural chronological changes that affect the entire human body over time. Extrinsic aging is defined as additional body changes exacerbated by environmental factors such as UV exposure and smoking. Fine wrinkles, thinning of the epidermis, reduced subcutaneous fat, and laxity are characteristic features of intrinsic skin aging.

In contrast, extrinsic aging involves additional changes exacerbated by environmental factors such as UV exposure and smoking [3,8,39–41]. As individuals age, intrinsic and extrinsic factors contribute to permanent skin modifications, resulting in thinner, dry, unevenly pigmented, and wrinkled skin with a sagging appearance [42,43]. Fig. 3 (Ref. [44]) illustrates the characteristic features of young and aged skin.

All layers of human skin undergo structural, physiological, and functional changes with age. The main structural changes in the epidermis include a reduction in thickness and changes in composition. The thinning of the epidermis is more noticeable in exposed regions of the body, with an overall reduction rate of 5–7% per decade. Decreases in dermal collagen and elastin, along with the reduction of subcutaneous fat in the hypodermis, are the major contributors to the overall thinning of the skin [45,46]. With aging, the number of cells and epidermal turnover rate decrease, causing cells and tissues to undergo characteristic changes (Fig. 3).

Some age-related cellular changes in the epidermis include shorter and fatter keratinocytes, enlarged corneocytes, and reduced melanocytes, leading to uneven pigmentation. The number of Langerhans cells also declines with age, reducing antigen-trapping capability and hence impairing cutaneous immunity [47,48]. Finally, subcellular changes due to aging also occur. For example, the dermo-epidermal junction, which provides strength, resistance, and nutrition to the skin, flattens with advanced age, increasing the skin's vulnerability to damage from shear forces. The reduced nutrient and oxygen supply poses a risk for dermo-epidermal separation, contributing to wrinkles [45,49].

Collagen, elastin, and hyaluronic acid, the main extracellular components of the dermis, all deplete in the ag-

Table 1. Changes in the structure of aged skin components.

Skin component	Observed change in skin	Reference
Epidermis	Reduced stratum corneum hydration	[51–53]
	Dysfunction in epidermal permeability barrier	[54,55]
	Dermo-epidermal junction flattens	[56]
	Decrease of the number of melanocytes	[57,58]
	Decrease of the number of Langerhans cells	[57]
	Decrease of Merkel cells	[59]
	Elevation of skin surface pH	[60,61]
Dermis	Reduction of dermal fibroblasts	[62]
	Decrease of collagen synthesis	[62,63]
	Surface of collagen bundles become rougher, and fiber bundles become stiffer and harder	[50]
	Decrease of blood vessels and nerve endings	[40]
	Reduction of the thickness (dermis thinning)	[42]
	Decrease of elastic fibers	[64]
	Reduction of functional sweat glands and reduced sweat rate	[65]
	Decrease of Meissner's corpuscles	[59]
	Sebaceous glands (SG) hyperplasia, SG atrophy, decreased sebum secretion, and altered sebum composition	[66]
	Decreased melanin production in hair shaft and reduction of bulbar melanocyte numbers	[67]
Hypodermis	Decrease of the overall volume	[68]

ing skin (see Table 1, Ref. [40,42,50–68]). Dermal fibroblasts synthesize collagen, which strengthens and provides elasticity to the skin, and occurs in multiple forms. Type I collagen predominates in the skin's connective tissue, followed by smaller amounts of type III [69]. Disorganized and fragmented collagen fibrils are a characteristic feature of the aged dermis. Collagen fiber bundles become stiffer and more rigid with age, creating rougher surfaces [50].

Elastic fibers, a highly durable macromolecular component of the ECM, provide elasticity to the skin and other tissues, but become fragmented and thinned with age, leading to reduced tissue elasticity [70,71]. Oxidative damage, enzymatic degradation, calcification, carbamylation, aspartic acid racemization, formation of advanced glycation end products, and mechanical fatigue intrinsically lead to functional impairment of elastic fibers [71–74]. Meanwhile UV-induced extrinsic aging fragments functional elastin and collagen, deposits non-functional elastotic material, and causes the accumulation of damaged elastin. All these effects contribute to solar elastosis [72,75]. Table 1 further illustrates the changes associated with the structure of aged skin.

3. Molecular Mechanisms of Skin Aging

3.1 Oxidative Stress

Oxidative stress contributes to both intrinsic and extrinsic aging processes. The skin is constantly challenged with intrinsically generated reactive oxygen species (ROS) through normal biological processes. ROS are independent molecules with at least one oxygen (radical) atom and one or more unpaired electrons. They include molecules such as hydroxyl radical (·OH), superoxide anion radical (O_2^-), hydrogen peroxide (H_2O_2), peroxynitrite ($ONOO^-$), nitric oxide (NO), and singlet oxygen ($^1O_2$), that are highly reactive and capable of forming free radicals [76,77].

External insults such as UV radiation, volatile and non-volatile chemical pollutants, and smoking cigarettes further increase ROS production beyond the levels generated by intrinsic factors. The skin undergoes oxidative stress when the level of reactive species surpasses the neutralizing capability of its endogenous antioxidant defense systems. The excess ROS can induce DNA mutations, damage proteins, lipids, and carbohydrates, regulate inflammatory cytokines, and trigger cell apoptosis [76,78,79]. ROS also affects other biological responses and signaling pathways related to aging. These pathways include mitogen-activated protein kinase (MAPK), nuclear factor kappa B (NF-κB), phosphoinositide-3-kinase/AKT (PI3K/Akt), and Kelch-like ECH-Associating protein 1-nuclear factor erythroid 2-related factor 2-antioxidant response element (Keap1-Nrf2-ARE) [80–82].

