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Role of antioxidants in skin aging and the molecular mechanism of ROS: A comprehensive review

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ABSTRACT

Skin aging is a multifaceted and gradual process influenced by both internal and external factors, including environmental stressors. These two mechanisms contribute to oxidative stress, triggered by ROS, which accelerates the aging of the skin. UV exposure increases the production of ROS in cells, which collectively contribute to the various skin changes linked to aging. However, the skin has a sophisticated antioxidant defense system that shields it from oxidative damage caused by both internal and external factors. The use of topical antioxidants have been shown to shield the skin from harmful free radicals generated intrinsically by regular cellular metabolism or as a result of UV light exposure. This review focuses on the assessment of the injury environmental factors cause to the skin, molecular mechanism of ROS in the skin aging, and the use of antioxidants to prevent that damaging and producing a protection against UV radiation from environmental factors. The systematic search was done for eligible articles which including in vivo and in vitro studies from studies between (1997 until 2024).

1. Introduction

Skin is the largest organ in the body, which serves as the main barrier between the internal and exterior environments, shielding the body from radiation, chemicals, microbes, pollutants, and pressure. It is composed of three layers: epidermis, dermis, and subcutaneous tissue. As the skin ages, these layers degenerate, with the dermis showing the most visible alterations (Gallo, 2017; Poon et al., 2015). Skin aging is caused by the gradual decline and eventual stoppage of keratinocyte and fibroblast cell division within the skin. Skin becomes less elastic and drier as a result of denaturing the extracellular matrix, which leads to the development of wrinkles (Lee et al., 2021b; Shin et al., 2019). The main two factors that influence skin aging are intrinsic (genetic, chronological) and extrinsic (photoaging). Both intrinsic and extrinsic aging are related to changes in the physical, morphological, and physiological features of the epidermis and dermis (Juliana et al., 2020; Koohgoli et al., 2017). Intrinsic skin aging, also known as natural aging, is caused by changes in skin elasticity as time passes. Ultraviolet (UV) radiation is a crucial extrinsic factor. Reactive oxygen species (ROS) are produced when biological macromolecules, such as lipids, proteins, and nucleic acids, interact with UV light. The primary mechanism is the direct absorption of UV radiation, which can excite and ionize molecules, leading to the formation of free radicals. This is particularly significant for nucleic acids, which can result in structural damage. Another important mechanism is photosensitization, where photosensitizers react with molecular oxygen upon activation, produces singlet oxygen and other ROS, amplifying oxidative damage within the cell (Di Meo et al., 2016). Lipid peroxidation is also a critical process initiated by UV radiation, where free radicals attack polyunsaturated fatty acids in cell membranes, generates lipid peroxides, which can propagate additional ROS, such as hydroxyl radicals and superoxide anions. Furthermore, proteins can undergo oxidative modifications due to ROS, leading to cellular stress and dysfunction. Finally, DNA damage induced by UV radiation can result in strand breaks and modifications of nucleobases, leading to an imbalance between ROS production and cellular antioxidant defense mechanisms (Fisher et al., 2002).

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Additionally, high ROS levels promote the growth of matrix metalloproteinases (MMPs), such MMP-1, which cleave and improperly bind collagen or elastin chains to decompose collagen and speed up the aging process of the skin (Lee et al., 2021a). Antioxidants are a critical category of pharmaceutical compounds that safeguard the skin from harmful free radicals generated by normal cellular metabolism, as well as from UV radiation and skin aging (Lim et al., 2022a; Rizwan, 2018).

This review article examines the impact of oxidative damage on both intrinsic and extrinsic skin aging. It discusses the advantages of antioxidants in postponing skin aging, along with the effects of both endogenous and exogenous antioxidants (Ergünol et al., 2024; Warraich et al., 2020).

1.1. Factors promoting skin aging

1.1.1. Environmental (Extrinsic) aging

Environmental aging, also known as extrinsic aging, refers to the aging of the skin induced by external factors in the environment like smoking, air pollution, UV radiation, and increased exposure to environmental conditions like extreme temperatures, dust, and smoke. Sun exposure, in addition to intrinsic variables, has been considered a cause of skin aging since 1969. UV radiation is the primary cause of extrinsic skin aging, accounting for over 80% of face aging (Matsumura and Ananthaswamy, 2004; Vierkötter and Krutmann, 2012; Krutmann et al., 2016). Lifestyle behaviors such as eating, exercise, and sleep patterns, as well as anxiety and illnesses, all have an impact on aging. Oxidative stress leads to various detrimental effects, including cellular damage, disruption of mitochondrial function, impairment of electron transport, degradation of ribosomes, DNA damage, telomere repair deficiencies, inflammation, compromised cell membrane integrity, immune system dysfunction, and an increased risk of cancer. UV rays from sunlight have the greatest destructive impact on skin of any external element, leading to photoaging (Kassis et al., 2023). The epidermis becomes brittle and less elastic. Dermis's tiny blood capillaries diminish in quantities, while the remaining blood vessels expand and become convoluted. Collagen is replaced by a thicker mass produced when elastic fibers deteriorate (elastosis). Even minor quantities of regular, habitual sun exposure may have long-term repercussions that intensify with time (Yousef et al., 2023; Baroni et al., 2012).

1.1.2. Biological (intrinsic) aging

Biological aging, also known as intrinsic aging, refers to the natural and inevitable process that occurs within the body over time. Intrinsic aging is triggered by various factors and results in physiological changes that occur progressively. These changes include the thinning of the skin, loss of elasticity, flattening of the epidermis-dermis boundary, and a significant reduction in the constituents of both the cellular structure and extracellular matrix within the dermis. Additionally, the dermal compartment undergoes atrophy, with fewer blood vessels in the dermis and capillary collapse. The number and functionality of sweat glands and hair follicles also decrease (Zhang and Duan, 2018). Structural proteins, organelles like mitochondria, and glycosaminoglycans-key components of the dermal ground substance are reduced. Maintenance of telomere structure, DNA repair, and other cellular functions decline. Furthermore, with chronological aging, hormonal balance and alterations occur (Fisher et al., 2002).

1.2. Molecular mechanisms of reactive oxygen species (ROS) in skin aging

To explain the molecular basis of skin aging, various models have been proposed. These include the theory of cellular senescence, a decline in cellular DNA repair capacity, telomere loss, extra-nuclear mitochondrial DNA point mutations, oxidative stress, an increased frequency of chromosomal abnormalities, single-gene mutations, reduced glycation, chronic inflammation, and more. Some experts suggest that the majority of these effects are driven by extrinsic factors, with only 3% of aging factors having an intrinsic origin (Table 1) (Fig. 1) (Zhang and Duan, 2018; Hussen et al., 2024a).

