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The state of the art in anti-aging: plant-based phytochemicals for skin care

Merve Tomas[1], Deniz Günal-Köroğlu[1], Senem Kamiloglu[2,3], Tugba Ozdal[4] and Esra Capanoglu[1,5*]

Abstract
Phytochemicals help mitigate skin aging by scavenging free radicals, modulating key enzymatic pathways, and promoting the skin's structural integrity. Carotenoids, vitamins, essential fatty acids, and phenolic compounds work by acting as antioxidants, inhibiting enzymes like hyaluronidase, collagenase, and elastase, which degrade skin structure, and reducing levels of inflammatory markers (IL-6, IL-8, etc.) and matrix metalloproteinases (MMP-1, MMP-2) linked to aging. Recent research highlights that plant-based phytochemicals can improve skin elasticity, reduce hyperpigmentation, prevent the breakdown of important skin proteins, and support wound healing, making them valuable components for skin care and treatments. This review explores the multifaceted roles of phytochemicals in maintaining and improving skin health, highlighting their mechanisms of action and potential in skin anti-aging innovations.

Keywords Skin care, Anti-aging, Phytochemicals, Polyphenols, Carotenoids, Fatty acids, Saponins, Alkoloids

Introduction

The skin serves as the body's primary barrier against environmental stressors. There are two main types of skin aging: intrinsic (natural or chronological) aging, which occurs inevitably within the body, and extrinsic (photoaging), which is caused by external factors like environmental pollution, UV light, and lifestyle (alcohol, smoking, etc.). Further, extrinsic aging accelerates skin damage by increasing reactive oxygen species (ROS) and activating enzymes that degrade essential skin components, leading to wrinkles, sagging, laxity, roughness, and loss of elasticity [1–6].

The skin is composed of three layers: the epidermis, dermis, and subcutaneous tissue [3, 6]. The dermis is made up of proteins in the extracellular matrix, including collagen (~28 types), elastin, and proteoglycans [6]. Collagen and elastin are key proteins in the extracellular matrix found in connective tissues, particularly in the skin, providing structural support and stability [3], and holding high levels of moisture, which keeps the skin elastic, strong, and hydrated, supported by substances like hyaluronic acid Type I collagen makes up 90%, while type III collagen makes up 10% of these proteins [6]. Thus, healthy skin is characterized by flexibility and resilience, featuring well-structured rete ridges, abundant collagen, and numerous elastic fibers [3]. In contrast, aging skin undergoes thinning of the epidermis, reduced hydration, breakdown of collagen and elastic fibers, accumulation of modified extracellular matrix components, and slower cell regeneration [7, 8].

*Correspondence:
Esra Capanoglu
capanogl@itu.edu.tr
[1]Department of Food Engineering, Faculty of Chemical and Metallurgical Engineering, Istanbul Technical University, 34469 Maslak, Istanbul, Türkiye
[2]Department of Food Engineering, Faculty of Agriculture, Bursa Uludag University, 16059 Gorukle, Bursa, Türkiye
[3]Science and Technology Application and Research Center (BITUAM), Bursa Uludag University, 16059 Gorukle, Bursa, Türkiye
[4]Department of Food Engineering, Faculty of Engineering and Natural Sciences, Istanbul Okan University, 34959 Tuzla, Istanbul, Türkiye
[5]School of Food and Biological Engineering, Jiangsu University, Zhenjiang 212013, China

Proliferation is important for forming granulation tissue and fibroblast activity, which in turn adjusts collagen, leading to scar formation. In older skin, healing is slower and less effective, making it more prone to damage. Fibroblasts play a crucial role by building the extracellular matrix, releasing growth factors, and contracting wounds [7]. For this reason, many in vitro studies focus on dermal fibroblast cells about skin health.

Nonenzymatic glycation of proteins leads to advanced glycation end products (AGEs), which cause oxidative stress and tissue damage, negatively affecting skin proteins like collagen and elastin. This process is linked to aging; thus, reducing AGEs, particularly through natural substances, may help mitigate their effects [8]. Furthermore, increased activity of matrix metalloproteinases (MMPs), which degrade collagen and elastin, is associated with decreased collagen synthesis and levels, contributing to wrinkles and skin aging [2, 6, 9]. Excessive MMPs and ROS can further damage skin, leading to premature aging and heightened skin cancer risk [10]. Nonetheless, to evaluate the anti-aging effects of compounds, in vitro assays also measure their impact on collagenase (collagen structure), elastase (elasticity), tyrosinase (pigmentation), and hyaluronidase (hydration) enzyme activities [1, 4, 8, 11, 12] on the grounds that inhibiting collagenase, elastase, tyrosinase, and hyaluronidase is crucial for preserving collagen and elastin integrity.

Cellular senescence is a key feature of aging, characterized by a decline in the ability of cells to grow and divide due to accumulated damage from ROS produced in mitochondria. When ROS levels exceed a certain threshold, cells enter a state of senescence by halting their cell cycles and activating signaling pathways associated with aging, such as p16/Rb and p53/p21 [13]. The primary markers of senescence are the Senescence-Associated Secretory Phenotype (SASP), SA-β-gal, p21, p53, and p16 [14]. The human body has an antioxidant system made up of enzymes and non-enzymatic antioxidants that work together to protect the skin from oxidative damage caused by ROS. Key enzymes include superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px), and glutathione reductase (GSH-Re) [15]. Furthermore, some inflammatory markers, like tumor necrosis factor-alpha (TNF-α), cyclooxygenase-2 (COX-2), and interleukins (IL), can induce the expression of antioxidant enzymes as part of the cellular response to inflammation [16].

Phytochemicals, such as polyphenols, carotenes, vitamins, and fatty acids, have anti-inflammatory, anti-obesity, and anti-cancer effects and are also known to combat degenerative neurological and cardiovascular diseases [17]. They also protect skin cells from oxidative stress, reduce inflammation, and enhance collagen synthesis, which is vital for maintaining skin elasticity and firmness [18]. Their anti-aging effects on the skin involve several interconnected changes, including cellular senescence, telomere shortening, oxidative stress, chronic inflammation, and alterations in gene expression [19]. Phenolic compounds, including protocatechuic acid [1, 2], chlorogenic acid [20, 21], green tea catechins [3, 22], quercetin [12, 18], and resveratrol [23, 24], are renowned for their bioactive properties and protective effects against skin aging. Similarly, carotenoids like astaxanthin, β-carotene [25, 26], lycopene [27], lutein [28, 29], and fucoxanthin [30] offer remarkable benefits for skin health, including anti-aging effects, UV protection, and enhanced hydration and elasticity. Vitamins C [31, 32], B_3 [33], A, and E [34, 35] offer a wide range of benefits, including stimulating collagen synthesis, providing antioxidant protection, enhancing hydration, and reducing pigmentation. Essential fatty acids, such as omega-3 (ALA, EPA, DHA) and omega-6 (LA, AA), are pivotal in repairing the skin barrier, reducing inflammation, and mitigating aging, with oils like walnut [36], tamarind seed [36], and avocado [37] demonstrating exceptional wound-healing and anti-aging properties. On the other hand, oxidative stress is a key factor in skin aging, resulting from an imbalance between free radicals and the skin's natural antioxidant defenses. Natural ingredients such as polyphenols, vitamins, carotenoids, and fatty acids play a vital role in protecting skin cells by detoxifying and repairing oxidative damage. These powerful agents help reduce fine lines, boost skin elasticity, and maintain overall skin health. Skincare products formulated with these natural antioxidants, either individually or in combination, offer an effective solution to minimize oxidative stress, slow the aging process, and deliver visibly healthier, younger-looking skin [38–41].

In this review, we aimed to highlight the role of plant-based phytochemicals, including polyphenols, carotenoids, vitamins, and fatty acids, in supporting skin health, focusing on their mechanisms of action and potential in skin anti-aging innovations.

Effect of plant-based phytochemicals on skin anti-aging

Phytochemical compounds act by neutralizing free radicals, reducing oxidative stress, and modulating inflammatory pathways, thereby protecting against UV damage, enhancing collagen synthesis, and preventing the degradation of skin structures (Fig. 1). These actions promote skin repair, hydration, elasticity, and overall resilience, supporting anti-aging and skin health.

Polyphenols

Polyphenols are commonly used in traditional medicine to treat chronic skin diseases including skin cancer, atopic dermatitis, acne vulgaris, psoriasis, chronic urticaria, and vitiligo, and they are also effective in promoting wound

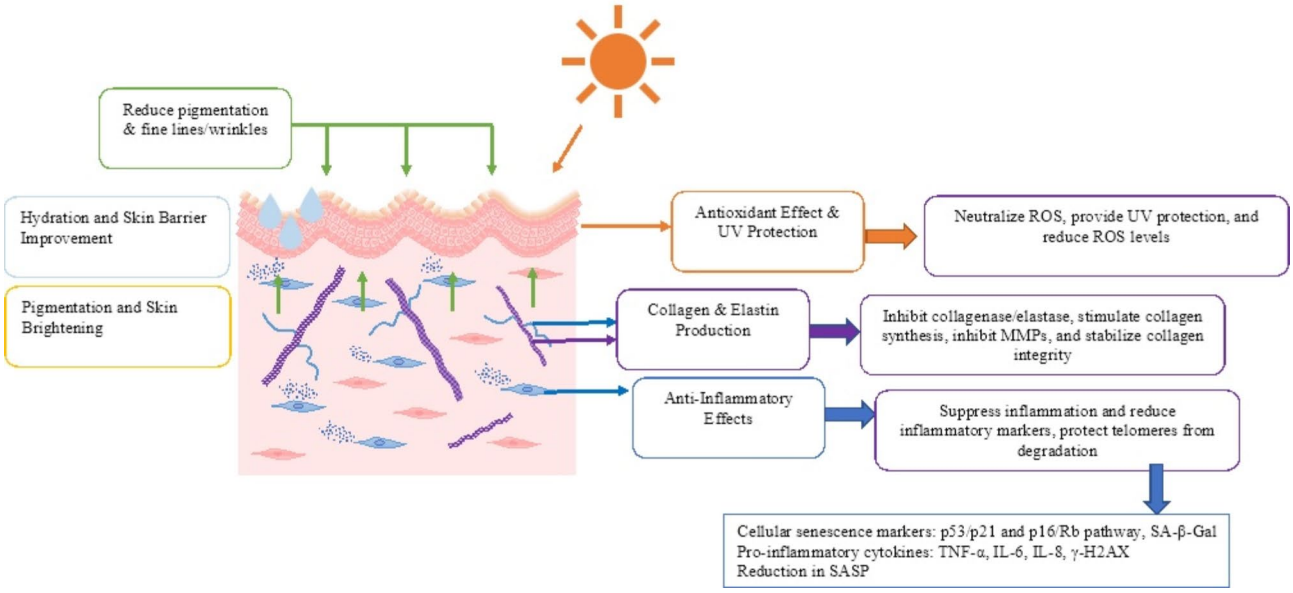

Fig. 1 Mechanisms of phytochemical action including antioxidant protection, collagen synthesis, and skin barrier improvement

healing and providing anti-inflammatory benefits when applied topically. The ortho-phenolic hydroxyl group in phenolic compounds easily oxidizes to form a quinone structure, which is effective at neutralizing free radicals, especially ROS [15], through its ability to scavenge free radicals via various mechanisms, including single electron transfer, hydrogen atom transfer, and metal chelation [1, 2]. Additionally, phenolic acids (punicalagin, protocatechuic acid, ellagic acid, chlorogenic acid), flavonoids (epigallocatechin gallate, quercetin, hesperidin, hesperetin, naringenin), and punicalagin are found to have no cytotoxic effects on skin cells [2, 7, 8, 12, 20, 42, 43]. Table 1 shows the potential anti-aging effects of polyphenols on the skin.