Skin cells contain multiple antioxidant substances and enzymes, which have protective functions to negate oxidative stresses. Compared to the dermis, antioxidant enzymes such as superoxide dismutases, peroxidases, glutathione reductases, and catalases display elevated activity in the epidermis. Antioxidant substances like alpha-tocopherol (vitamin E), ubiquinol-10, glutathione, uric acid, and ascorbic acid are also significantly higher in the epidermis. Other enzymatic antioxidants such as thioredoxin reductase, methionine sulfoxide reductase, heme oxygenase-1, and peroxiredoxins have also been observed in the epidermis and dermis [83–86]. Given the enhanced exposure of the superficial layers of the skin to external insults, elevated levels of antioxidants in the epidermis are expected [87].

3.2 DNA Damage

Intrinsic and extrinsic factors that cause DNA damage accelerate skin aging [88]. During chronological aging, skin cells produce more ROS, which oxidatively damage bases and lead to single-strand breaks and basic sites (apurinic/apyrimidinic site) in DNA [89]. Prolonged exposure of skin cells to ROS may influence the shortening of telomeres, further promoting cellular senescence [90]. Age-related reduction in DNA repair in the skin may also lead to the accumulation of damaged DNA in cells [91].

UV radiation predominantly causes the formation of cyclobutane-pyrimidine dimers (CPD) and 6-4 pyrimidine-pyrimidone (6-4PP) photoproducts in DNA [92,93]. Additionally, UV radiation causes less common photoproducts such as Dewar valence isomers [94], purine photoproducts [93], and single and double-strand breaks in the phosphate backbone of DNA [95]. These DNA damages may disturb essential cellular functions, causing cell cycle arrest, apoptosis, or uncontrolled growth, leading to malignancy [92].

3.3 Protein p53

The tumor suppressor protein p53 functions as a transcriptional regulator modulating the expression of numerous genes that control cell death, senescence, cell cycle arrest, aging, DNA repair, carcinogenesis, and oxidative stress [96,97]. p53 gets activated upon UVB-induced DNA damage and promotes G1 arrest in the cell cycle, providing time to recover from the DNA damage. Under weak to moderate oxidative stress, p53 protects the cell by stimulating antioxidant genes [98]. Irreversibly damaged cells will be eliminated by p53 through the triggering of apoptosis [99]. With these functions, p53 is critical in preventing skin cancers and recovering from skin photo damage. However, long-term skin exposure to UV radiation can cause mutations in the p53 gene. Mutated p53 has been observed in 50% of skin cancers, emphasizing the impact of these mutations [100,101].

3.4 Inflammation

Persistent low-level systemic inflammation is a main contributor to the aging process. 'Inflamm-aging' describes the age-related activation of a persistent pro-inflammatory state via immune system dysregulation, which results in immuno-senescence [102]. Furthermore, inflammation plays a pivotal role in the degradation of ECM components, including elastin, collagen, and dermal hyaluronic acid, thus promoting the formation of wrinkles. Degraded collagen acts as a potent chemoattractant for immune cells, leading to increased inflammation [103].

UVR-induced DNA and ECM damage triggers cellular stress and activates inflammatory responses in the skin. Cellular senescence from photoaged skin has been detected in keratinocytes, fibroblasts, melanocytes, and subcutaneous preadipocytes. Cells undergoing senescence arrest their proliferation and secrete both anti-and pro-inflammatory mediators [104]. These mediators include interleukins (IL-1, IL-3, IL-6, IL-8, IL-33), platelet-derived growth factor (PDGF), various colony-stimulating factors (GM-CSF, M-CSF, G-CSF), high-mobility group box 1 (HMGB1) protein, and transforming growth factor α and β (TGF-α, TGF-β) [105,106]. Finally, UV irradiation enhances the transcription of NF-κB, a pivotal mediator of inflammatory response [105,107]. Inflammation plays a major role in the intrinsic aging process as well. Inflammatory mediators like IL-1β, IL-6, cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), and tumor necrosis factor-α (TNF-α), were found at elevated levels in various human tissues during chronological aging [108,109].

3.5 Changes in Collagen and Elastin

Fragmented dermal collagen is a characteristic feature of aged skin. The low level of collagen production from aged fibroblasts and the age-related increase in collagen-degrading matrix metalloproteinases (MMPs) are the key contributors to the changes in collagen [50,69,110–112].

The MMPs constitute a group of zinc-dependent endopeptidases secreted by multiple cells, including keratinocytes and fibroblasts, and are responsible for breaking down nearly all components of the ECM. Based on the substrate specificity, the MMPs are divided into collagenases, gelatinases, stromelysins, and membrane-type MMPs [113,114]. The collagenases (MMPs 1, 8, 13, and 18) degrade interstitial collagen I, II, and III; Gelatinase A (MMP-2) degrades type I and IV gelatin, whereas gelatinase B (MMP-9) degrades type IV collagens [113]. The activity of tissue inhibitor metalloproteinase-1 (TIMP-1), which inhibits many members of the MMPs, declines with advancing age [115], contributing to collagen fragmentation.

Finally, fragmentation of dermal collagen can occur due to internal factors stimulated by external and internal stresses. For example, during UV-induced photo-aging, ROS production and activation of cell surface receptors trigger the activation of MAP-kinase (mitogen-activated protein kinase) p38, JNK (c-Jun amino-terminal kinase), and ERK (extracellular signal-regulated kinase), which in turn recruit transcription factors like c-Fos and c-Jun. This cascade leads to the expression of the transcription factor AP-1 (activator protein-1) and induces the expression of collagen-degrading MMPs 1, 3, and 9 in fibroblasts and keratinocytes [116]. The observation of two elastolytic MMPs, matrilysin (MMP-7) and human macrophage metalloelastase (MMP-12), around elastotic material suggests the possible involvement of MMPs in the remodeling of elastotic areas in photodamaged skin [117].

3.6 Other Mechanisms Associated with Skin Aging

Age-associated changes have been detected in epidermal proteins such as keratin 10, involucrin, pre-albumin, Hsp 27, and Rho B, which are involved in human ker-

atinocytes' differentiation and proliferation. These proteins are abundant in the epidermis of young individuals, but their expression diminishes with age and often becomes undetectable in older individuals [41]. Other mechanisms, such as epigenetic modifications [118] and the formation of advanced glycation end products [119], also significantly contribute to the skin's aging process.