1 Oxidative Stress

ROS are believed to play a significant role in the modifications of the cutaneous extracellular matrix caused by both intrinsic aging and photoaging. Enzymatic and non-enzymatic processes are both involved in the production of ROS, which add to the total oxidative stress in biological systems. Numerous substances can generate ROS, including the electron transport chain of the mitochondria, proteins found in the ER and peroxisomal membrane, the Fenton reaction, and enzymes like nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, cyclooxygenases, lipoxygenases, and xanthine oxidases (Fig. 2) (Andrés et al., 2022; Sies et al., 2022). ROS can be categorized into two classifications: oxygen molecules characterized by the presence of an unpaired electron and oxygen molecules in an excited state. The first classification encompasses superoxide anion radicals (O_2^-), hydroxyl radicals (•OH), lipid peroxyl radicals (LOO•), and nitric oxide radicals (•NO). The second classification comprises singlet oxygen ($^1O_2$). These ROS are typically generated via various enzymatic pathways (Sies et al., 2022; Babior et al., 2002; Poillet-Perez et al., 2015). The oxidative pathway begins with the generation of lipid radicals and O_2^-, These molecules are either spontaneously transformed into hydrogen peroxide (H_2O_2) or processed by the enzyme superoxide dismutase (SOD). SOD facilitates the dismutation of O_2^- into oxygen (O_2) and hydrogen peroxide (H_2O_2), while catalase further degrades H_2O_2 into oxygen and water (H_2O) (Lim et al., 2022b). Together, SOD and catalase effectively scavenge ROS initiated by O_2. H_2O_2, which is more stable and able to cross the plasma membrane, can generate OH via the Fenton reaction in the presence of Fe^{2+} or Cu. Both hydroxyl radicals and $^1O_2$ oxidize the unsaturated bonds in lipids, resulting in the formation of lipid peroxides and aldehydes, such as 4-hydroxynonenal. Additionally, OH radicals and these aldehydes can react with protein amino acid residues, leading to the production of carbonylated proteins (Neha et al., 2019; Domínguez et al., 2019).

2 Inflammation

Sunburn is a disorder that develops when UVB light exposure causes the skin to become erythematous, or red and irritated. Numerous biochemical pathways mediate this inflammatory response, but NO and prostaglandin E2 (PGE2) are key players. Effective reduction of UVB-induced erythema has been demonstrated with the cyclooxygenase (COX) inhibitor indomethacin and the nitric oxide synthase (NOS) inhibitor NG-monomethyl-L-arginine (Zamora and Hidalgo, 2005). Although NO is classified as a reactive nitrogen species (RNS), it can affect inflammatory responses and is intimately associated with the generation of ROS. It participates in the signaling cascades that result in PGE2 synthesis, a crucial mediator of inflammation. By upregulating COX-2, a crucial enzyme involved in the creation of PGE2, ROS significantly contribute to the initiation of the inflammatory process. This increase highlights the interdependent functions of NO, ROS, and COX-2 in the inflammatory cascade caused by UVB exposure and contributes to the erythematous response seen in sunburn (Ansary et al., 2021).

3 Surface Oxidation of the Skin

An important component of skin health is oxidized squalene (also known as squalene monohydrope'roxide), particularly when environmental variables cause oxidative stress. The oxidation process, which causes inflammation and skin damage, can be started by smoking, pollution, and UV radiation exposure (Hussen et al., 2024b). Squalene oxidation is also encouraged by inflammatory skin disorders like acne, which compromises the integrity of the skin's barrier and overall health

Table 1
The effect of ROS on skin damage and skin aging.

Effect of ROS on skin	Skin Damage	Mechanism for Skin Aging	Ref.
Oxidative Stress	Accumulation of ROS leads to cellular damage and dysfunction	Oxidative stress, caused by DNA damage and telomere erosion, leads to cellular senescence, a long-term loss of cell proliferative capacity, accelerated by environmental factors like UV radiation	(Domínguez et al., 2019; Neha et al., 2019; Lim et al., 2022b; Poillet-Perez et al., 2015; Babior et al., 2002; Sies et al., 2022; Andrés et al., 2022)
Inflammation	Increased ROS levels can trigger inflammatory responses in the skin	ROS, including NO, induce skin erythema through prostaglandin E2 synthesis, upregulating COX-2 expression and stimulating inflammation	(Zamora and Hidalgo, 2005; Ansary et al., 2021)
Lipid peroxidation	By initiating oxidative stress, compromising cell membrane integrity, producing toxic byproducts, and promoting inflammation	ROS oxidize membrane phospholipids, causing lipid peroxidation and unsaturated lipid chains to form hydroperoxidised lipids and alkyl radicals, affecting membrane structure, fluidity, and lipoperoxidation.	(Hussen et al., 2024b; Rhie et al., 2001; Irato and Santovito, 2021)
Melanogenesis	ROS imbalance can affect melanin production, leading to pigmentation disorders	UV-induced ROS and RNS can stimulate skin melanogenesis, a melanin production process, leading to dermatological issues like melasma, hyperpigmentation, and actinic lentigo due to abnormal melanin production	(Uwa, 2017; Özkan et al., 2005; Darvin et al., 2006; Rattanawiwatpong et al., 2020; Glynn et al., 2007; Kamei et al., 2009; Trela-Makowej et al., 2022)
Skin Matrix	ROS promote the breakdown of collagen and elastin in the dermis	ROS trigger growth factors and cytokines, causing collagen degradation and inflammatory cytokines, attracting neutrophils, monocytes, and macrophages, contributing to skin aging and increased ROS production	(Pinnell, 2003; Santos et al., 2021; Al-Niaimi and Chiang, 2017; Ohshima et al., 2009; Chambial et al., 2013; Ernster and Dallner, 1995; Aaseth et al., 2021; Ayunin et al., 2022; Mortensen et al., 1997; Du et al., 2017)

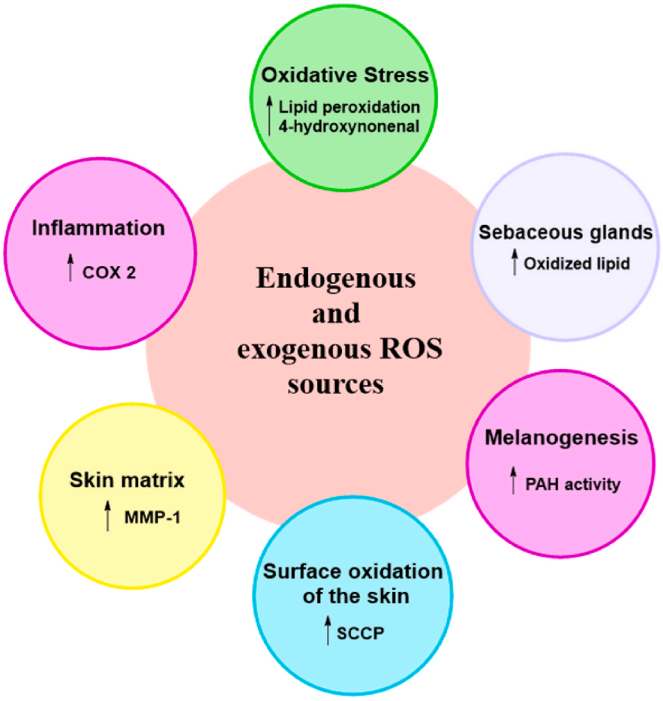

Fig. 1. The molecular mechanisms of reactive oxygen species (ROS) contribute to skin aging.