Polyphenols can inhibit enzymes (e.g., collagenase, tyrosinase) that are crucial for maintaining skin health and combating signs of aging. They also boost mitochondrial function, reduce oxidative stress, and inhibit melanin formation, providing UV protection and anti-wrinkle effects [1]. Girsang et al. [1] reported that protocatechuic acid and ferulic acid were effective on tyrosinase, collagenase, and hyaluronidase. Protocatechuic acid has more hydroxyl groups than ferulic acid, enhancing its antioxidant efficacy through greater radical scavenging and metal chelation compared to ferulic acid. Specifically, Shin et al. [2] stated that protocatechuic acid significantly increased type I collagen production (2.4-fold) in human dermal fibroblasts and inhibited UVA-induced MMP-1 expression, which degrades collagen. In ex vivo skin explants, protocatechuic acid at 0.02% enhanced collagen synthesis by 2.7-fold, demonstrating its potential against skin aging. A clinical trial showed that a lotion with 0.02% protocatechuic acid reduced wrinkle parameters in women with crow's feet over 8 weeks, indicating its anti-wrinkle efficacy. Illescas-Montes et al. [7] highlighted that punicalagin and ellagic acid, found in pomegranate, significantly enhance fibroblast viability, proliferation, and migration and enhance the expression of fibronectin and α-actin without affecting the cell cycle.

Xue et al. [20] found that chlorogenic acid enhanced type 1 collagen production in human skin fibroblasts by increasing Col1A2 gene expression and total collagen secretion while reducing collagen breakdown. It also protects against UVA-induced damage by decreasing apoptosis and ROS and activates the transforming growth factor beta (TGF-β)/Smad signaling pathway. Furthermore, a study by Wang et al. [21] showed that chlorogenic acid significantly reduced skin damage in a lupus mouse model and improved joint inflammation, while cyclophosphamide (a drug) completely prevented skin damage but caused weight loss. Both treatments lowered anti-dsDNA antibodies, with chlorogenic acid also decreasing pro-inflammatory cytokines (IL-17 A and IL-17 F), suggesting benefits for lupus management.

Recent studies highlight the protective effects of green tea catechins against skin damage and aging. A meta-analysis by Kapoor et al. [64] indicated that oral intake of green tea catechins significantly reduces ultraviolet radiation-induced erythema, while the topical application shows varied results depending on the dosage. Sheng et al. [3] noted that epigallocatechin gallate (EGCG: 25 mg/mL) protected BALB/c mice against UVB-induced damage but is prone to degradation from light, oxygen, and heat. However, its more stable epimer, gallocatechin gallate (12.5, 25, and 50 mg/mL), demonstrated stronger antioxidant activity and improved skin quality indicators

Table 1 Anti-aging potential of polyphenols

Source	Stress Source	Study Type	Results	References
Protocatechuic acid and Ferulic acid: Series of different concentration between 2.08–166.57 µg/mL	--	In vitro: Skin health-related enzyme activity inhibition	Outperformed effect of protocatechuic acid Protocatechuic acid: Inhibition of tyrosinase (246.42 µg/mL), collagenase (126.16 µg/mL), elastase (57.69 µg/mL), and hyaluronidase (107.57 µg/mL) Ferulic acid: Inhibition of tyrosinase (253.58 µg/mL), collagenase (52.85 µg/mL), elastase (75.61 µg/mL), and hyaluronidase (396.12 µg/mL)	[44]
Protocatechuic acid: 10, 20, 50, and 100 µg/mL	UVA: 5 J/cm^2	In vitro: Human dermal fibroblasts	↑ Type I collagen amount and inhibition of MMP-1 secretion	[45]
Protocatechuic acid: 0.02% in carboxymethyl cellulose gel	--	Ex vivo: Human skin explants	↑ Collagen synthesis	
Protocatechuic acid: 0.02% in lotion, 8 weeks	--	In vivo: 22 womans' crow's feet treatment	↓ Skin roughness	
Punicalagin and Ellagic Acid: 10^{-5} to 10^{-9} M	--	In vitro: Human dermal fibroblasts (CCD-1064Sk)	↑ Expression of fibronectin and α-actin mAbs	[46]
Chlorogenic acid: 40 mg/kg, 12 weeks	--	In vivo: MRL/lpr mice with lupus erythematosus	↓ Incidence of skin damage, pathological score of acanthosis/ hypertropy, dsDNA expression andIL-17, IL-17 F, IL-6, IFN-γ level ↔ ANA concentration	[47]
Chlorogenic acid: 0.1, 0.3, 1, 3, and 10 µM	UVA: 12 J/cm^2	In vitro: Human dermal fibroblasts (CCC-ESF-1)	↑ Type 1 collagen, total collagen secretion, phosphorylated Smad2/3, Rad51 ↓ Col3A1, Col5A1, MMP-1, MMP-3 mRNA ↓ Late apoptotic cells, cleaved PARP, ROS level, γ-H2AX expression	[48]
Epigallocatechin gallate: 25 mg/mL Gallocatechin gallate: 12.5, 25, and 50 mg/mL	UVB: 1.7 µmol/m^2 s	In vivo: BALB/c mice	↑ Pigmentation, elasticity, collagen fibers, melanosomes ↑ Mitochondria injury index	[49]
Epigallocatechin-O-Gallate and Withaferin A	--	In vitro: Molecular docking on Skin health-related enzyme inhibition	Significant inhibitory effects on key enzymes involved in skin aging and oxidative stress, especially when combined	[50]
Epigallocatechin Gallate: 25 µg/mL	UVA: 10 J/cm^2	In vitro: Human dermal fibroblasts (CCC-ESF-1)	↓ SA-β-Gal positive cells, hTERT gene, relative telomerase activity ↑ SOD, CAT and GSH-Px ↓ MMP-1, MMP-3, MMP-10, MDA and P66 ↑ Telomere length, TGF-β1 secretion, and mRNA level of TIMP-1	[51]
Epicatechin gallate, Epigallocatechin gallate, Epicatechin, Catechin and Epigallocatechin: 1, 5, 10, 20, 50 and 100 µM	--	In vitro: Human dermal fibroblasts (WS1)	↑ Instances of mitophagy, LC3B-I to LC3B-II Ratio ↑ Average number of lysosomes that co-localize with mitochondria	[52]
Quercetin: 2, 10, and 20 µM	--	In vitro: Human skin fibroblasts, mouse skin fibroblasts, L929, and HaCat cells	↑ Cell proliferation, scratch closure rate	[53]
Quercetin: 1.5, 3, and 6 mg/mL, 8 days	--	In vivo: C57BL/6 mice with 4 mm wound	↑ Wound healing rate, positive area of collagen fiber ↑ Relative protein expression of FGF, VEGF, α-SMA, Wnt, β-catenin	
Quercetin-loaded olive oil: 5 µg/mL		In vitro: Tyrosinase inhibition assay	Tyrosinase activity inhibition: 56.24%	[54]
Kaempferol-3-O-robinobioside	--	Molecular docking on Skin health-related enzyme inhibition	Binding through active sites of collagenase, elastase, and tyrosinase Collagenase (58.24%), elastase (26.29%), and tyrosinase (69.84%) inhibition	[55]

Table 1 (continued)

Source	Stress Source	Study Type	Results	References
Quercetin-3- O-rhamnoside (Que-3-Rha) and kaempferol-3-O-galactoside	--	Molecular docking on Skin health-related enzyme inhibition	Binding through active sites of collagenase, elastase, and tyrosinase Que-3-Rhamnoside: Collagenase (60.24%), elastase (50.28%), tyrosinase (46.54%) inhibition. Kae-3-Gal: Collagenase (59.84%), elastase (55.56%), and tyrosinase (51.14%) inhibition	[56]
Apigenin: 1 and 2.5% in cream	Hydroquinone: 2.5% in cream	In vivo: C57BL/6 mice	↓ Area of white patches ↓ Cholinesterase activity, MDA, CAT activity ↓ IL-6, TNFα, and IFN-γ, and expression of p38 MAPK	[57]
Hesperidin: 50 µM	Particulate matter$_{2.5}$: 50 µg/mL	In vitro: Human HaCaT Keratinocytes	↓ ROS in mitochondria, mithochondrial depolarization ↓ Cytochrome c release and DNA damage: phospho-H2A.X protein expression ↓ G_0/G_1, p53, p27, p21, p16, Bim, Bax, MMP-1, MMP-2, MMP-9, SA-βGal ↑ Cyclin D1, cyclin E, Cdk2, and Cdk4 Restoration of anti-apoptotic proteins Mc-1 and Bcl-2	[58]
Hesperidin, Hesperetin: 1-100 µM Rutinose, and Rhamnose: 0.25–100 mM	--	In vitro: Skin health-related enzyme activity inhibition	Inhibition of collagenase, elastase, and hyaluronidase Strong inhibition effect of rutinose on all enzymes Primarily inhibition effect of hesperidin and hesperetin on hyaluronidase	[59]
Hesperidin, Hesperetin: 1 and 10 µM Rutinose, and Rhamnose: 1 and 10 mM	Low/high glucose: 25 or 50 mM AGEs	In vitro: Human dermal fibroblasts	↓ MMP-1, MMP-2, IL-6, and IL-8 ↑ Collagen I production	
Resveratrol: 10, 20, 40, 60, 80, and 100 µM	UVB: 50 mJ/cm^2	In vitro: Human HaCaT Keratinocytes	↑ Cell viability, mRNA levels of GSSH and SOD, GPX-4 and HO-1, VEGF-B ↓ ROS level, Caspase3 and Caspase9, MMP-1, MMP-9, IL-6 and TNF-α	[60]
Resveratrol: 2 mg/kg	UVB: 40, 80, and 120 mJ/cm^2	In vivo: ICR mice	Prevented roughness, hypertrophy, erythema, and deep wrinkles Restored collagen fiber structure ↑ Type III collagen immunoreactivity, COX-2, MAPK pathway-related proteins ↓ Caspase3 and Caspase9, MMP-1, MMP-9, IL-6 and TNF-α ↓ m RNA levels of GSSH and SOD, GPX-4 and HO-1, VEGF-B	
Resveratrol: 5, 10, 25, 50, 75, 100, and 200 µmol/L	UVA: 4, 8, 12, 16, 20, 24, 28, and 32 J/cm^2	In vitro: Human dermal fibroblasts	↑ Cell Viability, Collagen I expression Cell Morphology: Normal spindle-shaped morphology maintained; reduced cellular debris. ↓ MMP-1, SA-β-gal activity, apoptosis rates, G1-phase arrest ↑ LC3B and Beclin-1 expression and ↓ p62 expression	[23]
Resveratrol: 100 µmol/L	UVA: 0.35 J/cm^2	In vivo: BALB/c mice	Improved erythema and reduced wrinkles ↓ Epidermal thickness, inflammatory cell infiltration, MMP-1 ↑ Collagen fiber content ↑ LC3B and beclin-1 expression and ↓ p62 expression ↑ p-AMPK/AMPK ratio	
Naringenin: 5 and 10 µM	Lipopolysaccharide: 1 µg/mL	In vitro: Human dermal fibroblasts	↓ NF-κB activity, IL-1β, IL-6, IL-8 ↓ mRNA expression of COX-2 and iNOS, PGE2 levels, NADPH oxidase	[43]
Naringenin: 150 µM	UVA: 30 mJ/cm^2	In vitro: Human HaCaT Keratinocytes	↓ TRPV1 expression, phosphorylated TRPV1, apoptosis, p53, p21, p16, MMP-1, MMP-9	[61]