4. Vitamin D's Protective Effect During Skin Aging

Vitamin D has exhibited protective roles, preventing intrinsic and extrinsic skin aging. These include inducing collagen production, regulating oxidative stress and inflammation, reversing the damage caused by UV radiation, increasing epidermal barrier function, and contributing to wound healing [77,120].

Recent research has investigated the protective role of vitamin D against chronological and photo-aging of the skin. A study conducted by Chaiprasongsuk *et al.* [121] reported the potential of 1,25$(OH)_2$D, cytochrome P450 11A1 (CYP11A1)-derived D_3-hydroxyderivatives [20$(OH)D_3$, 1,20$(OH)_2D_3$, 20,23$(OH)_2D_3$, 1,20,23$(OH)_3D_3$], lumisterol, and its hydroxy-derivatives [20$(OH)L_3$, 22$(OH)L_3$, 20,22$(OH)_2L_3$, and 24$(OH)L_3$] to protect human epidermal keratinocytes against UVB-induced damage. Supplementation of any of the previously mentioned compounds at a concentration of 100 nM significantly reduced oxidant formation in human epidermal keratinocytes treated with 50 mJ/cm^2 of UVB radiation [121]. In the treated keratinocytes, p53 phosphorylation at Ser-15 and nuclear localization of p53 were increased. The treatments also increased the expression of Nrf2-regulated antioxidant genes [121].

4.1 Reversal of DNA Damage

VDR plays a critical role in protecting the skin from UV-induced DNA damage. The impaired ability of VDR-null mice to remove 6-4 PP and CPDs and their susceptibility to UV-induced epidermal tumors suggests an association between VDR and DNA repair [38,122]. In keratinocytes, VDR promotes nucleotide excision repair (NER) by facilitating the timely dissociation of Xeroderma Pigmentosum Complementation Group C (XPC) from the site of damaged DNA. This allows the timely assembly of downstream NER proteins and the pre-incision complex, thereby promoting DNA repair [123]. When keratinocytes are exposed to UV, vitamin D derivatives employ a variety of mechanisms to enhance DNA repair. These mechanisms include reduced reactive oxygen species, increased DNA repair and p53 expression, and higher energy allocation [124].

4.2 Regulation of p53 Signaling

Vitamin D regulates genome-wide p53 signaling, protecting the cells against photo-aging and skin cancers [101]. When treated with 1,25$(OH)_2$D, UV-irradiated skin cells produce increased levels of nuclear p53 ($p < 0.01$) compared to untreated cells. p53 upregulation facilitates skin pigmentation, thereby protecting against DNA damage and photo-aging. Treatment with 1,25$(OH)_2$D also reduced the number of sunburn cells ($p < 0.01$), production of nitric oxide ($p < 0.05$), and thymidine dimers ($p < 0.001$) in the treatment group compared to the control [101,125].

Apart from directly controlling gene expression, vitamin D exerts its regulatory effect by controlling the regulators of p53. One such example is the murine double minute (*Mdm2*) gene, a negative regulator of p53. Evidence suggests that 1,25$(OH)_2$D and VDR receptors regulate *Mdm2* gene expression in a p53-dependent manner [126]. However, future research investigating the indirect control of vitamin D on p53 regulators is required to solidify the novel regulatory pathways controlled by vitamin D in humans.

4.3 Vitamin D and Antioxidant Enzymes

The enzymes superoxide dismutase (SOD) and catalase are key players in the cutaneous enzymatic antioxidant defense system. Studies show that SODs protect type I and type IV collagen from oxidative damage by interacting through the matrix-binding domain or heparin [127,128]. The results of a longitudinal study comparing extracellular (EC)-SOD–overexpressed transgenic and wild-type mice indicate that the expression of cutaneous EC-SOD gradually declines with advancing age. EC-SOD promotes collagen production in aged mice by activating adenosine monophosphate-activated protein kinase and nuclear factor erythroid-2 related factor 2 (Nrf2)/heme oxygenase-1 pathways, thus reducing skin aging [128]. Untari *et al.* [129] observed decreased SOD activity in vitamin D deficiency, suggesting a correlation between vitamin D levels and SOD activity.

Further, supplementation of vitamin D has increased the expression of the antioxidant defense enzymes SOD and glutathione peroxidase (GPX) in various human organ systems [130,131]. However, vitamin D's role in regulating these enzymes' expression in human keratinocytes remains largely unknown, leaving an avenue for future research.

1,25$(OH)_2$D-treated keratinocytes displayed a significant reduction ($p < 0.05$) in free radical nitric oxide (·NO) [125]. This reactive nitrogen species is created from the nitric oxide synthase (iNOS) enzyme in the skin, which is induced in a UV radiation-dependent manner. When combined with superoxide, the radical ·NO generates a cytotoxic oxidant, peroxynitrite ($ONOO^-$), causing DNA damage and oxidative stress [132].

4.4 Vitamin D and Matrix Metalloproteinases (MMPs)

MMPs degrade collagen, thus challenging the integrity of the skin. Recent research has provided evidence for the protective role of calcipotriol against MMPs. The dose-dependent suppression of mRNA and proteins in the