(Rhie et al., 2001). Understanding how the stratum corneum, carbonylated proteins (SCCP), and oxidized squalene interact is essential to comprehending the integrity and health of the skin. Lipids such as squalene are abundant in the stratum corneum, the skin's outermost layer. Carbonylated proteins and oxidized lipids, which are linked to skin aging and other conditions, can be produced as a result of oxidized squalene. This interaction emphasizes how protein modification, lipid oxidation, and general skin health are all related (Irato and Santovito, 2021).

4 Melanogenesis

Melanogenesis is the biological process by which melanocytes make melanin, the pigment that gives skin, hair, and eyes their color. The first step in this process is the enzymatic transformation of the amino acid tyrosine into melanin. Tyrosinase, the primary enzyme in this pathway, catalyzes the first stages of melanogenesis, such as the conversion of tyrosine to L-DOPA and the subsequent oxidation of L-DOPA to L-dopaquinone. The subsequent processing of L-dopaquinone can result in the production of either pheomelanin, a yellow/red pigment, or eumelanin, a brown/black pigment, contingent on the presence of particular substrates and enzymes (Uwa, 2017). ROS, which are byproducts of several cellular processes, such as mitochondrial respiration and the enzymatic reactions involved in melanin synthesis, are directly associated with the molecular mechanisms of melanogenesis. Tyrosinase and other melanogenic enzyme activities can cause a rise in ROS production during melanogenesis. Excessive ROS accumulation can lead to oxidative stress, which is harmful to skin cells and causes skin aging, even though ROS are involved in signaling pathways that can encourage melanocyte proliferation and melanin production (Özkan et al., 2005). The equilibrium between ROS generation and antioxidant defenses is upset in aging skin, resulting in inflammation, cellular damage, and a reduction in the skin's ability to regenerate itself. UV light and other environmental factors worsen this oxidative damage (Darvin et al., 2006; Rattanawiwatpong et al., 2020). Antioxidant studies highlight the role of ROS in melanogenesis. Administering *N*-acetyl cysteine, a precursor to glutathione (GSH), helps counteract the effects of UVB-induced increases in α-melanocyte-stimulating hormone (Glynn et al., 2007). Additionally, melanocytes activate metallothionein, an endogenous antioxidant, which inhibits melanogenesis (Kamei et al., 2009). Furthermore, H_2O_2 activates epidermal phenylalanine hydroxylase (PAH), an enzyme that converts the essential amino acid L-phenylalanine into L-tyrosine, thereby promoting melanogenesis by increasing the concentration of L-tyrosine, the precursor substrate for tyrosinase. A single modest dose of UVB radiation can boost PAH activity for up to 24 h, with this increase correlating positively with skin phototypes (I-VI). UVB light triggers PAH activation by generating H_2O_2, which is essential for UVB-induced melanogenesis (Trela-Makowej et al., 2022; Orabi et al., 2023).

Skin phototypes are classifications that describe how different skin types respond to UV radiation, including their susceptibility to sunburn and tanning ability. The Fitzpatrick scale, developed by Thomas B. Fitzpatrick in 1975, categorizes skin into six types based on melanin content and sun exposure reaction. Type I is pale white skin with freckles, blue or green eyes, and red hair, which burns and doesn't tan. Type II is fair skin with light eyes, burns easily and tans minimally. Type III is medium white, burns moderately, tans gradually, and Type IV is

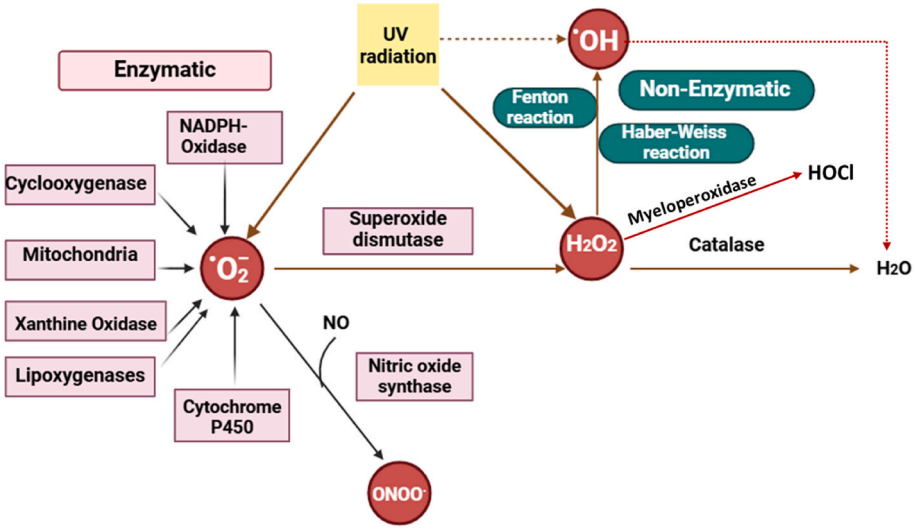

Fig. 2. Chemical enzymatic and non-enzymatic reactions generating ROS.

olive or light brown. Type V is brown skin that rarely burns and tans profusely (D'Orazio et al., 2013). The differences between these skin types are primarily based on their inherent melanin content and their responses to UV radiation. Lighter skin types (I and II) have less melanin, making them more susceptible to sunburn, while darker skin types (V and VI) have more melanin, providing better UV radiation protection and a lower risk of burning. Understanding these classifications is crucial for assessing risk factors for skin damage and cancer (Gupta and Sharma, 2019).

5 Skin Matrix

ROS have been linked to UV-induced skin aging and the development of wrinkles. Wrinkles often result from changes in the dermal matrix, such as increased collagen breakdown and decreased collagen production. UVA irradiation triggers the release of interleukin (IL)-1a and IL-6, which in turn stimulate MMP-1 formation in cutaneous fibroblasts (Pinnell, 2003; Santos et al., 2021). Oxidized lipids, such as linoleic acid hydroperoxide, further promote the activity of MMP-1 and MMP-3 (Al-Niaimi and Chiang, 2017). In addition, ROS trigger the activation of c-Jun N-terminal kinase (JNK) following UV exposure, which stimulates the production of MMP-1. ROS cause persistent phosphorylation of the epidermal growth factor receptor by blocking protein tyrosine phosphatase, which activates JNK (Ohshima et al., 2009). An in vivo study has shown that the accumulation of hydrogen peroxide (H_2O_2) in the skin, due to decreased catalase activity, directly enhances MMP-1 expression (Chambial et al., 2013). UV exposure further decreases new collagen production by altering activator protein (AP)-1, which is regulated by ROS and affects MMP-1 expression (Ernster and Dallner, 1995). Collagen production decreases in human dermal fibroblasts when they are exposed to ROS (Aaseth et al., 2021). However, extracellular thioredoxin can reverse the reductions in collagen production caused by UVA/UVB and infrared radiation (Ayunin et al., 2022). In scleroderma, a condition characterized by excessive collagen production, ROS not only regulate but also increase collagen synthesis. Skin fibroblasts from scleroderma patients produce higher levels of alpha1 (I) and alpha2 (I) collagen mRNAs and generate more O_2 and H_2O_2 compared to normal fibroblasts. N-Acetyl cysteine can block this increase in collagen mRNA expression (Mortensen et al., 1997). Additionally, sufficient nitric oxide (NO) levels stimulate heat shock proteins, which act as molecular chaperones in collagen production, enhancing collagen synthesis in cutaneous fibroblasts (Du et al., 2017).