Table 1 (continued)

Source	Stress Source	Study Type	Results	References
Cyanidin-3-O-glucoside and cyanidin-3-O-rutinoside: 10, 50, 100 and 200 μM	Blue light: 2,500 to 20,000 lx	In vitro: Human dermal fibroblasts	↓ ROS level, TNF-α, IL-6, and IL-8, cleavage of caspase-3 and PARP, FAK and MAPK phosphorylation	[62]
Cyanidin 3-O-arabinoside: 1 μM	Dihydrotestosterone 100 nM	In vitro: Human follicle dermal papilla cells	↓ SA-β-gal, upregulation of p21 and p16 ↓ Mitocondrial ROS levels and calcium accumulation ↑ FGF6 and FGF4, phosphorylation of p38 MAPK ↓ Expression of SA-β-gal, p21, p16	[63]

↑: Upregulation, ↓: Downregulation, ↔: No obvious change

α-SMA: Alpha smooth muscle actin, AGEs: Advanced glycated end products, ANA: Anti-nuclear antibodies, AMPK: AMP-activated protein kinase, Bcl-2: B-cell lymphoma 2, CAT: Catalase, Cdk2: Cyclin-dependent kinase 2, Cdk4: Cyclin-dependent kinase 4, COX2: Cyclooxygenase-2, dsDNA: Double-stranded DNA, FAK: Focal Adhesion Kinase, FGF: Fibroblast growth factor, GSH-Px: Glutathione peroxidase, GSSH: Glutathione, HaCaT: Human keratinocyte cells, hTERT: Human telomerase reverse transcriptase, IFN: Interfelon, IL: Interleukin, iNOS: Inducible nitric oxide synthase, LC3B: Microtubule-associated protein 1 light chain 3 beta, mAbs: Monoclonal Antibodies, MAPK: Mitogen-activated protein kinase, Mc-1: Myeloid cell leukemia-1, NF-κB: Nuclear factor kappa B, MDA: Malondialdehyde, MMP: Matrix metalloproteinase, mRNA: Messenger RNA, PGE2: Prostaglandin E2, p53: Tumor protein p53, p-AMPK: Phosphorylated AMP-activated protein kinase, PARP: Poly(ADP-ribose) polymerase, ROS: Reactive oxygen species, TIMP-1: Tissue inhibitor of metalloproteinases-1, SA-β-Gal: Senescence-associated beta-galactosidase, SOD: Superoxide dismutase, TGF-β1: Transforming Growth Factor Beta 1, TRPV1: Transient receptor potential vanilloid 1, VEGF: Vascular endothelial growth factor

in UVB-exposed hairless mice, despite low gallocatechin gallate levels showing minimal protective effects. Devi et al. [10] found that combining epigallocatechin gallate with withaferin A significantly inhibited key skin aging enzymes, with 1.5 times greater collagenase inhibition compared to ascorbic acid, indicating a synergistic effect on skin health. Jia et al. [42] reported that epigallocatechin gallate reduced the proportion of aging cells and suppressed UVA-induced SA-β-gal expression, enhancing telomerase activity, mitigating oxidative stress, restoring TGF-β1 secretion, and promoting extracellular matrix stability by inhibiting MMPs. Lastly, Auguste et al. [22] demonstrated that green tea catechins (epicatechin gallate, epigallocatechin gallate, epicatechin, catechin, and epigallocatechin) effectively induce mitophagy in WS1 cells, suggesting a role in the anti-aging effects of green tea. Overall, these findings underscore the potential of green tea catechins in promoting skin health and combating aging.

Flavonoids, a diverse group of polyphenolic compounds found abundantly in fruits, vegetables, and various plant-based foods, have garnered significant attention for their potent biological activities, particularly in skin health. Mi et al. [18] demonstrated that quercetin enhanced skin cell proliferation and migration and accelerated wound healing in mice by promoting collagen production, reducing inflammation cytokines (TNF-α, IL-1β, IL-6) and nitric oxide, boosting glutathione (GSH) levels, and activating the Wnt/β-catenin pathway. Silva et al. [12] found that quercetin nanoemulsion significantly inhibited tyrosinase activity, outperforming free quercetin and hydroquinone. Nutho & Tungmunnithum [4, 11] reported that quercetin and kaempferol derivatives effectively inhibited enzymes linked to skin aging.

Moreover, Chauhan et al. [57] showed that apigenin demonstrated protective effects against hydroquinone-induced skin depigmentation and inflammation in mice. It significantly reduced depigmentation in both exposed and non-exposed areas and improved tyrosinase activity, essential for melanin production. Apigenin decreased oxidative stress markers (MDA, cholinesterase) and increased catalase activity. It also reduced pro-inflammatory cytokines (IL-6, TNF-α, IFN-γ) and the expression of the p38 MAPK pathway. Herath et al. [19] revealed hesperidin protects HaCaT cells from PM2.5-induced oxidative stress by inhibiting the JNK pathway and reducing mitochondrial dysfunction, DNA damage, and the overexpression of proteins involved in cell cycle arrest. Novotná et al. [8] demonstrated that rutinose and rhamnose inhibit aging-related enzymes (MMP-1 and MMP-2 levels) and inflammatory markers (IL-6 and IL-8 levels).

Resveratrol exhibited protective effects against UV-induced photoaging through several mechanisms. In human skin fibroblasts and HaCaT keratinocytes, it enhanced cell viability, reduced oxidative stress, and preserved collagen structure [23, 24]. Resveratrol promoted autophagy by upregulating proteins such as LC3B and Beclin-1 while decreasing p62 levels. Additionally, it mitigated senescence markers and apoptosis and restored cell cycle progression [23]. In mouse models, resveratrol reduced photoaging indicators, including wrinkles, erythema, and collagen degradation, while decreasing inflammatory cell infiltration [23, 24]. These effects were largely attributed to the activation of the AMPK signaling pathway, which enhanced autophagy and reduced the expression of collagen-degrading enzymes, contributing to its anti-photoaging properties [24].

Lastly, naringenin was shown to counteract UVB-induced skin damage by reducing inflammation, cellular senescence, and MMP expression [43]. Naringenin, a bioflavonoid found in citrus fruits, has shown potent anti-inflammatory effects on human dermal fibroblasts or HaCaT keratinocytes [43, 61]. Kuo et al. [43] found that naringenin reduced LPS-induced inflammatory responses in a dose-dependent manner by suppressing inflammatory cytokines and inhibiting the NF-κB

signaling pathway. It also decreased COX-2 and prostaglandin E2 (PGE2) expression, suggesting its potential in treating inflammatory skin conditions. Zhu et al. [61] showed that naringenin protected HaCaT cells from UVB-induced damage by inhibiting TRPV1 and its phosphorylated form, which reduced apoptosis and promoted cell proliferation. It also downregulated senescence markers (p53, p21, p16) and MMPs (MMP-1, MMP-9), thereby mitigating collagen and elastic fiber degradation and slowing UVB-induced cellular aging.

Anthocyanins are extensively utilized in beauty and cosmetic applications due to their broad spectrum of vibrant colors, which range from red and purple to blue. Their versatility not only enhances the visual appeal of products but also offers antioxidant properties that support skin health and protection. Jung et al. [65] demonstrated that cyanidin 3-arabinoside reduced DHT-induced senescence in dermal papilla cells and promoted hair follicle stem cell proliferation, enhancing hair regrowth in an alopecia model. Cyanidin 3-arabinoside mitigated the negative effects of DHT by decreasing mitochondrial reactive oxygen species (mROS), blocking mitochondrial calcium overload, and inhibiting p38-mediated VDAC1 expression. This disrupted mitochondria-associated ER membrane formation and calcium transfer, thereby reversing dermal papilla cell senescence and stimulating hair follicle stem cell proliferation. Lee & Kim [62] found that cyanidin 3-O-glucoside and cyanidin 3-O-rutinoside suppressed blue light-induced cytotoxicity and inflammation in HaCaT keratinocytes. These compounds inhibited excessive ROS production, reduced pro-inflammatory cytokine levels, and mitigated apoptosis under high-intensity blue light exposure.

Polyphenols offer a range of benefits for skin health, including anti-aging, UV protection, wound healing, and inflammation reduction. These compounds, such as protocatechuic acid, chlorogenic acid, green tea catechins, quercetin, and resveratrol, enhance collagen production, inhibit skin-aging enzymes like collagenase and tyrosinase, and reduce oxidative stress. Studies show that polyphenols stimulate fibroblast activity, decrease MMP expression, and activate protective signaling pathways, leading to improved skin quality. Their effectiveness in both preclinical and clinical studies highlight their significant potential in advancing skincare treatments and cosmetic applications.

Carotenoids

Carotenoids, a class of naturally occurring pigments found in various fruits and vegetables, including lycopene, beta-carotene, lutein, and astaxanthin, have been shown to significantly affect skin aging through their potent antioxidant and anti-inflammatory properties, which help prevent photoaging, support collagen synthesis and preservation, and improve skin tone, texture, and hydration [66, 67]. The effects of carotenoids on potential skin anti-aging activity are presented in Table 2.

Reactive oxygen species, commonly referred to as free radicals, generated by UV radiation, can disrupt the dermal structure, resulting in reduced skin elasticity and the formation of wrinkles. Prolonged exposure to ultraviolet (UV) light may lead to chronic inflammation, which can degrade collagen and elevate the production of sunburn cells, contributing to the process of photoaging. According to Wilianto et al. [68], incorporating 0.5% astaxanthin into SPF 50 sunscreen effectively suppressed the rise in sunburn cells and mitigated the reduction in collagen fibers in rats exposed to UVB light. This effect is attributed to astaxanthin's antioxidant properties, which enhance the sunscreen's protective capacity and reduce skin damage caused by UVB exposure. In another study, Liu et al. [30] examined the impact of dietary fucoxanthin on photoaging-associated dysfunction in UVA-irradiated hairless mice by measuring TEWL and analyzing wrinkle formation. Additionally, they investigated gene expression and ceramide composition to uncover the underlying mechanisms involved. Oral supplementation with 0.001% fucoxanthin resulted in the accumulation of its metabolites in the skin, effectively preventing pathological changes caused by UVA irradiation, such as compromised skin barrier function and increased wrinkle formation. Gene expression analysis suggested that fucoxanthin's anti-photoaging effects may stem from its ability to regulate the synthesis of NMF, desquamation, and ceramide composition in the epidermis, while also inhibiting UVA-induced collagen degradation and inflammation in the dermis. The findings highlight the potential of dietary fucoxanthin as a novel ingredient in nutricosmetics for combating photoaging. The decline in stem cell function is widely regarded as a primary driver of aging, making the mitigation or reversal of stem cell aging a central focus of anti-aging research. Aging is often accompanied by inflammation-related changes, marked by elevated levels of pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α, in the circulatory system. Zheng et al. [74] investigated the anti-aging effect of β-carotene in vivo and in vitro (using mesenchymal stem cells). β-Carotene appeared to exert its anti-aging effects by modulating the lysine acetyltransferase 7 (KAT7)-P15 axis, resulting in G1-phase cell cycle arrest. Moreover, Sa-β-gal staining revealed that tissue and organ aging was attenuated, tissue damage was significantly reduced, and levels of tissue and organ fibrosis—an aging-related phenotype—were decreased. These findings suggest that β-carotene demonstrates anti-aging effects in vivo [74]. Collagen and elastin are key proteins essential for skin tone, elasticity, and resilience. Collagen fibers are a