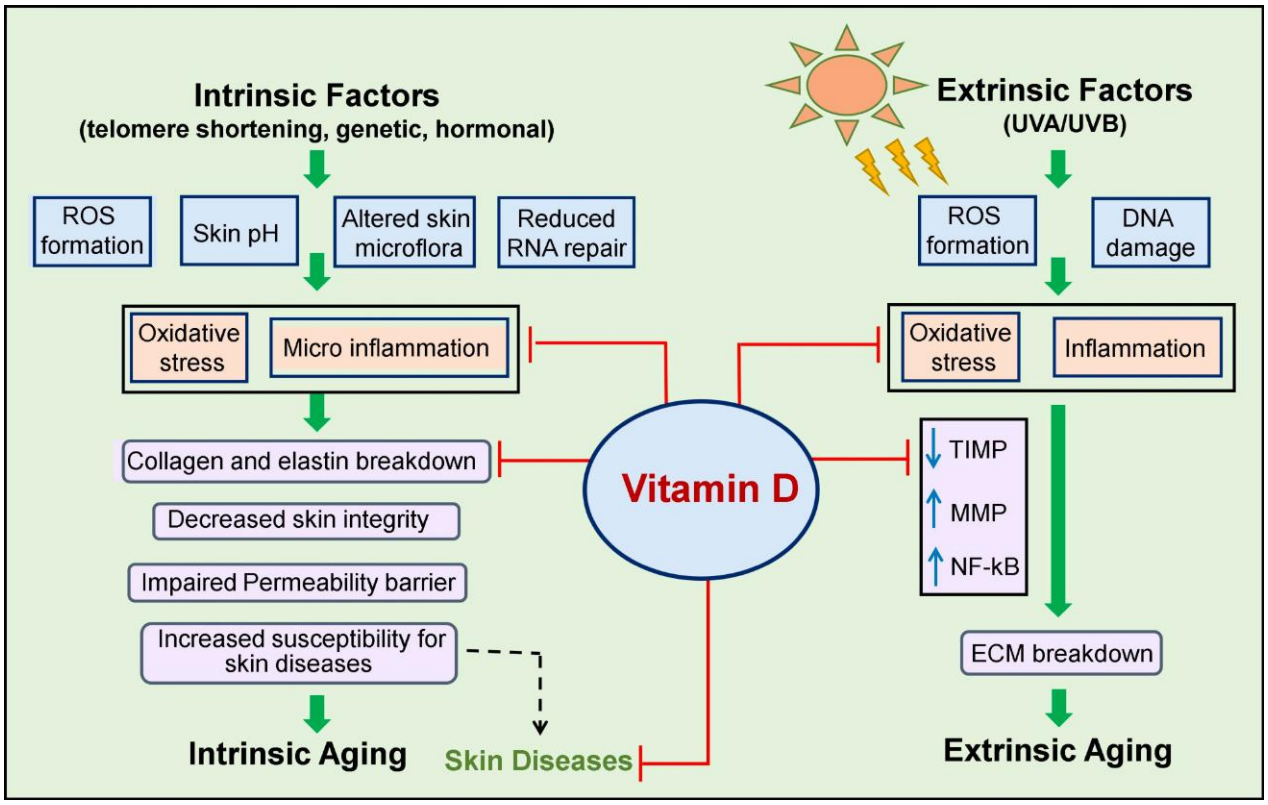

Fig. 4. The impact of Vitamin D against intrinsic and extrinsic skin aging and age-associated skin diseases. ECM, extracellular matrix; ROS, reactive oxygen species; UVA, ultraviolet A; UVB, ultraviolet B; TIMP, tissue inhibitor metalloproteinase; MMP, matrix metalloproteinase; NF-κB, nuclear factor kappa B.

MMP-9 and MMP-13 families by calcipotriol has been shown in a human squamous cell carcinoma (SCC) cell line [133]. Similar experiments using other cell lines have provided evidence of vitamin D's protective role against MMPs. Stimulation of human lung fibroblast (HFL-1) cells with interleukin-1β (IL-1β) promotes MMP-9 production and mRNA expression, while trypsin converts MMP-2 and MMP-9 into active forms. The expression of MMP-9 mRNA and activation of MMP-2 and MMP-9 are significantly reduced by 1,25(OH)$_2$D (100 nM) and 25(OH)D (100 nM). IL-1β suppresses the mRNA expression of TIMP-1 and TIMP-2, but vitamin D, including 25(OH)D and 1,25(OH)$_2$D, can notably counteract this inhibition caused by IL-1β. As a result, there is a reduction in the activity of MMPs. IL-1β inhibits the mRNA expression of TIMP-1 and TIMP-2, but vitamin D, 25(OH)D, and 1,25(OH)$_2$D can significantly reverse the IL-1β mediated inhibition of TIMP-1 and TIMP-2 leading to less active MMPs [134].

Li *et al.* [135] investigated the possible impact of vitamin D on articular cartilage degradation by MMPs using the rat vitamin D deficiency model and rat articular chondrocyte cells. Rat articular cartilage under vitamin D deficiency displayed elevated MMP-9 and MMP-13 expression and treating with 1,25(OH)$_2$D reversed this effect. Supplementation with TNF-α or phorbol-12-myristate-13-acetate (PMA) further induces the production of MMP-9 and MMP-13 in the articular chondrocytes, and this effect is subsequently reversed by treatment with 1,25(OH)$_2$D *in vitro* [135].

5. Vitamin D Against Inflammation

Recent research has investigated the protective role of vitamin D against autoimmune diseases. A randomized controlled trial involving 25,871 patients with autoimmune diseases observed that vitamin D supplementation over five years could reduce the risk of autoimmune diseases by 22% [136].

Calcitriol helps counteract the inflammatory responses caused by UV damage. It reduces the levels of suppressive inflammatory cytokines such as TNF, IL-1, IFN-gamma, and IL-2α, while increasing anti-inflammatory cytokines IL-4 and IL-10 derived from Th2 and Tregs, respectively [137,138]. Vitamin D also downregulates the differentiation of pro-inflammatory T helper-1 (Th1) and Th17 lymphocytes [139]. In contrast, a reduction in vitamin D$_3$ is associated with aging and may contribute to the increased inflammation and occurrence of diseases in the aged skin [140]. The impact of vitamin D against intrinsic and extrinsic skin aging and age-associated skin diseases is illustrated in Fig. 4.

Table 2. Common dermatological diseases among the elderly.