6 Sebaceous Glands

The oxidative stress caused by UV radiation leads to increased concentration of cholesterol hydroperoxides, triglyceride hydroperoxides, and oxidized lipids, which in turn enhance the function of sebaceous glands and ultimately boost sebum production (Simioni et al., 2018). The Gram-positive anaerobic bacteria *Propionibacterium acnes* (*P. acnes*) produce coproporphyrin during the inflammatory phase of acne vulgaris. When *P. acnes* is exposed to UVA radiation, it produces singlet oxygen ($^1O_2$). This process is key to development of inflammatory acne lesions. The oxygen released by *P. acnes*-infected keratinocytes exacerbates the inflammatory reaction (Valko et al., 2006).

1.3. Antioxidant and skin aging

Antioxidants regulate autoxidation by disrupting the replication of free radicals or by hindering their production through various mechanisms. These compounds scavenge the species that trigger peroxidation, break the autoxidative chain reaction, neutralize $\bullet O_2^-$, and inhibit peroxide generation. The most effective antioxidants are those that can disrupt the chain reaction of free radicals. These antioxidants typically contain aromatic or phenolic rings, which enable them to provide hydrogen atoms (H•) to free radicals generated during oxidation. The radical intermediates are subsequently stabilized through the resonance delocalization of electrons within the aromatic system. Research shows that maintaining redox status of cell is essential for mitochondrial function and ROS-mediated signaling. A substantial decrease in intracellular GSH significantly increases mitochondrial ROS production and causes depolarization of the mitochondrial membrane (Forman et al., 2008). The polarization of the mitochondrial membrane is crucial in skin aging, as it influences cellular energy production and ROS regulation. The mitochondrial membrane potential is vital for the electron transport chain, generating ATP through oxidative phosphorylation. A healthy mitochondrial membrane polarization is essential for efficient ATP production in skin cells, including keratinocytes and fibroblasts (Martic et al., 2023). In fact, supplementing with exogenous antioxidants can reverse the enhancements in antioxidant gene expression and insulin sensitivity that exercise usually generates (Gęgotek and Skrzydlewska, 2022). Vitamins, minerals, carotenoids, cofactors, polyphenols, and glutathione are low-molecular-weight antioxidants that act as fundamental contributor in the antioxidant defense systems of cells and organisms. Ascorbic acid (vitamin C) and tocopherol (vitamin E) are key low molecular weight antioxidants that the human body cannot produce on its own. Additionally, several molecules synthesized within the human body also have antioxidant properties, such as, coenzyme Q, lipoic acid, taurine, keto acids, uric acid, melatonin, glutathione, and

melanin (Kwon et al., 2019). Among antioxidants, glutathione stands out as a major cellular protector. It safeguards cells from damage caused by ROS, including lipid peroxides, heavy metals, peroxides, and free radicals. Glutathione can neutralize ROS through both non-enzymatic and enzymatic reactions. The free thiol group in glutathion is responsible for its non-enzymatic antioxidant activity. Glutathione is considered a non-essential nutrient; the body can produce it from amino acids L-glutamic acid, L-cysteine, and glycine (Briganti and Picardo, 2003).

1.4. Endogenous antioxidants

The regulation of the antioxidant defense system in the skin is complex and varies between intrinsic aging and photoaging processes. Studies have shown that the activities of catalase and GSH reductase increase in the epidermis of both photoaged and naturally aged skin (Bickers and Athar, 2006). However, compared to young-looking skin, photoaged and aged skin has been found to have significantly lower levels of endogenous antioxidants, such as glutathione, ascorbic acid, and α-tocopherol. People's α-tocopherol levels decrease with age, and photoaged skin has extremely low levels due to oxidative damage from UV exposure (Sander et al., 2002). The levels of ascorbic acid also decrease with age; elderly individuals see a 40–60% decrease in ascorbic acid levels compared to younger individuals. This degradation hinders the skin's ability to create collagen and protect against oxidative damage, which speeds up the aging process. Glutathione levels in elderly skin decrease by 50% compared to younger skin. This decline is significant because it is necessary to protect skin cells from oxidative damage and maintain the redox balance in those cells (Tan et al., 2018). Both natural aging and UV exposure can deplete the skin's antioxidant defenses, leading to increased ROS generation and oxidative damage to proteins, lipids, and nucleic acids. Consequently, supplementing the skin with natural and plant-derived antioxidants is crucial for providing protection. Antioxidant molecules in the skin interact with ROS or their by-products to neutralize them or reduce their harmful effects. While ascorbic acid and GSH act as soluble antioxidants, vitamin E, being membrane-bound, can intercept free radical-mediated chain reactions. Administering agents that enhance tissue GSH levels, such as N-acetylcysteine, can protect against the damaging effects of ROS-generating agents (Uwa, 2017).

1.5. Antioxidant protection for skin aging

Antioxidants neutralize reactive molecules and counteract harmful free radicals, thereby protecting cells from both external and internal stresses and helping to prolong their lifespan and vitality. The skin relies on various natural enzymatic and non-enzymatic antioxidants to defend against free radical damage under optimal conditions. Non-enzymatic antioxidants include vitamin C, glutathione, vitamin E, coenzyme Q10, and alpha-lipoic acid. Enzymatic antioxidants encompass glutathione peroxidase, superoxide dismutase, and catalase. Inadequate antioxidant defense allows free radicals to contribute to skin aging (Michalak, 2022). It has been shown that incorporating additional antioxidants to the skin can improve its look, decrease inflammation, delay the aging process, and provide better protection against UV damage. The newest wrinkle-correcting cosmetic procedures employ plant extracts including acai berry, white and green tea, rosemary, and turmeric, as well as antioxidants like superoxide dismutase (SOD), vitamins C and E, and alpha-lipoic acid (Rovero et al., 2022). Botanical antioxidants have gained popularity for both topical and ingestible applications, with significant emphasis on their capability to decrease free radical-induced photo carcinogenesis and photo-aging. Skincare routines now consider topical antioxidants essential for comprehensive sun protection and beneficial for any anti-aging regimen. These antioxidants provide extensive benefits in protecting and improving UV-damaged and aging skin (Rattanawiwatpong et al., 2020).

Although antioxidants are frequently touted for their ability to prevent skin aging, study has shown that they have little or no impact on important signaling pathways including transforming growth factor-beta (TGF-β) and mitogen-activated protein kinase (MAPK), which are implicated in skin aging. Cellular reactions to stress and injury depend on these pathways, and preserving the integrity of the skin depends on their control (Fisher et al., 2002).