Table 2 Anti-aging potential of carotenoids

Treatment	Stress Source	Model	Duration	Results	Reference
Astaxanthin 0.5% in sunscreen SPF 50	UVB:3100 mJ/cm^2	In vivo: 36 male Wistar rats	5 weeks	• Sunburn cell count was higher in the SPF 50 sunscreen group without astaxanthin (0.47 ± 0.27 cells/hpf) than in the group with 0.5% astaxanthin (0.16 ± 0.18 cells/hpf). • The study showed that adding 0.5% astaxanthin to SPF 50 sunscreen reduced sunburn cell formation and collagen fiber loss in rats exposed to UVB light.	[68]
Fucoxanthin (0.001% and 0.01%)	UVA: 20 J/cm^2	In vivo: Female, six-week-old, hairless Hos: HR-1 mice	10 weeks	• Oral supplementation of 0.001% fucoxanthin was enough for its metabolites to accumulate in the skin, preventing UVA-induced damage such as impaired skin barrier function and accelerated wrinkle formation. • Gene expression analysis suggested that fucoxanthin's antiphotoaging effects may result from its modulation of NMF synthesis, desquamation, and ceramide composition in the epidermis, as well as inhibiting collagen degradation and inflammation in the dermis.	[30]
Astaxanthin (1 mg/mL)	Phthalic acid	In vivo: HR-1 mice (8-weeks-old, $n = 9$)	4 weeks	• ↓ TNF-α, IL-1, IL-6, MDA, H_2O_2 • ↑ GSH, the expression of HO-1, GPx-1	[69]
Lutein, zeaxanthin	UV irradiation (equivalent to 14 mJ/cm^2; i.e., 260∼400 nm) was carried out using UV simulators	In vivo: 8 male Swiss albino mice of 8∼12 weeks	6 weeks	• It was concluded that the proprietary lutein, zeaxanthin, and rosemary formulation, along with the standard drug HA, effectively protects UV-irradiated skin from dehydration.	[29]
Phytosomes of crocin and lutein from *Nyctanthes arbor-tristis* and *Tagetes patula*	-	In vivo: Swiss albino male mice, 6–8 weeks old	6 weeks	• ↑ GSH level, and ↓ MDA levels in skin tissues of mice • Upregulated expression of elastin and collagen genes, leading to increased skin firmness and elasticity, as evidenced by thicker dermal and epidermal layers	[70]
Tomato extracts formulation (25 mL/bottle)	-	In vivo: 62 female volunteers	8 weeks	• 35.63% ↑ in stratum corneum hydration, 29.39% ↓ in TEWL, suggesting enhanced skin hydration • 15.03% ↑ in skin color, 11.41% ↑ in gloss index • 18.59%in the skin gloss and 6.36% in ITA value, leading to a lighter skin tone. • Blood levels of SOD and GPx ↑, while MDA levels ↓	[71]
Lutein (20 mg daily) in the form of a liquid food supplement	UVB: 0.114 J/cm^2	In vivo: 30 healthy women	12 weeks	• The study indicated that dietary lutein supplementation enhances skin photoprotection and supports defense against UVR-induced damage.	[28]
Astaxanthin–zeaxanthin nanoemulsions radiance serum (0.5 mL)	-	In vivo: 15 women (mean age 42 years)	4 weeks	• The serum demonstrated significant anti-wrinkle effects, 80–93% reduction in wrinkles over 28 days.	[72]
Lumenato supplementation: a mix of tomato carotenes (phytoene, phytofluene, zeta-carotene) and natural phytonutrients	-	In vivo: 63 females	12 weeks	• Improvements were observed in skin elasticity, firmness, brightness, tone, hydration, texture, reduction of dark spots and periorbital dark circles, as well as fine lines and wrinkles. • The overall skin appearance improved in 35.48% of subjects after 4 weeks, increasing to 66.13% after 8 weeks and 62.9% after 12 weeks.	[26]
E/Z-isomers of lutein and fucoxanthin	UV-A and UV-B	In vitro: Human dermal fibroblasts and B16 mouse melanoma cells		• Z-Isomers showed superior UV-A- and UV-B-blocking abilities than all-E-isomers. • Z-isomer-rich carotenoids showed enhanced lipid peroxidation-scavenging activity. • Both isomers exhibited strong anti-elastase and anti-tyrosinase activities.	[73]

Table 2 (continued)

Treatment	Stress Source	Model	Duration	Results	Reference
E/Z-Isomers of lycopene and β-carotene	UV-A and UV-B	In vitro: Human dermal fibroblasts and B16 mouse melanoma cells		• The Z-isomers exhibited superior UV-light-shielding abilities compared to the all-E-isomers. • The Z-isomers demonstrated greater skin anti-aging and whitening activities than the all-E-isomers.	[25]
Lycopene-loaded niosomes	UV-B: 10 mJ/cm^2	In vitro: Human keratinocytes (HaCaT) and B16F10 melanoma cells.	24 h	• Demonstrated high effectiveness in protecting against UVB radiation. • Showed strong potential in inhibiting melanogenesis.	[27]

UVB: ultraviolet B-light, UVA: ultraviolet A-light hpf: high power field, NMF: natural moisturizing factor, TNF-α: Tumor necrosis factor-alpha, IL-1: Interleukin-1, IL-6: Interleukin-6, MDA: Malondialdehyde, H_2O_2: Hydrogen peroxide, GSH: Glutathione, HO-1: Heme oxygenase-1, GPx-1: Glutathione peroxidase-1, TEWL: Transepidermal water loss, ITA: individual typology angle, SOD: superoxide dismutase, GPx: glutathione peroxidase

major component of the dermis, while elastin maintains skin integrity and flexibility. With age, the levels of these proteins significantly decrease, leading to saggy and less elastic skin. Preventing the degradation of these primary structural components is crucial to avoiding wrinkle formation. The formulation comprising phytosomes of crocin and lutein, derived from *Nyctanthes arbor-tristis* and *Tagetes patula* extracts, respectively, shows significant potential in delaying the skin aging process by promoting the upregulation of collagen and elastin gene expression while reducing oxidative stress in the skin [70]. In a clinical study, the effects of an orally administered tomato extract formulation on skin aging and pigmentation were evaluated [71]. The treatment group receiving the sample formulation demonstrated significant improvements in various skin parameters. After eight weeks, stratum corneum hydration increased by 35.63%, and TEWL decreased by 29.39%, indicating enhanced skin hydration. Visual assessments revealed improvements in skin color and gloss indices of 15.03% and 11.41%, respectively. Additionally, the skin gloss index and individual ITA value increased by 18.59% and 6.36%, respectively, resulting in a lighter and more uniform skin tone. Enhancements were also observed in skin pigmentation, color uniformity, and redness. Biochemical analysis showed elevated blood levels of SOD and GPx, alongside a reduction in MDA levels, suggesting improved antioxidant capacity. The results demonstrate that consistent consumption of the tomato extract formulation over an eight-week period effectively enhanced skin whitening and hydration in volunteers, leading to a visibly brighter skin tone through its antioxidant properties [71]. In recent years, carotenoids like astaxanthin and zeaxanthin have garnered significant attention for their potential in cosmetic and dermatological applications. Furthermore, nanoemulsions are used in cosmetics to deliver active ingredients (i.e., carotenoids) for anti-aging, skin hydration, UV protection, and skin brightening. An efficacy study was conducted to evaluate the anti-wrinkle properties of the Astaxanthin–Zeaxanthin nanoemulsions radiance serum on 15 women with a mean age of 42 years [72]. The study aimed to assess the product's impact on reducing wrinkles and enhancing skin texture. Key parameters, including wrinkle levels, were measured using a smart skin analyzer device at baseline and on days 7, 14, 21, and 28. Participants applied approximately 0.5 mL of the serum to their faces twice daily, in the morning and evening, as per the provided instructions. The results demonstrated a substantial reduction in wrinkle levels after 28 days of product use. All participants experienced a significant decrease in wrinkles, with reductions ranging from 80 to 93% and an average reduction of 84%. Both longer wavelengths of UV-A (320–400 nm) and shorter wavelengths of UV-B (280–320 nm) radiation

are well-known to have harmful effects on the skin, including premature aging, sunburn, DNA damage, and an increased risk of skin cancer. Understanding the differences between all-E- and Z-isomers of carotenoids is crucial for their effective application in skincare. More recently, Banik et al. [73] investigated the UV-light-blocking ability and skin anti-aging activities of lutein and fucoxanthin isomers. They showed that Z-isomers of lutein and fucoxanthin had significantly greater UV-A- and UV-B-blocking abilities than their all-E-isomers. This effect could be explained by the fact that the Z-isomers of lutein and fucoxanthin, particularly their 13Z- and 13′Z-isomers, have a distinct maximum absorption spectrum in the UV region (around 330 nm) and absorb at shorter wavelengths compared to the all-E-isomers. Notably, Z-isomer-rich lutein samples demonstrated significantly higher anti-elastase activity compared to all-E-isomer-rich lutein, underscoring its enhanced anti-aging potential. This is likely due to the structural configuration of the Z-isomer, which may improve its interaction with the elastase enzyme. Both lutein and fucoxanthin isomers also significantly inhibited tyrosinase activity, contributing to their skin-whitening properties. Similarly, Z-isomers of lycopene and β-carotene showed the same effects [25]. Lycopene-loaded niosomes derived from tomatoes, carrots, and mixed red vegetables demonstrated UVB protective potential by enhancing the viability of HaCaT cells exposed to UVB irradiation [27] On the other hand, these niosomes exhibited skin-whitening effects by reducing melanin content and inhibiting tyrosinase activity, with no cytotoxicity observed in B16F10 cells. These results suggest that lycopene-loaded niosomes could be effectively incorporated into skincare products, such as gels or creams, to provide UV protection and skin-lightening benefits. Overall, regular consumption of carotenoid-rich foods or the topical application of carotenoid-based formulations can support youthful, healthy skin by enhancing elasticity, minimizing fine lines, and improving the overall appearance of the skin.

Vitamins

The studies in the literature highlight the promising anti-aging and skin-enhancing properties of various formulations and treatments incorporating vitamins, particularly vitamin C, vitamin B_3, vitamin A, and vitamin E, and unique delivery mechanisms such as sonophoresis, microneedling, and encapsulation (Table 3). The formulations containing vitamins have shown efficacy in improving skin quality, reducing wrinkles, and enhancing elasticity, with applications spanning diverse age groups and skin types.

Vitamin C (L-ascorbic acid or L-ascorbate), originally identified through research on scurvy prevention and treatment, is vital to human physiology. Its main biochemical role originates from its redox properties; it can easily oxidize by releasing electrons in water, allowing it to function as a water-soluble antioxidant that neutralizes ROS or free radicals. Additionally, vitamin C acts as a cofactor, supporting enzyme catalytic functions by reducing metal ions at enzyme active sites [83]. This vitamin is recommended for both dietary intake and topical skin use as it promotes collagen synthesis in the dermis and helps defend against UV-induced damage [84].

Vitamin B_3 (nicotinic acid or niacin) deficiency results in pellagra, a systemic condition characterized by dermatitis, diarrhea, dementia, and, in severe cases, death. This vitamin is crucial for synthesizing the nicotinamide adenine dinucleotide (NAD^+) family of coenzymes, which are key for cellular energy production and defense mechanisms. Nicotinamide, also called niacinamide, is the amide form of water-soluble vitamin B_3 and shares the same biological activity as nicotinic acid. Supplementation of nicotinamide provides important health benefits, supporting both overall wellness and skin health [85].