Category	Condition/Disease	Source
Fungal infections of skin	Tinea pedis	[143,144]
	Candidiasis	[145]
Fungal infections of nails	Onychomycosis	[146]
	Onychauxis	[147]
Inflammatory scaling dermatoses	Eczema	[148]
	Contact dermatitis	[149]
	Seborrheic dermatitis	[150]
Diseases of the dry skin	Xerosis	[151,152]
	Pruritus	[153]
Vascular disorders	Pressure ulcers	[154]
	Rosacea	[155]
Cutaneous autoimmune disorders	Bullous pemphigoid	[156,157]
	Benign mucous membrane Pemphigoid	[158]
Pigmentation disorders	Guttate hypomelanosis	[159]
Benign tumors	Seborrheic keratosis	[150]
Premalignant cutaneous lesions and skin cancers	Actinic keratosis	[160]
	Basal cell carcinoma	[161]
	Squamous cell carcinoma	[162]
	Melanoma	[163,164]
Viral infections	Herpes zoster (shingles)	[165]

6. Age-Associated Skin Diseases

With advancing age, the likelihood of developing skin conditions tends to increase. One study estimated that 50% of otherwise healthy older adults experience cutaneous diseases at some part of their adult life [141]. Cutaneous disorders can be painful, uncomfortable, and disfiguring, causing considerable physical and emotional distress in older people. They can negatively affect the appearance of already-aged skin, harming self-confidence and promoting self-isolation and social withdrawal. Skin diseases can also interfere with daily activities, decreasing the quality of life in aged populations [142]. The progressive immunosenescence contributes to the increased severity of infections associated with aging. The most common immunosenescence-associated diseases in geriatric populations are listed in Table 2 (Ref. [143–165]).

6.1 Vitamin D Protects Against Skin Diseases in the Elderly

The World Health Organization estimates that over 2 billion people worldwide suffer from deficiencies in essential vitamins and minerals [166]. Geriatric patients exhibit a higher prevalence of skin diseases and are generally low in serum vitamin D levels [167]. Recent studies have reported that vitamin D may play a role in protecting the skin against various diseases [168–171].

6.2 Vitamin D Enhances Innate and Adaptive Immunity

Infections are common in aged skin; vitamin D regulates innate and adaptive immunity, protecting the skin from infections. Calcitriol is essential for adequately functioning immuno-modulating cells, such as T and B lymphocytes, monocytes, macrophages, and dendritic cells [172]. It directly stimulates the production of antimicrobial peptides, such as cathelicidin and β-defensin 2, and other proteins to control microbial infections [173]. The effect of vitamin D on immunity has been critically evaluated in the review by Wimalawansa SJ [138].

6.3 Fungal Infections

A continuous layer of microbes inhabits human skin. These microbes reside in the epidermis, dermis, and skin-associated glands and follicles, forming a diverse community known as the ‘normal skin microbiota’. Natural skin microbiome consists predominantly of bacterial species belonging to *Actinobacteria*, *Firmicutes*, *Proteobacteria*, and *Bacteroidetes*, and fungi belonging to *Ascomycota* and *Basidiomycota* [174]. Comparative studies have suggested age-related changes in the diversity and abundance of the skin microbiome and shown that any alterations to the native microbiota influence disease risk [175].

Cutaneous fungal infections are prominent among the aged populations. Factors including keratinocyte retention due to slower cell turnover, poor barrier function, and im-

munosenescence increase these infections [176]. Dermatophytosis, cutaneous candidiasis, and onychomycosis of the toenails are common fungal diseases affecting older people. Although direct studies investigating the role of vitamin D in combating fungal skin infections are lacking, there is a substantial amount of evidence proving the antifungal potential of vitamin D, as discussed below.

Vitamin D exhibits direct antifungal activity against the invasive fungus *Cryptococcus neoformans*. This fungus causes acute and chronic infections, including cryptococcal meningitis in humans. The broth microdilution assay indicates that vitamin D_3 inhibits the fungus at a minimum inhibitory concentration (MIC 90) of 0.4 mg/mL. Vitamin D-induced intracellular ROS accumulation, altered cell membrane permeability, and compromised cell wall integrity in *C. neoformans* are the proposed mechanisms of fungal inhibition. Further, vitamin D reduces fungal cell adhesion and hydrophobicity while inhibiting biofilm formation in different *C. neoformans* developmental stages. The *in vivo* studies involving *G. mellonella* larval infection model demonstrated significantly reduced fungal burden in the vitamin D-treated group with enhanced survival of *G. mellonella* larvae [177].

Vitamin D_3 also exhibits antifungal activity against several Candida species, including *Candida albicans* (ATCC 10261), *C. krusei* (ATCC 6258), *C. tropicalis* (ATCC 750), *C. glabrata* (ATCC 90030), *C. dubliniensis* (CBS 8501), and *C. parapsilosis* (ATCC 4344) with MIC ranging from 1–128 µg/mL. Further, it showed a significant reduction in *Candida* biofilm formation of up to 88% at 60 µg/mL with an IC_{50} value of 7.5 µg/mL [178]. According to a study by Lei *et al.* [179], vitamin D_3 exhibited anti-Candida activity against standard and clinically isolated Candida species, with 90% growth inhibition achieved at a concentration of 0.4 mg/mL. The initiation, development, and maturation processes of biofilms in *Candida albicans* were also significantly affected. Reverse transcription-quantitative PCR analysis of vitamin D_3 exposed *C. albicans* ATCC MYA-2876 cells proved the involvement of vitamin D_3 in carbon metabolism, biogenesis of ribosomes, and biosynthesis of enzymes. A recent *in vivo* study conducted in IAC mouse models demonstrated that the fungal burden in the liver and kidney was reduced from day 3 to 14 with daily intraperitoneal treatment of high dose vitamin D_3 (24,000 IU) [179].

A randomized, placebo-controlled clinical trial involving 416 pediatric patients between 12 months and five years has also provided evidence for the reduction of Candida infections upon supplementation of 300 IU/Day vitamin D in a yogurt drink. The prevalence of Candidaemia and Candiduria was significantly reduced in the vitamin D-treated group compared to the placebo group [180]. Finally, several studies have reported the role of vitamin D in enhancing host pulmonary resistance to the fungal pathogen *Aspergillus fumigatus* since vitamin D regulates the autophagy and Treg cells involved in *A. fumigatus* infection [181–184].