1.6. Common antioxidants with antiaging benefits for skin (see Table 2)

1.6.1. Vitamin E

Vitamin E is made up of eight structurally related lipophilic chromanol congeners. It commonly appears in foods as four tocopherols and four tocotrienols, each having saturated or three double bonds in their phytyl tails. Tocopherols and tocotrienols are categorized into α-, β-, γ-, and δ-forms based on the substitutions in their phenolic rings. The antioxidant function of tocopherols partly results from the hydroxyl group in the chromanol ring, which donates a hydrogen atom to neutralize free radicals (Glynn et al., 2007; Kamei et al., 2009). Tocopherol helps prevent various forms of oxidative stress by inhibiting the activation of H_2O_2, myeloperoxidase, and xanthine oxidase, as well as lipid peroxidation (Trela-Makowej et al., 2022; Pinnell, 2003) (Fig. 3).

1.6.2. Vitamin C

Ascorbic acid, commonly known as vitamin C, is one of the most prevalent water-soluble antioxidants (Fig. 3). Physiologically, ascorbic acid features four hydroxyl (-OH) groups that can provide hydrogen atoms to an oxidizing system. Due to the proximity of these OH groups to the carbon atoms, ascorbic acid is susceptible to chelating metal ions such as Fe^2. Ascorbic acid acts as a reducing agent, scavenging free radicals and neutralizing $\bullet O_2$. It also alters the equilibrium between ferric iron (Fe^{3+}) and ferrous iron (Fe^{2+}), scavenges oxygen, and inhibits oxidation (Santos et al., 2021; Al-Niaimi and Chiang, 2017). The decline in ascorbate levels associated with aging is complex and involves multiple cellular signaling pathways, including increased turnover, higher utilization, reduced cellular uptake, and decreased absorption/reabsorption (Ohshima et al., 2009). Additionally, ascorbic acid may provide prevention of cancer. High concentrations of ascorbic acid can induce cytotoxicity in cancer cells in vitro by eliminating most ROS generated from the oxidation of ascorbate to monodehydroascorbate and then to dehydroascorbate. Ascorbic acid plays various roles in maintaining physiological balance in humans. It acts as a cofactor for prolyl hydroxylase, an enzyme essential for hydroxylating prolyl residues in procollagen and elastin. Recent research has identified new functions of ascorbic acid, including its contribution to skin barrier formation by enhancing epidermal differentiation and stimulating blood flow through NO production. This is accomplished by making tetrahydrobiopterin, a cofactor for constitutive nitric oxide synthase (NOS), more stable (Chambial et al., 2013; Ernster and Dallner, 1995). The stabilization of NOS is crucial in the context of aging skin due to its role in maintaining vascular health and promoting skin repair processes. NO, produced by NOS, is a signaling molecule that plays a significant role in various physiological functions, including vasodilation, which enhances blood flow to the skin. This increased blood flow is essential for delivering nutrients and oxygen to skin cells, promoting cellular metabolism, and facilitating the removal of waste products. In aging skin, the production of NO tends to decline, leading to reduced blood flow and impaired skin function, which can exacerbate the visible signs of aging such as dryness, loss of elasticity, and increased wrinkle formation (Papaccio et al., 2022).

1.6.3. Coenzyme Q10

Coenzyme Q10 (CoQ10) is an endogenous antioxidant and rejuvenating substance that reduces UVA irradiation-induced DNA damage in human keratinocytes. CoQ10 hinders the production of MMP-1 (Fig. 3) (Aaseth et al., 2021; Ayunin et al., 2022; Mortensen et al., 1997).

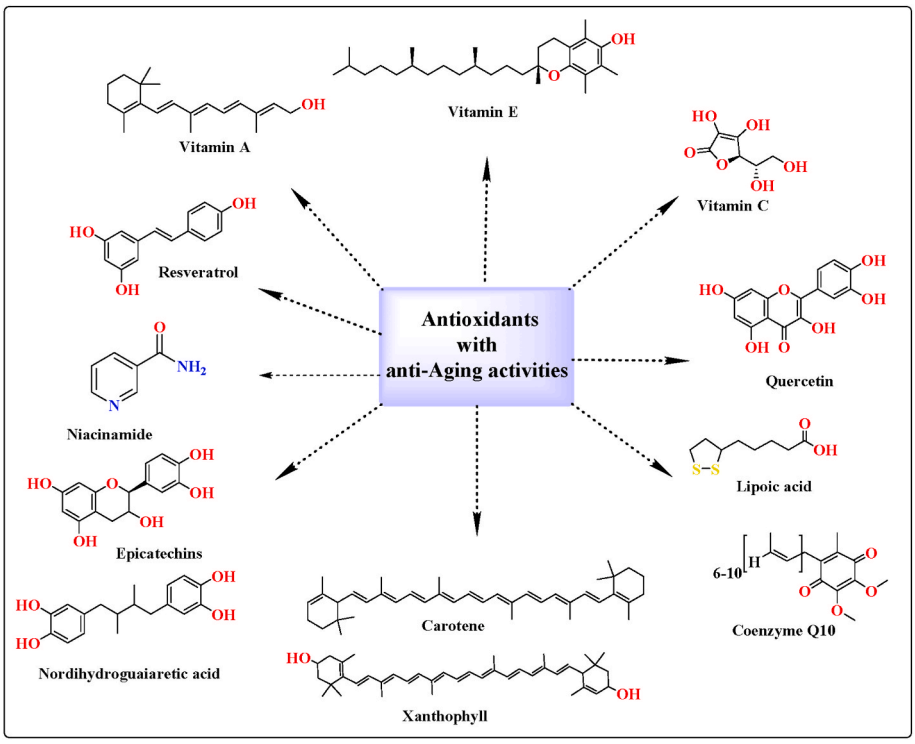

Fig. 3. Antioxidant chemical structures are known to have antiaging benefits for the skin.

1.6.4. Carotenoids

Carotenoids are natural pigments found in plants, algae, certain fungi, and bacteria, with spiders and red pea aphids being the only known animal producers. Typically, carotenoids absorb light ranging from 400 to 550 nm, resulting in their characteristic yellow, orange, or red hues. Carotenoids are categorized into carotenes and xanthophylls based on their chemical composition. The majority of carotenoids consist of tetraterpenoids, which are made up of atoms. Every carotenoid contains a polyisoprenoid structure consisting of a lengthy conjugated chain next to several double bonds, with a central double bond displaying nearly symmetrical properties. Oxygen-rich functional groups have the ability to modify this simple acyclic structure. The polyene structure's electron-rich conjugated system enables carotenoids to act as effective radical eliminator by extinguishing singlet oxygen and capturing peroxyl radicals (Du et al., 2017; Camera et al., 2009). The protective mechanisms of carotenoids in preventing UV-induced damage have been investigated in a model of UVA-irradiated human dermal fibroblasts to understand the mechanisms involved. Moderate levels of UVA exposure prompt fibroblast cell death; enhance oxidative stress by producing ROS; lower antioxidant enzyme levels; disrupt cell membranes; and trigger the production of heme oxygenase-1 (Tan and Norhaizan, 2019; Mutha et al., 2021) (Fig. 3).