Vitamin A and its metabolites play critical roles in numerous bodily functions, such as immune response, vision, epithelial barrier maintenance, and cell differentiation [86]. Retinoic acid, the active form of vitamin A, is derived from retinol and retinyl esters through several enzymatic steps involving oxidation and hydroxylation [87]. Among retinoids, retinol is especially valued for its proven anti-aging effects on the skin. It enhances collagen production, inhibits MMPs, reduces oxidative stress, and influences gene expression [88].

Vitamin E (alpha-tocopherol) is the most well-known fat-soluble non-enzymatic antioxidant, mainly for its ability to inhibit the activity of prooxidant agents generated by ROS. The antioxidant activity of vitamin E is directly linked to its ability to inhibit the lipid peroxidation in unsaturated fatty acids, incorporating itself into cell membranes, which effectively inhibits lipid peroxidation. Topical applications of Vitamin E are designed for treating melasma, protecting against UV radiation, and improving aging damages [89].

One study aimed to assess the impact of ascorbic acid delivered via sonophoresis and microneedling on photoaging signs in sensitive, redness-prone skin. The findings confirmed that ascorbic acid helps reduce wrinkles and boosts skin elasticity by protecting collagen from photoaging and natural aging. Additionally, this treatment was found to be highly effective for sensitive skin, notably reducing erythema. The formulation, along with these two application methods, significantly decreased redness and lowered skin reactivity. The therapies also proved to be effective and safe, causing only mild skin irritation in a few participants, which resolved within minutes to hours after treatment [75]. In a related clinical trial, 10% vitamin C ampoules used over 30 days in women aged

Table 3 Anti-aging studies conducted with formulations containing vitamins

Treatment	Model	Duration	Results	Reference
500 mg of vitamin C application with microneedling or sonophoresis	In vivo: 25 healthy probands aged 25–63 years, with erythematous changes and sensitive skin	6 months	• Vitamin C helped to reduce wrinkles and boosted skin elasticity. • Treatment was effective for sensitive skin, reducing erythema. • The formulation along with application methods significantly decreased redness and lowered skin reactivity. • The therapies were effective and safe, causing only mild skin irritation in a few participants.	[75]
Peptide-C ampoules (PC) containing peptides, 10% of vitamin C, hyaluronic acid, and mineralizing water	In vivo: 1756 women aged ≥ 30 years, with signs of skin aging	28 days	• 63% of participants experienced a reduction in forehead wrinkles. • 64% saw improvements in crow's feet wrinkles. • Skin hydration increased in 67% of participants. • Comparable outcomes were found when PC was used alone or alongside with other skincare treatments. • 98% of participants rate product tolerance as good to very good.	[76]
Mixture of polydeoxyribonucleotide, vitamin C (25%), and niacinamide (55%) with microneedling	• In vitro: HEKn cells radiated to UV-B • In vivo: HRM-2 mice (female, 5 weeks old, 20–25 g) radiated with UV-B	In vitro: 24 h In vivo: 28 days	• Levels of Nrf2/HO-1 increased, roxidative enzyme activity educed, and antioxidant enzyme activity enhanced in the skin. • Expression of proteins linked to pigmentation and skin aging, tumor protein p53 and tyrosinase, decreased. • Inflammatory markers and MMP levels linked to collagen breakdown were reduced. • The treatments boosted collagen and elastin fiber content, along with fibrillin and fibulin, supporting skin elasticity.	[77]
Serum containing vitamin C (15% w/v) and vitamin E with palmitoyl tripeptide-38 (5 ppm)	In vivo: Women aged ≥ 40 years, with visible signs of photoaging	2 months	• Statistically significant reductions in signs of aging, including smoother skin, brighter tone, and improvements in wrinkles and skin structure were observed. • The changes in skin isotropy and anisotropy were modest. • Skin evenness, radiance, and wrinkle appearance were improved.	[78]
Azelaic acid (20%), phytic acid (30%), and vitamin C (40%)	In vivo: 20 Polish female volunteers aged 35–60 years	8 weeks	• Application of the ingredients improved skin elasticity, reduced wrinkles, hyperpigmentation, erythema, and telangiectasia, and enhanced overall skin tone. • No irritation or allergic reactions were observed.	[79]
Serum with 15% vitamin C, vitamin E, neohesperidin, *Pinus pinaster* bark, and hyaluronic acid	• Ex vivo: Human skin samples • In vivo: 40 women showing visible signs of photoaging, including facial hyperpigmentation	90 days	• The topical antioxidant serum significantly reduced air pollution-induced skin pigmentation and expression of proinflammatory genes. • A significant improvement of skin aging signs was observed after 90 days. • Local tolerance was good.	[80]
Encapsulated serum with vitamin C (20%), vitamin E, and European raspberry leaf cell culture extract	In vivo: 50 women aged 30–65 years	2 months	• The serum improved several signs of aging—such as darkening, elasticity, radiance, smoothness, scaliness, and wrinkles. • Elasticity improvement did not lead to visible lifting effects. • The serum was well-tolerated by participants.	[31]
Vitamin C lotion (10%, 15%, 20%, and 25%)	• In vitro: Corneal epithelial cells, mice melanocytes • In vivo: 34 women aged 24–58 years	28 days	• For all lotions, vitamin C effectively penetrated the skin, with 20% lotion achieving the highest transdermal efficiency, reaching 85% diffusion in 24 h, surpassing the control group by 1.43 times. • Irritation tests showed low cytotoxicity, and patch testing confirmed no allergic reactions. • The use of vitamin C lotion demonstrated significant improvements: 10.5% increase in skin radiance, a 9.2% boost in elasticity and firmness, and a 12.3% reduction in wrinkle area.	[32]

Table 3 (continued)

Treatment	Model	Duration	Results	Reference
Niacinamide (2%) with fractional ablative laser treatment	• In vivo: 25 women aged 27–62 years • In vitro: HaCaT cells irradiated with UV-B	3 weeks	• The treatment led to greater reductions in wrinkles and pigmentation compared to a standard formulation. • The stem cell medium with niacinamide provided antiinflammatory benefits and boosted wound healing and skin cell turnover.	[81]
Product containing genistein (4%), vitamin E (1%), vitamin B_3 (1%), and ceramide (0.2%)	In vivo: 50 postmenopausal women aged 48–65 years	6 weeks	• The product showed significant improvement in skin hydration, and fine pore size and area, and increased skin redness reduction. • Among older participants (age > 56) with high compliance, the product significantly improved most wrinkle parameters.	[33]
Topical gel containing vitamins (50,000 IU of vitamin A and 50 mg of vitamin E) and 0.02% retinoic acid	In vivo: 60 participants (56 women and 4 men) aged > 50 years	12 weeks	• After 6 weeks, skin aging global scores dropped by 13% in the group using topical gel alone and by 14% in the group using gel with vitamins. • By week 12, the reductions were 22% and 27% for the groups using topical gel alone and the gel with vitamins, respectively.	[35]
4% retinol solution containing TGF-β activators and antioxidants	In vivo: 15 women	30 day intervals	• Skin tone, pigmentation, hydration, structure, oil control enhanced. • Pigmentation, especially in those with early aging signs, post-inflammatory hyperpigmentation, acne scars, and enlarged pores significantly improved. • The treatment was well-tolerated, cost-effective, easy to use, and associated with minimal side effects.	[34]
Retinyl palmitate (5%)-loaded nanocapsules (100 and 1000 µg/mL)	In vitro: NIH 3T3 mouse fibroblast and RAW264.7 macrophage cells	24 h	• The chitosan coating retinyl palmitate's skin penetration and showed significant antioxidant and anti-inflammatory effects without cytotoxicity to dermal fibroblasts. • Cell proliferation and collagen synthesis promoted.	[82]

MMP: Matrix Metalloproteinases, Nrf2/HO-1: Nuclear Factor Erythroid 2-Related Factor 2/Heme Oxygenase-1, PC: Peptide-C Ampoules, TGF-β: Transforming Growth Factor Beta

30 and above reduced forehead wrinkles in 63% of participants, while 64% saw improvements in crow's feet wrinkles. Moreover, skin hydration was increased in 67% of participants. Both investigator and participant evaluations indicated significant enhancements in skin quality, radiance, signs of aging, wrinkles, complexion, and pore appearance by day 30. Comparable outcomes were found in subgroup analyses, whether the ampoule was used alone or alongside other skincare treatments. Product tolerance was rated as good to very good by 98% of participants [76]. Further research using a microneedling technique applied a topical formula containing polydeoxyribonucleotide, vitamin C, and niacinamide (PVN) to UV-B-exposed skin. Results showed that PVN boosted levels of nuclear factor erythroid 2-related factor 2/heme oxygenase-1 (Nrf2)/HO-1, reduced pigmentation and oxidative stress, and increased collagen and elastin, thereby enhancing skin elasticity. The findings support PVN as an effective treatment for pigmentation and UV-induced collagen degradation [77].

A topical serum combining vitamins C and E with palmitoyl tripeptide-38 also demonstrated clinically significant improvements in skin appearance over 56 days. The serum smoothed the skin, improved tone, and reduced wrinkles, confirming the synergistic benefits of these ingredients for anti-aging [78]. Similarly, a Polish study tested a layered application of azelaic acid, phytic acid, and vitamin C, which collectively improved elasticity, reduced pigmentation, and enhanced overall skin tone without causing irritation [79]. Another study explored the impact of environmental factors on skin aging, finding that a topical antioxidant serum with 15% vitamin C, vitamin E, neohesperidin, *Pinus pinaster* bark, and hyaluronic acid effectively protected skin from air pollution-induced pigmentation and aging. Clinical assessments confirmed reduced pigmentation and aging signs, positioning the serum as an effective environmental defense [80].

Encapsulated serums containing vitamin C, vitamin E, and raspberry leaf cell culture extract were also tested for anti-aging benefits. Dermatological assessments showed that the serum improved several signs of aging—such as darkening, elasticity, radiance, smoothness, scaliness, and wrinkles. However, the elasticity improvement did not lead to visible lifting effects. The serum was also well-tolerated by participants [31]. Another study examining

the skin permeability, irritation potential, and anti-aging effects of vitamin C in a lotion formulation revealed that vitamin C concentrations of 10%, 15%, 20%, and 25% effectively penetrated the skin, with the 20% lotion achieving the highest transdermal efficiency, reaching 85% diffusion in 24 h and surpassing the control group by 1.43 times. The irritation tests showed low cytotoxicity, and patch testing confirmed no allergic reactions. After 28 days of using the vitamin C lotion, participants demonstrated significant improvements: a 10.5% increase in skin radiance, a 9.2% boost in elasticity and firmness, and a 12.3% reduction in wrinkle area. Overall, the 20% vitamin C lotion proved to be effective in enhancing skin appearance, elasticity, and wrinkle reduction [32].

Niacinamide's rejuvenating effects were shown in combination with an adipocyte-derived stem cell medium following fractional ablative laser treatment. The treatment decreased wrinkles and pigmentation, showing potential as a rejuvenation treatment due to its anti-inflammatory and wound-healing properties [81]. A topical product combining genistein, vitamins E and B3, and ceramide demonstrated significant benefits for postmenopausal women. Applied twice daily for 6 months, the products significantly improved skin hydration, reduced fine pore size and area, and increased skin redness. Among older participants (age > 56) with high compliance, it significantly improved most wrinkle parameters. Overall, the product demonstrated efficacy in enhancing hydration, reducing wrinkles, and improving skin redness for postmenopausal women, particularly benefiting older individuals [33].