6.4 Urticaria and Pruritus

Dry skin (xerosis) and pruritus are common dermatological conditions affecting most elderly people. It is speculated that pruritus affects virtually all individuals by the time they reach eighty years of age [185]. Chronic urticaria is another common allergic skin condition that causes itchy wheals lasting six weeks or more [186]. Multiple studies have examined the importance of serum vitamin D levels and the effects of vitamin D supplementation on these diseases [187–189].

In a retrospective case series, 57 patients with low vitamin D levels [25(OH)D <32 ng/mL] and pruritus, rash, and urticaria/angioedema were treated with 50,000 IU weekly doses of vitamin D for 8 to 12 weeks, followed by daily supplementation [168]. In the vitamin D treatment group, 70% (40/57) of patients achieved complete resolution of symptoms in a mean time of 4.2 weeks. The patient group who responded to vitamin D treatment had significantly lower mean 25(OH)D levels than the non-responsive treated group (mean 25(OH)D of 16.8 ng/mL *vs.* 20.9 ng/mL, $p = 0.02$, unpaired *t*-test). Symptom recurrence was observed in the patients who acquired vitamin D insufficiency in the following months [168].

A randomized case-control study involving 192 patients with chronic urticaria (CU) observed that vitamin D deficiency [25(OH)D <20 ng/mL] or insufficiency (<30 ng/mL) was present in 91.3% of CU patients. Vitamin D_3 supplementation combined with antihistamines and systemic corticosteroids for six weeks significantly improved CU patients' 5-dimension itch and visual activity scores [190]. Li *et al.*'s meta-analysis [191] concluded that the urticarial population had reduced serum 25(OH)D levels by 9.35 ng/mL compared with healthy individuals. Highly significant improvements in the urticarial severity score were detected in vitamin D-supplemented studies [191]. Pooled results from randomized controlled trials observed a significant reduction in severity by –3.63 using a dosage of about 4000 IU daily for 12 weeks. The results from repeated measure trials observed a reduction of clinical urticarial score by –1.54 with a daily supplementation of 7000–20,000 IU vitamin D for 6–12 weeks [191].

6.5 Atopic Dermatitis

Atopic dermatitis (AD) is an inflammatory, pruritic skin disease commonly occurring among pediatric and elderly (>65 years old) populations. The presentations and associated clinical signs differ depending on the age, duration, and complications of eczema [175]. Dry skin (xerosis) and pruritus are significant clinical symptoms present universally among AD patients.

Recent research has demonstrated a link between low serum vitamin D levels and atopic dermatitis. In a meta-analysis of eleven studies, a mean difference of –14 nmol/L 25(OH)D (95% CI –25 to –2) was observed in the AD patient group compared to healthy controls [192]. Another study showed that 84.3% of Bangladeshi children and young adults living in London with eczema had deficient or insufficient 25(OH)D levels. The research revealed a correlation between 25(OH)D deficiency and worse eczema severity among the study population [193].

Multiple studies have identified vitamin D supplementation as a promising treatment for AD. A meta-analysis of three trials identified that the supplementation of vitamin D significantly lowered scores on the scoring atopic dermatitis (SCORAD) by 11 points (95% CI –13 to –9, $p < 0.00001$). The result surpassed the minimal clinically significant difference of 9 points. The selected studies for this analysis maintained 1500–1600 IU/daily as the mean weighted dose. Better outcomes were achieved in trials lasting at least three months [192]. Several other studies involving pediatric, mixed, and adult populations have observed significant improvements in the clinical outcomes of AD patients with vitamin D supplementation [194–201]. However, in a randomized, placebo-controlled trial with 101 pediatric patients, weekly vitamin D supplementation did not affect the severity of AD or type 2 immunity biomarkers compared to placebo [202].

6.6 Seborrheic Keratosis (SK)

Seborrheic keratosis is a common slow-growing, non-cancerous skin growth, usually appearing in sun-exposed areas of the elderly population [169,203]. SK is typically removed via surgery and other methods, including liquid nitrogen freezing and laser therapy. Various gene mutation studies and the utilization of topical vitamin D analogs such as Calcitriol evidence an association between vitamin D deficiency and SK [203,204].

In a clinical study carried out by Mitsuhashi *et al.* [170], when 116 SK patients were treated with topical vitamin D_3 ointments (tacalcitol 2 µg/g, calcipotriol 50 µg/g or maxa-calcitol 25 µg/g) for 3- to 12-months, 35 (30.2%) patients showed 100% or more than 80% decrease in the tumor volume, while 54 (46.6%) patients achieved a volume reduction between 40–80%. A Serbian study treating 12 patients with facial solitary seborrheic keratosis using 0.005% calcipotriol ointment for 3–8 months resulted in a complete regression of the lesions [169].

Finally, 30 adult SK patients (mean 52.7 $\pm$ 14.04 years) were instructed to apply calcipotriol 50 µg/g twice daily for 12 weeks, after which more than 80% reduction in the diameter of the tumor was observed in 76.7% of lesions [205]. However, Herron *et al.* [206] failed to observe significant clinical improvements in SK when using 0.005% calcipotriene for four months. Given these mixed findings, additional clinical studies are needed to determine the potential benefits of vitamin D for SK.