1.6.5. Phenolic compounds

Phenolic substances like flavonoids (catechins, isoflavones, proanthocyanidins, and lutein) are examples of natural anti-aging chemicals. The contents include phenolic acids (benzoic, gallic, and cinnamic), anthocyanins, stilbenes, and other compounds derived from plants like fern block, rooibos, grapefruit, and red orange. Each of these substances has the capacity to prevent penetration. They have the ability to lessen radiation's absorption by the skin. The skin needs to control numerous signaling pathways, lower oxidative stress, and reduce inflammation in order to defend itself from UV rays (Tungmunnithum et al., 2018, AMIN HUSEEN, 2020; Deepika & Maurya, 2022; Salehi et al., 2018).

1 Resveratrol

A polyphenolic antioxidant with potent anti-inflammatory and antiproliferative properties, phytoalexin resveratrol (*trans*-3, 4′, 5-trihydroxy-stilbene) is also abundant in grape seeds (Fig. 3). One dose of resveratrol applied to a hairless prior to UVB light exposure, mice's skin developed the Skin edema, cyclooxygenase, and ornithine inhibition skin lipid peroxidation and decarboxylase induction (Sharifi-Rad et al., 2022; Bastianetto et al., 2010). Interestingly, human skin contains specific resveratrol binding sites, which can prevent mitochondrial malfunction and apoptosis delay in skin aging via keratinocytes. Resveratrol, HSP70 expression, and increased TNF- levels can modify cytokines like IL-6, IL-8, and other cytokines in human keratinocytes (Katiyar and Elmets, 2001).

2 Green Tea (Polyphenols)

Green tea contains polyphenolic compounds known as epicatechins, which are plant-derived molecules characterized by their phenolic structure. These compounds possess strong antioxidant and anti-inflammatory properties (Afzal et al., 2015; Prasanth et al., 2019). Research has shown that the topical application of green tea polyphenols affects UV-induced inflammatory indicators and biochemical pathways related to cell proliferation, inflammatory responses, and reactions to chemical tumor promoters. Several cosmetic companies incorporate the anti-aging properties of green tea polyphenols into their products. A notable polyphenol, epigallocatechin gallate (EGCG), has been found to significantly increase the minimal erythema dose to UV radiation and prevent disruption of the epidermal barrier when administered orally for 8 weeks. These results suggest that EGCG enhances the skin's tolerance to UV-induced stress (Xiao et al., 2022; Ullah et al., 2020).

3 Flavonoids

Flavonoids, which are polyphenolic secondary metabolites, are frequently ingested by humans through the consumption of plants. Flavonoids are the most researched category of polyphenols. The fundamental composition of flavonoid is a diphenyl propane framework,

Table 2
Common antioxidant compounds with natural sources, method of application, effect on intrinsic aging and extrinsic aging.

NO.	Antioxidants	Natural source	Method of application	Effect on intrinsic aging	Effect on extrinsic aging	Refs.
1	**Vitamin E**	Almonds, sunflower seeds, spinach, avocado, olive oil, wheat germ oil	Topically (serum, cream) orally	- Antioxidant Protection - Moisture Retention - Prevention of Lipid Peroxidation - Cellular Repair	- Photoprotection - Anti-inflammatory Properties - Reduction of Hyperpigmentation - Barrier Repair	He et al. (2023)
2	**Vitamin C**	Citrus fruits, berries, kiwi, bell peppers, broccoli, spinach, tomatoes	Topically (serum and cream)	- Collagen synthesis - Antioxidant protection - Reduction of fine line	- Reduction in Hyperpigmentation - Repair of Photoaging - Photoprotection	(Rattanawiwatpong et al., 2020; Bocheva et al., 2022)
3	**Coenzyme Q10**	Organ meats, fatty fish (salmon, sardines), spinach, oats, peanuts	Orally (dietary supplement) and topically (serum and cream)	- Boosts Cellular Energy Production - Prevents Collagen Breakdown - Improves Skin Renewal	- UV Protection - Improves Skin Elasticity - Reduces the appearance of fine lines - Reduces Environmental Damage	(Qian et al., 2023)
4	**Carotenoids**	Carrots, sweet potatoes, spinach, kale, tomatoes, peppers, mangoes	–	- potent antioxidant - Maintain skin cell integrity and prevents premature aging of skin cells - Collagen Preservation - Skin Repair and Regeneration	- Protection against UV-induced oxidative stress - Carotenoids inhibit excessive melanin production - Strengthen the skin barrier - Reduction of Inflammation	(Bakac et al., 2023)
5	**Resveratrol**	Red grapes, berries (blueberries, raspberries), peanuts, dark chocolate, Japanese knotweed	Orally (dietary supplement) and topically (cream, serum)	- **Anti-inflammatory Effects** - activates sirtuins, enzymes that play a role in cellular repair and longevity - Collagen Preservation	- Photoprotective and Anti-inflammatory Effects - Reduces Hyperpigmentation - maintaining the skin barrier and preventing signs of premature aging	(Hecker et al., 2022)
6	**B. Green Tea (Polyphenols)**	Green tea, matcha, black tea, white tea, oolong tea	Orally (dietary supplement) and topically (cream, serum)	- Promote skin health, reducing natural aging effects - Antioxidant Protection - Collagen Preservation	- UV Protection and Photoaging Prevention - Environmental Stress Protection - Reduction of Pigmentation - Strengthens Skin Barrier	(Menaa et al., 2014)
7	**Flavonoids**	Apples, berries (blueberries, strawberries), citrus fruits, onions, leafy greens (kale, spinach), peppers, nuts, seeds, parsley, tea, red wine	Topically (cream, serum)	- Antioxidant and anti-inflammatory properties - Stimulate the synthesis of collagen and inhibit collagen-degrading enzymes - Preserve skin's texture and resilience - Skin Cell Repair and Regeneration	- UV Protection and Photoaging Prevention - Protection Against Pollution and Environmental Damage - Protection Against Pollution and Environmental Damage - Strengthening of the Skin Barrier	Domaszewska-Szostek et al. (2021)
8	**Quercetin**	Apples, onions, berries, green tea, dark chocolate, broccoli	Orally (dietary supplement) and topically (cream, serum)	- Inhibits enzymes such as collagenase and elastase, which break down collagen and elastin - Potent Antioxidant Activity - Reduction of Cellular Senescence (Acts as a senolytic agent)	- Absorbs and mitigates UV-induced oxidative stress - Reduces pigmentation - Anti-inflammatory and Soothing Properties - Enhances the skin's natural barrier function	He et al. (2023)
9	**Lipoic acid**	Organ meats (liver, heart), spinach, broccoli, yeast, potatoes	Orally (oral supplement) and topically (serum and cream)	- Collagen Preservation - Enhances energy production in mitochondria, crucial for maintaining the metabolic activity of skin cells - Anti-inflammatory Effects	- UV Protection - Improves Skin Texture and Tone - Regenerates and recycles antioxidants like Vitamins C and E	Matsugo et al. (2011)
10	**Nordihydroguaiaretic acid (NDCA)**	Creosote bush (Larrea tridentata)	Topically (skincare formulation)	- Anti-inflammatory Effects - Preservation of Collagen - Regulation of Skin Lipid Production	- Inhibits tyrosinase activity, an enzyme involved in melanin production, which helps prevent or reduce hyperpigmentation and age spots caused by UV exposure	Kim et al. (2012)