A randomized trial compared oral vitamins (vitamins A and E) combined with a 0.02% retinoic acid gel versus the gel alone for moderate-to-severe facial aging. After 6 weeks, global skin aging scores dropped by 13% in the group using the topical gel alone and by 14% in the group using the gel with vitamins. By week 12, the reductions were 22% and 27%, respectively. Both treatments were well-tolerated, with the combination of oral vitamins and topical retinoic acid proving more effective for improving skin aging than the topical gel alone [35]. In another study, the effectiveness of a 4% retinol solution containing TGF-β activators and antioxidants for improving facial skin affected by aging and various skin disorders was assessed. All participants noted overall improvement post-treatment, with most reporting enhancements in skin tone, pigmentation, hydration, structure, and oil control. Objective assessments showed significant improvements in pigmentation, especially among individuals with early signs of aging, post-inflammatory hyperpigmentation, acne scars, and enlarged pores. The treatment was well-tolerated, cost-effective, easy to use, and associated with minimal side effects, yielding high patient satisfaction [34].

Retinyl palmitate (RP), a retinol ester with strong antioxidant and anti-inflammatory properties, is effective as an anti-wrinkle agent but has limited water solubility and degrades easily in topical applications. To overcome these limitations, chitosan-coated nanocapsules (ChiNCs) were developed using a simple nanoprecipitation method to encapsulate retinyl palmitate, enhancing stability and promoting deeper skin penetration. The retinyl palmitate-loaded nanocapsules (RP@ChiNCs) contained about 5% retinyl palmitate, had a size of 86 nm, and a surface charge of 24 mV, remaining stable after lyophilization. ChiNCs protected retinyl palmitate from degradation for four weeks at 37 °C and maintained strong antioxidant activity over time. The chitosan coating also improved retinyl palmitate's skin penetration and showed significant antioxidant and anti-inflammatory effects in vitro without cytotoxicity to dermal fibroblasts. Additionally, RP@ChiNCs promoted cell proliferation and collagen synthesis, making them promising for cosmetic and biomedical applications [82].

Overall, the evidence presented emphasizes the marked potential of vitamins in skin care and anti-aging treatments. Vitamins including C, B_3, A, and E exhibit multifaceted benefits, ranging from collagen synthesis and antioxidant protection to improved hydration and pigmentation reduction. These effects are further amplified through innovative application methods like sonophoresis, microneedling, and encapsulation, which enhance stability, skin penetration, and efficacy. Clinical trials consistently demonstrate significant improvements in skin elasticity, radiance, and wrinkle reduction across diverse formulations and population groups. With minimal side effects and growing consumer acceptance, formulations containing vitamins hold promise for advancing dermatological care and personalized skincare solutions, resulting in more effective and targeted anti-aging therapies.

Essential fatty acids

Barrier repair agents enhance skin barrier function and promote skin health. Natural oils comprise of fatty acids that are essential for preserving the skin barrier, as well as possessing anti-inflammatory and anti-stimulatory properties. The varying ratios of essential fatty acids are the primary factors influencing the barrier repair functions of natural oils. Omega-3 fatty acids (found in oils such as flaxseed, walnut, and some exotic oils) and omega-6 fatty acids (present in oils including grape seed, safflower, sunflower, blackcurrant, evening primrose, and borage oil) are two primary important fatty acids. Oils characterized by a high linoleic acid to oleic acid ratio, like sunflower seed oil, exhibit significant barrier repair capabilities, whereas oils with elevated oleic acid levels, such as olive oil, may detrimentally affect skin barrier function [90]. Essential long-chain PUFAs are crucial nutrients for

preventing age-related disorders. Table 4 presents a summary of recent research examining the effects of essential fatty acids on their anti-aging potential.

PUFAs have a crucial role in modulating cholesterol levels and serve as precursors to prostaglandins. Omega-3 (ω-3) and omega-6 (ω-6) fatty acids are essential constituents of cell membranes and serve as precursors to various chemical compounds in the body, including those that regulate blood pressure and mediate inflammatory reactions. The human body can synthesize all necessary fatty acids except for two: LA, an omega-6 fatty acid, and ALA, an omega-3 fatty acid. These must be obtained from the food and are referred to as "essential fatty acids." Both fatty acids are essential for growth and healing, and they can also be utilized in the synthesis of additional fatty acids. Omega-3 fatty acids, specifically EPA and DHA, can be generated from ALA; however, due to the restricted conversion, it is advisable to incorporate these sources into the diet as well. ALA and LA are present in vegetable and seed oils. While LA levels are often significantly greater than those of ALA, canola and walnut oil serve as excellent sources of the latter. EPA and DHA are present in fatty fish such as salmon, mackerel, and herring. AA can be sourced from animal products, including meat and egg yolk [96]. In a recent study, the efficacy of cannabidiol and EPA in preventing and treating skin aging was assessed. The effects of both compounds were evaluated utilizing established photoaging models of UV-induced damage, both in vitro (HaCaT cells) and ex vivo (human skin organ culture). A clinical validation study ($n = 33$) was conducted with an optimized topical cream formulation assessed at various time intervals up to day 56. EPA was discovered to enhance the protective benefits of cannabidiol by diminishing

Table 4 Anti-aging potential of essential fatty acids

Source	Stress Source	Study Type	Results	References
CBD (10 µg/mL), EPA (10 µg/mL), or both (1:1 ratio)	UVB-induced damage models UVB (VL-6.M lamp, UVB medium wave emission spectrum 280–350 nm, emission peak 312 nm)	In vitro (HaCaT cells) ex vivo (human skin organ culture). Clinical validation study ($n = 33$)	• Reduce the secretion of PGE2 and IL-8 • Enhance ECM remodeling subsequent to UV radiation exposure • Decrease in the area and volume of crow's feet wrinkles, along with a reduction in the volume of fine line wrinkles • age-dependent SLEB was diminished by 8.8% • Substantial decrease in the area and count of red spots • Enhance skin hydration and elasticity by 31.2% and 25.6%, respectively, after 56 days of cream administration	[91]
Omega-3 PUFAs including EPA	Natural and accelerated aging model	Mfat-1 transgenic mice (8 weeks old) received subcutaneous D-gal (150 mg/kg/day) for 8 weeks. A second group followed a control or EPA diet for 8 weeks.	• Omega-3 PUFAs and the fat-1 transgene may mitigate age-related pathological alterations • Impede the deterioration of organ function • Postpone aging by activating PPARα signaling, enhancing fatty acid oxidation and ATP production to reconfigure energy metabolism • Foster healthy aging in elderly mice	[92]
Omega-3 (2.5 g/d of omega-3, 1.25 g/d of omega-3, or a placebo for 4 months)	Trier Social Stress Test	Clinical trial	• Reduce general inflammation and cortisol levels during stress • Enhance repair processes during recovery	[93]
Omega-3 Threshold 1.103 g/day	Oxidative-stress	Cross-sectional study- 20,337 adult participants	• Linear negative association between Omega-3 intake and PhenoAgeAccel	[94]
n-3 PUFA or n-6 PUFA supplementation	UV-induced damage	Whole-genome proteomics and lipidomics analyses using a self-constructed photoaging mouse model	• n-3 PUFA may alleviate photoaging by upregulating Hmmr expression • Decrease Mmp9 expression • Reduce collagen degradation	[95]
Walnut oil and tamarind seed oil encapsulated in liposomal cream formulation	UV-induced damage	Animal study	• Walnut and tamarind seed oil were successfully entrapped in a liposomal formulation and are potent against ageing	[36]
Avocado oil nano emulsion	-	In vitro	• Avocado oil in ultrasound-assisted nanoemulsions showed the highest collagenese inhibition	[37]

CBD: Cannabidiol; EPA: eicosapentaenoic acid; UVB: ultraviolet B-light; HaCat: Human Adult Colonized Keratinocytes; PGE2: prostaglandin E2; IL-8: interleukin-8; SLEB: subepidermal low-echogenic band; PUFA: polyunsaturated fatty acids; PPARα: proliferator-activated receptor α; ECM: extracellular matrix; Hmmr: hyaluronic acid receptor; Mmp9: Matrix Metallopeptidase 9

the release of prostaglandin E2 (PGE2) and interleukin-8 (IL-8), two principal inflammatory mediators linked to photoaging. Furthermore, a qualitative histology analysis indicated that the application of the cream may enhance extracellular matrix remodeling subsequent to UV radiation exposure. Clinical evidence demonstrated a decrease in the area and volume of crow's feet wrinkles, along with a reduction in the volume of fine line wrinkles, as assessed by the AEVA system. The established age-dependent subepidermal low-echogenic band was diminished by 8.8%. Further clinical findings indicated a substantial decrease in the area and count of red spots, alongside an enhancement in skin hydration and elasticity by 31.2% and 25.6%, respectively, after 56 days of cream administration [91]. Another study [92] indicated that omega-3 polyunsaturated fatty acids, particularly EPA, had positive effects on sustaining energy metabolism and lipid homeostasis, hence decelerating organ aging. As the intrinsic agonist of peroxisome proliferator-activated receptor α (PPARα), omega-3 PUFAs markedly enhanced fatty acid β-oxidation and ATP synthesis in several aged organs. Consequently, omega-3 PUFAs significantly mitigated age-related pathological alterations, maintained organ function, and decelerated the aging process. The advantageous benefits of omega-3 PUFAs were also demonstrated in mfat-1 transgenic mice, which autonomously produce substantial endogenous omega-3 PUFAs. The delivery of omega-3 PUFAs in the diet mitigates aging via enhancing energy metabolism. The administration of omega-3 PUFAs or the fat-1 transgene offers a viable therapeutic strategy to enhance healthy aging in the elderly. A controlled trial investigated the effects of omega-3 supplementation on biomarkers associated with cellular aging after a laboratory-induced speech stressor. A total of 138 inactive, overweight, middle-aged individuals ($n = 93$ women, $n = 45$ males) were administered either 2.5 g/d of omega-3, 1.25 g/d of omega-3, or a placebo over a duration of 4 months. Omega-3 may mitigate accelerated aging and diminish the risk of depression by reducing general inflammation and cortisol levels during stress while enhancing repair processes during recovery [93]. A cross-sectional study [94] examined the correlation between dietary omega-3 fatty acid consumption and accelerated phenotypic aging, known as PhenoAgeAccel. PhenoAgeAccel is the disparity between phenotypic biological age, determined through blood biochemical markers, and chronological age. Upon controlling for other potential confounding variables, a significant negative association was identified between omega-3 fatty acid consumption and PhenoAgeAccel ($\beta = -0.071$; 95% CI: −0.119, −0.024; $p = 0.004$), suggesting that increased omega-3 intake correlates with a deceleration in PhenoAgeAccel. For each unit increase in omega-3 consumption, the rate of phenotypic aging diminished by an average of 0.071 units, indicating a substantial linear negative association between omega-3 intake and PhenoAgeAccel [94]. Telomeres are protective structures located at the termini of eukaryotic chromosomes, with their length being associated with health and longevity. Telomere attrition is a prevalent characteristic of aging and can be expedited by oxidative stress and chronic inflammation. Diverse nutrients affect telomere length, partly owing to their antioxidant and anti-inflammatory characteristics. Ali et al. [97] conducted a review on the impact of omega-3 fatty acids on telomere length, utilizing four databases since November 2021. Their findings demonstrated a significant positive impact of omega-3 fatty acids on telomere length. Although there are few clinical studies, existing evidence indicates that omega-3 fatty acids may have a beneficial impact on telomere length [97]. Omega-3 fatty acids have a preventive effect against ultraviolet damage. A potential mechanism for this was illustrated in a study involving mice, where omega-3 fatty acids diminished collagen degradation by lowering the production of matrix metalloproteinases, which are associated with extracellular matrix degradation [95]. AA, a prevalent PUFA, contributes to the fluidity of mammalian cell membranes. It is synthesized from LA and can be converted into several bioactive metabolites, including prostaglandins, thromboxanes, lipoxins, hydroxy-eicosatetraenoic acids, leukotrienes, and epoxyeicosatrienoic acids through distinct pathways. All these steps are crucial to amino acid metabolism. Qian et al. [98] examined and emphasized the significance of amino acid metabolism in aging, proposing novel techniques for addressing aging-related disorders. Walnut oil is a colorless to yellowish oil derived from the extraction of dried, mature seeds. It can be blended with other oils and contains varying proportions of alpha-linolenic acid (51.9–55.2%), saturated palmitic acid (approximately 7%), stearic acid (3.4–4.6%), and monounsaturated oleic acid (18.5–22.6%) [36]. Furthermore, the predominant fatty acids in tamarind seed oil are palmitic, oleic, and linoleic. The lipids comprise a significant proportion of unsaturated fatty acids, with linoleic acid constituting the largest quantity at 36–49%. Other significant fatty acids are oleic acid (15–27%) and palmitic acid (14–20%) [99]. Singh et al. [36] studied the anti-aging potential of walnut oil and tamarind seed oil-encapsulated cream on a 14-day animal study conducted on female Swiss mice. Their investigation on the anti-aging capabilities of walnut oil and tamarind seed oil, successfully encapsulated in a liposomal cream formulation, indicates their potential anti-aging effects.