6.7 Rosacea

Rosacea is an age-related chronic inflammatory skin condition mainly affecting facial skin, characterized by transient or persistent redness (erythema), telangiectasia, swelling, and lesions, including papules and pustules [207, 208]. Several studies reported an association between low vitamin D levels and the occurrence of rosacea. A study conducted by Park *et al.* [209] observed significantly reduced average serum 25(OH)D levels in rosacea patients than healthy controls (12.18 $\pm$ 5.65 vs. 17.41 $\pm$ 6.75 ng/mL, $p = 0.001$). A cross-sectional population-based cohort study utilizing UK-based 370,209 individuals supported an inverse correlation between the risk of rosacea and serum 25(OH)D level. The findings of this study reported a 23% reduction in the risk of rosacea with each increment in standard deviation in the serum 25(OH)D levels [210]. Contrary to these findings Akdogan *et al.* [211] observed higher vitamin D levels in the rosacea patients compared to healthy controls (12.9 $\pm$ 6.8 ng/mL *vs.* 10.5 $\pm$ 3.7 ng/mL, $p < 0.001$). Supporting the Akdogan *et al.* [211], a study conducted by Ekiz *et al.* [207] involving 44 rosacea patients also witnessed higher serum vitamin D levels in rosacea patients (21.4 $\pm$ 9.9 *vs.* 17.1 $\pm$ 7.9 ng/mL). No recent attempts have been reported on supplementation of vitamin D as a treatment for rosacea. Further studies with well-controlled randomized controlled trials (RCTs) are necessary to evaluate the impact of vitamin D on rosacea [212].

6.8 Vitiligo

Vitiligo is an autoimmune condition characterized by skin-depigmented white patches due to epidermal melanocyte damage [213,214]. Although the onset of vitiligo is most common in childhood or young adults, late-onset has also been reported in adults [215]. Cytokines play a crucial role in the development and progression of this disease. Reduced vitamin D levels may significantly contribute to the development of vitiligo by influencing Th1- and Th17-related immune responses [216]. Many studies with controversial results have investigated the association between vitamin D deficiency and vitiligo [217–221]. In a population-based study, no significant difference was observed when serum vitamin D levels were compared in patients with vitiligo and healthy controls [217]. Similarly, a significant difference was not detected between the patients and controls in studies conducted in Jordan [218] and Turkey [219]. Contrary to that, a case-control study identified significantly lower vitamin D levels in 100 Indian vitiligo patients (16.170 $\pm$ 8.629 ng/mL) compared to healthy controls (25.49 $\pm$ 1.02 ng/mL) ($p = 0.0001$) [220]. A meta-analysis conducted by Varikasuvu *et al.* [221] included 31 studies and further observed a decreased circulatory vita-

min D level (standardized mean difference = –1.03; $p <$ 0.0001) in vitiligo patients. A study involving Caucasian adult patients with vitiligo reported vitamin D deficiency ($\leq$20 ng/mL) (p = 0.036) or insufficiency (21–29 ng/mL) (p = 0.041) associated with active vitiligo, whereas the stability of the disease and re-pigmentation were associated with vitamin D sufficiency (30–100 ng/mL) (p = 0.043) [222].

The efficacy of vitamin D supplementation as an option for enhancing the success of laser-based treatments has been investigated in treating vitiligo. Intramuscular cholecalciferol injection could enhance the therapeutic effects of the excimer laser in vitiligo patients with low vitamin D levels (<20 ng/mL) [223]. In a meta-analysis, Liu *et al.* [224] concluded that supplementation of either tacalcitol or calcipotriol could enhance the efficacy of the narrowband ultraviolet B treatment compared to phototherapy alone.

6.9 Skin Cancers

Recent studies using *in vitro* cell lines, tissues, and animal systems have proven the protective role of vitamin D against various malignancies [225–227]. A daily intake of 1500 international units of vitamin D has been found to lower cancer mortality rates among men in the US by 30% [228]. However, conflicting results exist on the role of vitamin D against skin cancer. Patients who have acquired higher vitamin D levels through extended sun exposure are at an inevitably greater risk of developing skin cancer. This should be considered when evaluating the association between vitamin D and skin cancers.

6.10 Melanoma Skin Cancer

The term 'melanoma' refers to aggressive malignant tumors originating from melanocytes. Upon exposure to UV radiation, genetic alterations activate oncogenes, deactivate tumor suppressor genes, and obstruct DNA repair. Consequently, unchecked growth of melanocytes occurs, causing melanoma [229].

The association between melanoma skin cancer and serum vitamin D levels is controversial. Many studies have identified an association between lower plasma vitamin D levels and (1) the development of melanoma, (2) an increase in the severity of the malignancy, and (3) a reduced survival rate in metastatic melanoma patients [230–235].

In a retrospective study, higher 25(OH)D levels were associated with lower Breslow thickness of the melanoma at the diagnosis (p = 0.002) and better survival [236]. The highest survival was observed in the intermediate BMI group (24.9 to 29.9), which had the highest vitamin D levels (55 nmol/L). Previous research has observed the loss of vitamin D receptor expression in the cytoplasm and the nucleus of cutaneous melanoma (CM) cells. Vitamin D receptor expression negatively correlates with tumor progression; metastatic melanomas show the lowest cytoplasmic receptor staining out of all types of melanoma. The lack of VDR expression correlated to shorter survival of the patients [237,238]. However, conflicting evidence also exists [239,240]. A recent meta-analysis reported that each 12 ng/mL increment in 25(OH)D level was linked to a 42%, 30%, and 41% increase in cutaneous melanoma, keratinocyte cancer, and basal cell carcinoma, respectively [240]. Further evaluation is necessary to confirm whether increased safe sun exposure would reduce these risks.

6.11 Non-Melanoma Skin Cancer (NMSC)

Among skin cancers, non-melanoma skin cancers are the most common type of skin malignancy, particularly in fair-skinned populations of European descent. Most NMSCs are keratinocyte skin cancers, including basal cell carcinoma and squamous cell carcinoma [241]. Previous investigations into the role of vitamin D on NMSC have provided mixed results.

6.12 Basal-Cell Carcinoma (BCC)

Basal cell carcinoma is the most common type of skin malignancy worldwide [242]. UVB radiation has been identified as the most critical risk factor for BCC, especially for Fitzpatrick I, II, and other light skin types [243]. Based on a study conducted in South Africa of BCC and SCC patients, 49.5% had deficient (<20 ng/mL), and 41.3% had insufficient vitamin D levels. Moreover, in this study, female gender was identified as a risk factor for vitamin D deficiency (p = 0.047) along with the winter season ($p <$ 0.001) [244].