(*continued on next page*)

Table 2 (*continued*)

NO.	Antioxidants	Natural source	Method of application	Effect on intrinsic aging	Effect on extrinsic aging	Refs.
11	**Vitamin A**	Carrots, sweet potatoes, liver, egg yolks, spinach, kale, red peppers	Topically (serum, cream)	- Collagen Stimulation - Thickening of the Dermis - Reduction of Wrinkles - Cell Turnover	- Anti-Inflammatory Action - Antimicrobial Properties - Repair of UV Damage - Smoothing of Photoaging Signs - Protection Against Free Radicals - Reduction of Hyperpigmentation	Sadick et al. (2019)
12	**Niacinamide (Vitamin B3)**	Poultry, beef, tuna, peanuts, lentils, chickpeas, mushrooms, brown rice	Topical (serum, cream, and toner)	- Boosts Collagen Production - Improves Skin Barrier Function - Supports Cellular Repair	- Reduction of Pigmentation - Refines Skin Texture and Pores - Enhances Skin Barrier Against Pollutants - Anti-inflammatory Effects	Zhou et al. (2021)
13	**Zinc**	Seafood, beef, lamb, pork, chicken, cheese, milk, yogurt, Chickpeas, lentils, beans, pumpkin seeds, sesame seeds, cashews, quinoa, oats, spinach, mushrooms, broccoli, kale	Topical (sunscreen)	- Collagen Synthesis Support - Cellular Repair and Growth - Enhances skin's immune defense - Antioxidant Activity	- UV Protection - Wound Healing and Repair - Anti-inflammatory Properties - Wound Healing and Repair	Lee et al. (2024)

consisting of two benzene rings (A and B) linked by three-carbon chains that create a closed pyran ring (heterocyclic ring with oxygen, C ring) (Panche et al., 2016; Hasan et al., 2022; Al-Maqtari et al., 2024; Abdalla Ali et al., 2024). The pharmaceutical industry is interested in the anti-inflammatory, antioxidant, anti-mutagenic, and anti-carcinogenic properties of these compounds, as well as their ability to modulate key cellular enzyme functions. Flavonoids exhibit antioxidant actions through: (**1**) scavenging ROS; (**2**) reducing ROS formation by inhibiting enzymes and chelating trace elements; and (**3**) enhancing antioxidant defenses. Due to their low redox potential, flavonoids can reduce extremely oxidized free radicals, including superoxide, alkoxyl, hydroxyl, and peroxyl radicals, by donating protons to these radicals (Halliwell, 2024; Chagas et al., 2022). Flavonoids inhibit the activation of enzymes like xanthine oxidase and protein kinase C, which produce superoxide anions. They can also block other enzymes that generate reactive oxygen species, like COX, microsomal monooxygenase, mitochondrial succinoxidase, lipoxygenase, and NADH oxidase (Ramesh et al., 2021). Flavonoids have advantageous biochemical and antioxidant properties that may assist to manage various oxidative stress-related conditions in the elderly, including cancer, diabetic cardiovascular diseases, and Alzheimer's disease, and dementia. When applied topically, specific flavonoids can protect the skin by absorbing UV radiation, thereby preventing damage to cellular components and acting similarly to sunscreen. Key molecules in the epidermis that absorb UV light include melanin, urocanic acid, amino acids, and nucleic acids, all of which help to block UV rays from penetrating the skin (Svobodová et al., 2003).

1.6.6. Quercetin

Quercetin is a flavonoid polyphenol compound derived from plants (Fig. 3). Quercetin, present in numerous fruits and vegetables, assists in minimizing damage from UVB-induced radiation by eliminating ROS and strengthening the cell membrane and mitochondria to resist ROS-induced harm. Quercetin protects against oxidative harm caused by paraquat by decreasing the levels of ROS and boosting the overall GSH levels (Zhang et al., Salehi et al., 2019). Recent study by Son and co-worker has shown quercetin's potential as a therapeutic agent for skin health, highlighting its protective effects against oxidative stress. The study found quercetin increases the expression of antioxidant enzymes like catalase and decreases the production of ROS, suggesting quercetin may reduce inflammation and oxidative stress caused by UVB radiation, shielding skin cells from harm and apoptosis. Another important study by Khan et al. discovered quercetin to reduce UVB-induced erythema in mice, inflammatory cytokine levels, and oxidative stress markers. Quercetin's anti-inflammatory and antioxidant qualities may protect the skin from oxidative damage caused by UVB rays, indicating that it may have photoprotective effects (Son and Kim, 2023). Furthermore, a study from 2021 examined how quercetin affected human dermal fibroblasts subjected to hydrogen peroxide-induced oxidative stress. The researchers discovered that quercetin improved cell survival and dramatically decreased ROS levels (Yi et al., 2021). Moreover, quercetin administration enhanced the expression of antioxidant enzymes like GPx, and SOD, suggesting that it supports the skin's antioxidant defenses (Rochette et al., 2013).

1.6.7. Lipoic acid

Lipoic acid exhibits antioxidative characteristics through its capability to chelate metals, neutralize reactive oxygen species (ROS), regenerate antioxidants, and repair oxidative damage, whereas dihydrolipoic acid (DHLA), produced from the lipoic acid reduction, possesses even stronger antioxidant charactristics. Both DHLA and lipoic acid can chelate metal and remove ROS, but only DHLA can restore natural antioxidants and fix oxidative harm. Lipoic acid acts as a metal chelator and exhibits antioxidant properties by chelating Fe^{2+} and Cu^{2+}, while DHLA can chelate Cd^{2+} for the same purpose. In the majority of studies, lipoic acid and DHLA act as antioxidants by neutralizing ROS, but there have been instances where they demonstrate pro-oxidant activity. Yet, lipoic acid has the ability to function as an antioxidant in response to the pro-oxidant effects caused by DHLA (Rochette et al., 2013; Abd El-Fadile and Hussine, 2016).