The pulp oil of avocado comprises the following percentages of fatty acids: 24.06% saturated fatty acids, 52.06% monounsaturated fatty acids, and 23.94% polyunsaturated fatty acids. Oleic acid, palmitic acid, and

linoleic acid were recognized as prevalent in avocado oil. Kiattisin et al. [37] indicated that avocado oil exhibited low peroxide and IC_{50} values, making it appropriate for nanoemulsion development, and demonstrated the strongest collagenase inhibitory activity among the natural oils evaluated. The processing of avocado oil into ultrasound-assisted nanoemulsions may augment the benefits observed in fibroblast cells, including improved collagen activation and improved cell viability.

In conclusion, the advantages of natural oils and essential fatty acids, especially omega-3 and omega-6, are significant in skincare and general wellness. Recent research substantiates their significance in enhancing skin barrier function, mitigating inflammation, and enhancing anti-aging effects. Integrating these natural chemicals into everyday routines not only enhances skin health but also aids in sustaining energy metabolism and decelerating the aging process. As scientific knowledge advances, the potential uses of these substances in nutritional and cosmetic products are increasing, providing promising methods for promoting healthy aging and enhancing quality of life.

Other phytochemicals

Table 5 presents a summary of recent research examining the effects of saponins and alkaloids on their anti-skin aging potential.

Ginsenosides are saponins found in ginseng, classified as steroid glycosides. Dammarane ginsenosides include protopanaxadiols (ginsenoside Rk1, and Rg3) and protopanaxatriols (ginsenoside Rk3) distinguished by the attachment of sugar moieties at specific positions on the triterpene structure [108]. Jang et al. [13] demonstrated that ginsenoside Rg3 restored cellular senescence in human dermal fibroblasts by enhancing cell viability and reducing senescence markers such as p16, p21, and p53, particularly in old dermal fibroblasts, without cytotoxicity at concentrations up to 80 mM, with optimal effects at 10 mM. Ginsenoside Rg3 also decreased ROS levels and upregulated PRDX3, contributing to its antioxidant properties, thereby promoting cellular health and suggesting therapeutic potential in senescence-related conditions. Liu et al. [9] found that ginsenoside Rk1 protected both HaCaT cells and BALB/c nude mice against UVB-induced skin damage by reducing oxidative stress and inflammation while inhibiting the PI3K/AKT/NF-κB signaling pathway. Ginsenoside Rk3, as reported by Wan et al. [100], exhibited significant anti-photoaging effects by improving skin elasticity, moisture content, antioxidant defenses (SOD, GSH-Px), and the content of hydroxyproline while inhibiting MMPs and pro-inflammatory cytokine secretion (TNF-α, IL-6, IL-1) induced by UV irradiation. Additionally, Im et al. [101] noted that Ttimosaponin A-III protected against UVB damage by maintaining cell viability, inhibiting MMP-1, IL-1β, IL-8, TNF-α, and increasing TIMP mRNA levels in HaCaT cells, along with showing significant wrinkle reduction in clinical trials over 12 weeks.

Alkaloids are naturally occurring organic compounds that contain nitrogen in their structure. This nitrogen atom is responsible for the alkalinity of alkaloids, typically found within a ring system. Alkaloids play a crucial role in pharmacology, with indole-containing alkaloids, such as alkaloid N-glycoside, berberine, and piperine, being particularly significant in medicinal chemistry due to their chemical reactivity and diverse pharmacological activities [109]. Choi et al. [6] reported that alkaloid N-glycoside ginkgoside B dimethyl ester from *Ginkgo biloba* exhibited protective effects against TNF-α-induced skin damage in human dermal fibroblasts. It reduced the expression of MMP-1 and pro-inflammatory cytokines (IL-1β, IL-6, IL-8) while decreasing phosphorylation of MAPKs (ERK, JNK, p38) and Akt, and increasing heme oxygenase-1 (HO-1) expression. Another study by Sunilkumar et al. [102] revealed that berberine, an isoquinoline alkaloid, enhanced cell viability and reduced ROS, DNA damage, and senescent cells in L929 cells exposed to UV irradiation, demonstrating significant cytoprotective effects. Furthermore, Tanveer et al. [103] examined that trigonelline, a pyridine alkaloid, protected human dermal fibroblasts and BALB/c mice from UVB-induced cytotoxicity and oxidative stress by activating the PI3K-Akt-Nrf2 signaling pathway, thereby reducing DNA damage markers and cytotoxicity.

Higenamine, an aporphine alkaloid, reduced MMP-1 expression, an enzyme associated with collagen degradation, by inhibiting AP-1 and NF-κB transcription factors, and it decreased oxidative stress-related kinase phosphorylation, lowering ROS levels in HaCaT cells [104]. In vivo, higenamine (1–20 mg/kg) enhanced collagen synthesis in UVB-damaged hairless mice by increasing COL1A1, TGF-β, and phosphorylated Smad3 levels, while reducing skin thickening and promoting collagen fibers. It maintained COL1A1 levels in TGF-β knockdown fibroblasts, highlighting its protective role against collagen degradation [105].

Lu et al. [106] stated that piperine, a piperidine alkaloid, showed promise for psoriasis therapy by inhibiting psoriatic dermatitis in vitro and in vivo mouse models. It reduced HaCaT cell proliferation and promoted apoptosis via cleaved-PARP expression, downregulating psoriasis-associated markers S100A7 and pro-inflammatory cytokines. In vivo, piperine cream alleviated symptoms of psoriasiform dermatitis in an IMQ-induced mouse model, reducing skin thickening and erythema while inhibiting STAT3 phosphorylation. It also downregulated the psoriasis-associated markers S100A7 and various cytokines and chemokines. Piperine cream alleviated

Table 5 Anti-aging potential of other phytochemicals

	Source	Stress Source	Study Type	Results	References
Saponins	Ginsenoside Rg3: 5, 10, 20, 40, 80, and 160 μM	H_2O_2: 200 mM	In vitro: Human dermal fibroblasts	↑ PRDX3, PPP2R1A, Heat Shock Protein 60: Hsp60 ↓ p16, p21, p53, ROS level, SA-β-gal Staining	[13]
	Ginsenoside Rk1: 10, 20, and 40 μM	UVB: 40 mJ/cm^2	In vitro: Human dermal fibroblasts	↓ MDA, ROS, TNF-α, IL-6, IL-1β, IL-8, MMP-3, and MMP-9 level ↑ SOD, CAT, GSH-Px, Type I and III collagen ↓ Phosphorylation of pI3K, AKT, IκBα, and NF-κB	[9]
	Ginsenoside Rk1: 2.0 mg/cm^2	UVB: 100 mJ/cm^2/week	In vivo: BALB/c mice	Alleviated sunburn and wrinkles Normalized epidermal thickness ↑ Collagen fiber structure and density ↓ MDA, ROS, TNF-α, IL-6, IL-1β, IL-8, MMP-3, and MMP-9 level ↑ Type I and III collagen ↓ Phosphorylation of pI3K, AKT, IκBα, and NF-κB	
	Ginsenoside Rk3: Not specified	UVA: 340 nm and 40 W UVB: 313 nm and 40 W	In vivo: Kunming mice	Smooth and plump skin, minimal wrinkles, no ulcers or blisters ↓ Recovery time, MDA, MMP-1, MMP-3, TNF-α, IL-6, IL-1 ↑ SOD, GSH-Px, Hydroxyproline	[100]
	Timosaponin A-III: 0.1 μmol/L	UVB: 20 mJ/cm^2	In vitro: Human HaCaT Keratinocytes	↑ TIMP mRNA ↓ MMP-1, mRNA levels of IL-1β, IL-8, TNF-α	[101]
	Timosaponin A-III: 0.25% in lotion, 12 weeks	--	*Clinical*: 21 women, crow's feet treatment	Wrinkle Reduction ↓ Skin roughness, average roughness (after 8–12 weeks), smoothness depth (after 12 weeks), arithmetic average roughness, maximum roughness	

Table 5 (continued)

	Source	Stress Source	Study Type	Results	References
Alkoloids	Indole Alkaloid N-Glycoside: 10 mM	TNF-α: 20 ng/mL	In vitro: Human dermal fibroblasts	↓ MMP-1, p-Akt, COX-2, Il-8, IL-1β, IL-6 expression ↓ Phosphorylation of ERK, JNK, p38 ↑ Type I collagen mRNA expression	[6]
	Berberine: 3.1, 6.25, 12.5 and 25 µg/mL	--	In vitro: Murine fibroblast (L929) cells	↑ Tail length of DNA ↓ ROS, Comer length of DNA, SA-β-gal	[102]
	Trigonelline: 25 and 50 µM	UVB: 10 mJ/cm^2	In vitro: Human dermal fibroblasts	↓ Lactate dehydrogenase activity, γH2AX ↑ HO-1, Phosphorylation of PI3K, Akt, and Nrf2 ↓ Cyclobutane Pyrimidine Dimer Formation, TUNEL positive cells ↓ CAT, MDA	[103]
	Trigonelline: 100 and 200 µM	UVB: 180 mJ/cm^2	In vivo: BALB/c mice	↓ γH2AX, CHK2, CHK1, and p53 expression ↑ Phosphorylation of PI3K and Akt, Nrf2	
	Higenamine: 5, 10, and 20 µM	Fine dust. 25 mg/mL	In vitro: Human HaCaT Keratinocytes	↓ MMP-1, AP-1 and NF-κB transactivation, ROS ↓ Phosphorylation of Akt-p70S6K, MEK1/2-ERK1/2-p90RSK, JNK1/2, MKK3/6-p38	[104]
	Higenamine: 0.01, 0.1, 1, and 10 µM	UVB: 100–300 mJ/cm^2	In vitro: Human dermal fibroblasts	↑ Col1A1, Collagen fiber, Smad3 DNA-binding phosphorylation ↓ Skin and epidermal thickness, trans epidermal water loss	[105]
	Higenamine: 1, 5, 10, and 20 mg/kg		In vivo: Mice	↑ Col1A1, TGF-β, Smad3 DNA-binding phosphorylation, collagen fiber ↓ Skin and epidermal thickness, trans epidermal water loss	
	Piperine: 0.1, 1, 10, 100, and 1000 µM	M5: 10 ng/mL	In vitro: Human HaCaT Keratinocytes	↓ IL-6, IL-23, β-defensin 2, CCL20, S100A7 Expression ↑ Cleaved-PARP Expression	[106]
	Piperine: 2 or 4 mM in cream	Imiquimod: 62.5 mg on the back, 20 mg on the ear	In vivo: BALB/c mice	Attenuated thickening, erythema, and scales ↓ Average PASI Score, Epidermal hyperplasia and inflammatory cell infiltration ↓ Epidermal Thickness of back and ear skin lesions ↓ mRNA levels of IL-17 A, IL-17 F, IL-23, IL-6, S100A8, CCL20, CXCL2, and β-defensin2 ↓ IL-17 A in epidermis ↓ STAT3 phosphorylation	
	Piperine: 10, 20, and 40 µM	UVB: 40 mJ/cm^2	In vitro: Human HaCaT Keratinocytes	↓ Nitrite, ROS, iNOS, COX-2, Apoptotic cells, Prostaglandin E2, IL-6, IL-8 ↓ Phosphorylated p38 and JNK, AP-1 Protein Expression	[107]