In a comprehensive three-staged study involving 496 patients (mean age: 69 years), Ince *et al.* [171] observed that a serum vitamin D_3 level above 25 ng/mL could significantly reduce the recurrence rates of BCC. In a study conducted with a cohort of Latvian patients with different primary and recurrent BCC of the head and neck, 94.9% of patients were deficient in vitamin D. Furthermore, an inverse association was observed between serum vitamin D levels and tumor size [245]. When testing in the murine ASZ001 BCC line, potent antitumorigenic activity was detected when $1,25(OH)_2D$, $1,20(OH)_2D_3$, $1,20,23(OH)_3D_3$, $1,20,24(OH)_3D_3$, $1,20,25(OH)_3D_3$ and $1,20,26(OH)_3D_3$ hydroxy derivatives of vitamin D were supplemented. The classical and CYP11A1-derived D_3 hydroxy derivatives, including $1,25(OH)_2D_3$, $1,20(OH)_2D_3$, and $20(OH)D_3$, inhibited the expression of glioma-associated oncogene 1 (GLI1) and β-catenin in ASZ001 cells, providing a mechanism for this anticancer potential [246].

However, controversial studies report increased BCC risk at high serum vitamin D_3 levels. Liang *et al.* [247] reported that the women with >31.4 ng/mL 25(OH)D exhibited more than a 2-fold increased risk of BCC when compared to women with >20.4 ng/mL 25(OH)D ($p < 0.0001$). A linear dose-response meta-analysis by Mahamat-Saleh *et al.* [240] showed that every 30 nmol/L increment of 25(OH)D was linked with a 41% increase in BCC. A recent review by Abdelwahab *et al.* [248] suggested keeping

the vitamin D_3 level between 15–30 ng/mL for a safer balance. In a study that evaluated the effect of body mass index and 25-hydroxy-vitamin D level on BCC using Mendelian randomization, the authors concluded that vitamin D levels may not be casually associated with the risk of BCC [249].

6.13 Squamous-Cell Carcinoma (SCC)

In a systematic review and meta-analysis of BCC and cutaneous squamous-cell carcinomas (cSCC), Caini *et al.* [241] suggested a lack of a strong association between the serum vitamin D level and the NMSC risk. Moreover, a statistically significant association between 25(OH)D concentrations and cSCC was not detected among 1192 kidney transplant patients. Another study by de Gruijl *et al.* [250] observed a clear trend of higher 25(OH)D concentrations with the development of cSCC, possibly linked with the higher level of UV exposure promoting carcinogenesis. However, the intermittent supplementation of cholecalciferol has been proven helpful in enhancing photodynamic therapy-based treatments for SCC [251]. Therefore, further research is needed to uncover the potential of vitamin D supplementation as a monotherapy and/or in combination with other treatments for SCC.

7. Conclusions

The world population is aging, and there is a growing interest in understanding the physiological changes associated with advanced age. The skin undergoes intrinsic age-associated natural changes, such as telomere shortening, reduced DNA repair, oxidative damage to biomolecules, hormonal changes, immunosenescence, inflammation, and damage to ECM components. Extrinsic or environmental factors, such as UV radiation exposure can also cause DNA damage, oxidative stress, inflammation, ECM degradation, pigmentation changes, hyperkeratosis, and altered cell signaling, leading to "photo-aging". Both intrinsic and extrinsic aging contribute together to the aged appearance of the skin. The physiological, biochemical, and functional changes that occur with aging also contribute to the high prevalence of skin diseases in older people. Both skin aging and cutaneous diseases can impose a physical and psychological burden on geriatric populations, reducing their quality of life.

Despite causing photo-aging, UVB radiation also induces the cutaneous synthesis of vitamin D. Numerous beneficial effects of vitamin D on human health have been reported over the past 15 years [12,13]. However, the exact impact of this vitamin on skin aging remains poorly understood. Previous research has evidenced the potential of vitamin D derivatives to protect the skin by acting against various aging mechanisms, including oxidative stress, inflammation, activation of MMPs, and degradation of collagen and elastin. Furthermore, Vitamin D deficiency is a risk factor for various dermatological conditions. Studies suggest maintaining adequate levels of vitamin D to protect against the most common age-associated skin diseases. Maintaining the recommended vitamin D concentrations (above 40 ng/mL) via safe sun exposure or supplementation [17,20] should be considered an effective and affordable strategy for maintaining overall skin health.

Abbreviations

ECM, extracellular matrix; UV, ultraviolet; 25(OH)D, 25-hydroxyvitamin D; $1,25(OH)_2D$, 1,25-dihydroxyvitamin D/calcitriol; VDR, vitamin D receptor; CTR, calcitriol receptor; DBP, vitamin D binding protein; MPs, matrix metalloproteinases; ROS, reactive oxygen species; NF-κB, nuclear factor kappa B; AP, activator protein; TGF, transforming growth factor; Nrf2, Nuclear erythroid 2-related factor; Keap, Kelch-like ECH-associated protein; IL, Interleukins; CSF, colony-stimulating factors; TGF, transforming growth factor; $1,20(OH)_2D_3$, 1,20-dihydroxyvitamin D; SOD, superoxide dismutase; SCC, squamous cell carcinoma; TIMP, tissue inhibitor of metalloproteinase; TNF, tumor necrosis factor; CU, chronic urticarial; AD, atopic dermatitis; SK, seborrheic keratosis; IU, international units; BCC, basal cell carcinoma; NMSC, non-melanoma skin cancer.

Author Contributions

SSA: Conceptualization, writing-original draft, review and editing. GAA: Writing-original draft, conceptualization, review, and editing. SJW: Conceptualization, writing-original draft, review, and editing. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

The authors would like to thank Dr. Jacob Hogins for reviewing and editing the grammar and language of the manuscript.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

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