1.6.8. Nordihydroguaiaretic acid (NDCA)

NDGA primarily appears in chaparral tea and has been used as a nutritional supplement and antioxidant food preservative (Anthony et al., 2021). As a result of its ability to counteracting ROS, NDGA has been shown to reduce pro-oxidant effects of inflammation and inhibit lipoxygenases (LOX) activity, which in turn reduces lipid hydroperoxides, which are known to cause oxidative stress because they break down into free radicals (Manda et al., 2020). According to a study by Ming Lu et al., NDGA, a natural pigment, may protect against skin damage brought on by exposure to arsenic. The researchers employed N-acetylcysteine (NAC) as an antioxidant to stop oxidation after discovering that a 3% NDGA solution could permeate the skin without being harmful. This combination decreased oxidative stress and inflammation in the skin, indicating that NDGA may be a useful medicinal substance for wound care (Lü et al., 2010). Another study by Tsujii et al., NDGA

suppresses the PAR2-mediated signaling pathway, which is crucial for controlling inflammatory reactions and preserving the integrity of the epidermal barrier. In an AD model produced by oxazolone, topical NDGA treatment decreased blood IgE levels and enhanced skin barrier repair (Tezil et al., 2019).

1.6.9. Vitamin A

Vitamin A and carotenoids exhibit antioxidant properties owing to their hydrophobic polyene chains, which can effectively eliminate singlet oxygen, stabilize peroxyl radicals, and neutralize thiyl radicals. Generally, a longer polyene chain correlates with a greater capacity to stabilize peroxyl radicals. Additionally, due to their structural characteristics, vitamin A and carotenoids are prone to autoxidation when exposed to elevated O_2 levels, rendering them most effective as antioxidants under the low oxygen conditions typically found in physiological tissues (Li et al., 2016). According to VanBuren et al., vitamin A has a crucial role in the health of skin and hair by controlling cellular functions like differentiation, proliferation, and apoptosis. Additionally, they stress how crucial appropriate vitamin A levels are for pigmentation and hair growth (VanBuren and Everts, 2022). The function of vitamin A in skin immunity and its relationship to the skin microbiota are examined by Kim et al. They discovered that vitamin A and its derivatives, especially retinoic acid, alter the skin's immune response, making it less vulnerable to inflammation and infections. Retinoids support the skin's barrier function and increase the expression of antimicrobial peptides, which improves skin health and resistance to infections (Kim et al., 2019).

1.6.10. Niacinamide (vitamin B3)

Niacinamide, an essential vitamin B3 family member, plays a vital role in topical healthcare and cosmetic products. It includes nicotinamide or niacinamide, and niacin, or nicotinic acid, necessary for various physiological roles in eukaryotic cells (Srivastava, 2021). Niacinamide emerged as a fundamental component in numerous cosmetics and skincare items. This vitamin is essential for the production of NAD+ and plays a key role in helping skin cells generate energy and engage in redox reactions. Niacinamide is understood to impact human DNA repair and cellular stress responses via numerous metabolic pathways. Niacinamide, a cosmetic active ingredient with a long history of safe use, has gained popularity for meeting the skincare standards set by Kligman. Niacinamide is a versatile antioxidant with many benefits for the health of the skin. It enhances the skin's barrier protection, reduces water loss through the skin, regulates sebum levels, and helps fade hyperpigmentation. Additionally, niacinamide has anti-inflammatory properties, which can reduce redness and improve the skin's texture and tone. Niacinamide, a vitamin B3 family member, is a crucial component in topical healthcare and cosmetic products. It consists of nicotinamide or niacinamide and niacin or nicotinic acid, essential for various physiological functions in mammalian cells (Pérez-Gálvez et al., 2020).

1.6.11. Zinc

Zinc, a necessary mineral, can be found in a range of plant and animal sources as well as in supplement form. It has a significant impact on skin health, immune function, and cell growth and has the potential to provide protection against acne, inflammation, and other ailments (Zhen et al., 2019). Zinc ions can take the place of redox active molecules like iron and copper in vital locations within cell membranes and proteins; or they can prompt the production of metallothionein, which are proteins abundant in sulfhydryl groups and act as defense against free radicals. Regardless of their method of action, topical zinc ions could offer crucial and beneficial antioxidant protection for the skin (Levin and Momin, 2010; Rostan et al., 2002; Prasad, 2014; Marreiro et al., 2017).

2. Methodology

1 Data sources

Several pertinent databases such Google Scholar, since direct and MDPI through to collect relevant data for this review study.

2 Inclusion and exclusion criteria

The articles issued in peer-reviewed journals that investigated the Role of antioxidants in the skin and anti-aging effects had been elected, inclusive of in vivo, in vitro, ex vivo, and review based studies. However, the chosen research was restricted to papers published in English over the last ten years (1997–2024).

3 Search strategy

The approach used for collecting articles from google scholar was by utilizing the Medical Subject Heading (MeSH) terms: antioxidant and anti-aging. For other databases, search terms or keywords based on the topic title, "Role of antioxidants in the skin: anti-aging effects," were used. Furthermore, the following key phrases were employed in conjugation with antioxidant to acquire all the relevant studies: aging and skin defense against damage. Utilizing antioxidant and anti-aging treatment throughout the search procedure yielded additional study-related information. Afterwards, references cited in the establishing search were reviewed to determine additional relevant articles. Titles and abstracts of these articles were evaluated to eliminate repeated information. The entire contents, abstracts, and titles of the articles, were thoroughly evaluated and approved for inclusion. Irrelevant or incompatible papers were excluded accordingly.

3. Conclusion

Antioxidants are essential compounds that help shield the skin from the signs of aging. They reduce oxidative stress, which is brought on by unstable chemicals called free radicals, which can harm cells and hasten the aging process. Analyzing antioxidants' origins, processes, and affecting variables is necessary to comprehend their involvement in skin aging. One of the main mechanisms regulating skin changes, particularly those brought on by aging and UV exposure, is oxidative stress, which is started by the production of ROS. The human body has several natural mechanisms to combat oxidative stress. Administering antioxidants like ascorbic acid, tocopherols, and polyphenols can help boost the body's ability to resist oxidative stress and may aid in preventing or reducing skin aging. As our understanding of antioxidants and their role in skin aging expands, the potential for innovative and effective skincare solutions continues to grow, promising a brighter future for skin health and longevity. Advancements in technology and skin biology are paving the way for formulations that improve antioxidant efficacy, contributing to future clinical studies as well as potential therapies for skin diseases and age-related deterioration. Despite the fact that antioxidants are frequently promoted for their ability to prevent skin aging, research indicates that these benefits may not have a substantial influence on the molecular mechanisms at play. Due to one hypothesis, their inefficiency stems from their bioavailability in the skin, where their concentration could not be high enough to cause a noticeable biological reaction. This emphasizes the need for a more thorough comprehension of skin aging and the elements that contribute to it.

CRediT authorship contribution statement

Narmin Hama amin Hussen: Writing – review & editing, Validation, Conceptualization. **Sakar Karem Abdulla:** Writing – original draft, Formal analysis, Data curation. **Naza Mohammed Ali:** Writing – original draft, Methodology, Data curation. **Van Abdulqader Ahmed:**

Writing – original draft, Methodology, Conceptualization. **Aso Hameed Hasan:** Writing – review & editing, Validation, Supervision. **Eman Erfan Qadir:** Writing – original draft, Investigation, Conceptualization.

Declaration of competing interest

We wish to confirm that there are no conflicts of interest associated with this publication, has not been published before and not currently being considered for publication elsewhere.

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