↑: Upregulation, ↓: Downregulation, ↔: No obvious change

γH2AX: Phosphorylated H2A histone family member X, Akt: Protein kinase B, AP-1: Activator Protein 1, CAT: Catalase, CHK1, CHK2: Checkpoint Kinases 1 and 2, CCL20: Chemokine Ligand 20, Cleaved-PARP: Poly(ADP-ribose) Polymerase Cleaved, Col1A1: Collagen Type I Alpha 1 Chain, COX-2: Cyclooxygenase-2, ERK1/2: Extracellular Signal-Regulated Kinase 1 and 2, GSH-Px: Glutathione Peroxidase, HO-1: Heme Oxygenase 1, Hsp60: Heat Shock Protein 60, IL: Interleukins, iNOS: Inducible Nitric Oxide Synthase, JNK: c-Jun N-terminal Kinases, MDA: Malondialdehyde, MKK: Mitogen-Activated Protein Kinase Kinase, MMP: Matrix Metalloproteinases NF-κB: Nuclear Factor kappa-light-chain-enhancer of activated B cells, Nrf2: Nuclear factor erythroid 2-related factor 2, PASI: Psoriasis Area and Severity Index, p16: Cyclin-dependent kinase inhibitor 2 A, p21: Cyclin-dependent kinase inhibitor 1, p38: p38 Mitogen-Activated Protein Kinases, p53: Tumor Protein 53, PI3K: Phosphoinositide 3-Kinase, PPP2R1A: Protein Phosphatase 2 Regulatory Subunit A Alpha, PRDX3: Peroxiredoxin 3, ROS: Reactive Oxygen Species, SA-β-gal: Senescence-Associated Beta-Galactosidase, S100A7, S100A8: Calcium-binding proteins, Smad3: A signaling molecule in the TGF-β pathway, SOD: Superoxide Dismutase, TGF-β: Transforming Growth Factor Beta, TIMP: Tissue Inhibitor of Metalloproteinases, TNF-α: Tumor Necrosis Factor-alpha, TUNEL: Terminal deoxynucleotidyl transferase dUTP nick end labeling

symptoms of psoriasiform dermatitis in an IMQ-induced mouse model, demonstrating reduced skin thickening, erythema, and scaling. Additionally, it decreased the expression of pro-inflammatory cytokines and inhibited the phosphorylation of STAT3, a key pathway involved in psoriasis pathogenesis [106]. Moreover, Jaisin et al. [107] reported that piperine demonstrated significant photoprotection against UV-B-induced cytotoxicity in keratinocytes. It enhanced cell viability, decreased nitrite levels, and reduced intracellular ROS and nitric oxide after UV-B exposure. Piperine suppressed p38 and JNK activation, resulting in lower levels of inflammatory markers such as iNOS and COX-2, and significantly downregulated pro-inflammatory cytokines IL-6 and IL-8.

Cytotoxicity was not detected for ginsenoside Rg3 (up to 80 µM) [13], indole alkaloid N-glycoside (up to 100 µM) [6], higenamine (up to 10 µM) [105], and trigonelline

(up to 100 μM) [103]. Nonetheless, piperine at concentrations from 2.5 to 40 μM was non-toxic to keratinocyte cells; however, concentrations above 80 μM resulted in marked cytotoxicity [107]. Alkaloids have multifaceted roles in human health, offering both therapeutic advantages and potential health risks. A comprehensive understanding of their classification, sources, and effects is essential for making informed decisions regarding their use, dosage, and implications for skin aging [109].

Both saponins and alkaloids exhibit significant potential in combating skin aging through their antioxidant, anti-inflammatory, and collagen-boosting properties. Ginsenosides, such as Rg3 and Rk3, show promise in restoring cellular health, protecting against UV-induced damage, and reducing senescence markers. Alkaloids including berberine, piperine, and trigonelline also offer protective effects by reducing oxidative stress, improving cell viability, and mitigating the effects of UV damage. While these compounds hold therapeutic promise for skin aging, careful consideration of their concentrations and potential cytotoxicity is crucial for their safe application in skin care.

Conclusion and future perspectives

Skin aging is a natural process and cannot be avoided, leading to alterations in the skin's strength, structure, elasticity, and overall integrity. Plant-based phytochemicals have emerged as promising agents in anti-aging skin care. Phytochemicals such as polyphenols combat skin aging primarily through their antioxidant properties, which neutralize ROS and reduce oxidative stress, thereby preventing cellular damage. They inhibit key enzymes involved in skin aging, such as collagenase and tyrosinase, through the activation of the AMPK signaling pathway. They also promote collagen synthesis, which enhances autophagy and cellular repair by the Wnt/β-catenin or TGF-β/Smad signaling pathway. Additionally, polyphenols modulate inflammatory responses by reducing pro-inflammatory cytokines, thereby alleviating chronic inflammation associated with skin aging through pathways like the JNK, p38 MAPK, and NF-κB signaling pathways. Carotenoids also exhibit antioxidant, anti-inflammatory, collagen-stimulating, and photoprotective properties. These bioactive compounds contribute to the reduction of oxidative stress, protection against environmental damage, and modulation of intrinsic aging processes. The inclusion of these compounds in skincare formulations presents a sustainable and consumer-oriented approach to promoting skin health and postponing the visible effects of aging. Furthermore, recent literature stresses the impact of various vitamins and novel delivery systems in enhancing skin health, combating signs of aging, and addressing skin disorders. Vitamin C, B3, A, and E each play crucial roles in cellular function and antioxidant defense, collectively contributing to improved skin tone, hydration, elasticity, and reduced wrinkle formation. Novel application methods, including sonophoresis, microneedling, encapsulation, and the development of stable nanocapsules, offer promising advancements in targeted delivery, maximizing the impact of these vitamins on skin health. Despite these benefits, certain limitations remain. The variability in vitamin concentrations, application methods, and skin types across studies can hinder the ability to generalize results. Additionally, while irritation and side effects were generally minimal, the formulations are not entirely risk-free and require further evaluation for long-term safety, particularly with high concentrations or in sensitive individuals. The combination treatments involving vitamins with antioxidants, peptides, or other bioactives suggest synergistic effects that amplify skin benefits, but their complex interactions necessitate additional research to fully understand and design optimal formulations. Overall, these studies affirm the therapeutic and cosmetic potential of vitamins in skincare, especially when paired with innovative delivery technologies. Continued research could refine these formulations, potentially personalizing them to specific skin conditions, aging stages, and individual sensitivities, enhancing both efficacy and consumer satisfaction. On the other hand, consumers highly choose natural extract cosmetics for their safety and efficacy, which correspond with demands for natural, organic, efficient, and sustainable skincare principles. Many natural oils exhibit exceptional capabilities with essential oils in their formulation, such as moisturizing, barrier repair, antioxidant, UV protection, whitening, and anti-inflammatory effects, perfected through millennia of natural selection. These features allow essential fatty acid components to significantly augment the anti-aging effects of skincare products via several mechanisms, facilitating the development of natural anti-aging skincare formulations. Saponins and alkaloids can be toxic, but their safety varies based on the specific type, concentration, and preparation method. Understanding the context and source is crucial for assessing their toxicity. For example, compounds such as indole alkaloid N-glycoside, berberine, trigonelline, higenamine, and piperine exhibit different toxicity levels depending on the concentration, administration form, and individual health status.

Understanding the biological mechanisms underlying skin aging, including the role of ROS, the degradation of collagen and elastin, and cellular senescence, is crucial for developing effective anti-aging strategies. The application of phytochemicals demonstrates promising potential in mitigating oxidative stress, reducing inflammation, and promoting collagen synthesis, thereby enhancing skin elasticity and resilience. The innovative treatments that not only address the visible signs of aging but also

promote overall skin health and longevity may revolutionize skincare practices, offering consumers safer and more effective solutions that harness the natural properties of botanical extracts and other bioactive compounds to enhance skin vitality and resilience. To enhance the effectiveness of phytochemical labeling, it is essential to include the effects of various matrix structures (such as hydrogels, oleogels, and emulsions) in the literature, as these structures significantly influence the solubility of phytochemicals due to their hydrophilic and lipophilic properties. Furthermore, susceptibility to high temperatures and variations in pH should not be overlooked. It is noteworthy that many phytochemicals encounter challenges related to poor stability, limited skin penetration, and low bioavailability. However, advancements in nanotechnology, encapsulation methods, and formulation strategies hold the potential to significantly improve their efficacy and overall effectiveness in skincare applications. As consumer demand for natural and eco-conscious products rises, phytochemicals provide a promising avenue for innovation within the skincare industry. The collaboration of researchers, dermatologists, and the cosmetic industry will be pivotal in translating these bioactive compounds into advanced skincare solutions for the future.

Abbreviations

AGEs	Advanced glycation end products
AMPK	AMP-activated protein kinase
CAT	Catalase
COX-2	Cyclooxygenase-2
GSH-Px	Glutathione peroxidase
GSH-Re	Glutathione reductase
IL	Interleukin
IFN-γ	Interferon-gamma
MDA	Malondialdehyde
MMPs	Matrix metalloproteinases
mtROS	Mitochondrial reactive oxygen species
ROS	Reactive oxygen species
SASP	Senescence-Associated Secretory Phenotype
SOD	Superoxide Dismutase
TNF-α	Tumor necrosis Factor-alpha
TGF-β	Transforming growth factor-beta
TEWL	Transepidermal water loss
NMF	Natural moisturizing factors
ITA	Typology angle
GPx	Glutathione peroxidase
PUFAs	Polyunsaturated fatty acids
LA	Linoleic acid
ALA	Alpha-linolenic acid
EPA	Eicosapentaenoic acid
DHA	Docosahexaenoic acid
AA	Arachidonic acid

Author contributions

Conceptualization, M.T., E.C.; writing—original draft preparation, M.T., D.G.K., S.K., T.O.; review and editing, M.T., D.G.K., S.K., T.O., E.C. ; supervision, E.C. All authors have read and agreed to the published version of the manuscript.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

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