Clinical, Cosmetic and Investigational Dermatology

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REVIEW

The Role of Probiotics in Skin Photoaging and Related Mechanisms: A Review

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Abstract: Solar ultraviolet radiation (UVR) is the primary pathogenetic factor in skin photoaging. It can disrupt cellular homeostasis by damaging DNA, inducing an inflammatory cascade, immunosuppression, and extracellular matrix (ECM) remodeling, resulting in a variety of dermatologic conditions. The skin microbiome plays an important role in the homeostasis and maintenance of healthy skin. Emerging evidence has indicated that highly diverse gut microbiome may also have an impact on the skin health, referred to as the gut-skin axis (GSA). Oral and topical probiotics through modulating the skin microbiome and gut-skin microbial interactions could serve as potential management to prevent and treat the skin photoaging by multiple pathways including reducing oxidative stress, inhibiting ECM remodeling, inhibiting the inflammatory cascade reaction, and maintaining immune homeostasis. In this review, the effects of oral and topical probiotics in skin photoaging and related mechanisms are both described systematically and comprehensively.

Keywords: probiotics, skin photoaging, skin microbiome, gut-skin axis, ultraviolet radiation, reactive oxygen species, extracellular matrix

Introduction

The skin, as one of the largest organs, is most easily damaged by ultraviolet radiation (UVR) after long-term exposure to solar radiation. Photoaging is defined as premature aging of the skin as a result of repeated exposure to solar UVR[1–3] Figure 1. The majority of age-related skin disorders are caused by photoaging. Clinical manifestations of skin photoaging include wrinkles, discoloration, telangiectasias, and dry and roughed appearance.[4–7] These are associated with the pathophysiological changes of various cells and tissues in both the epidermis and dermis. For instance, wrinkles, as the most obvious clinical feature of photoaging, are mainly induced by a decrease in dermal fibroblasts, as well as slower collagen and elastin synthesis rate but a faster breakdown rate.[8,9] Skin photoaging not only affects the esthetic appearance but also damages the normal skin barrier function, increasing the risk of skin inflammatory diseases and even malignancies.[10–12]

A stable and healthy skin microenvironment is significantly influenced by the skin microbiome, which is primarily composed of bacteria including *Cutibacterium, Corynebacterium, Staphylococcus* and *Streptococcus*.[13] The skin microbiome, like the gut microbiome, plays an important role in protecting against external pathogens, regulating immune responses, and catabolite repression.[14] Studies have shown that the skin microbiome is not static and unchanging, but is always influenced by age or physiological structure aging.[15] Changes in metabolic capacity, oxidation resistance capacity (cofactor and vitamin metabolism), membrane integrity and cell signaling capacity (glycolipid metabolism), lipid metabolism capacity (glycolipid metabolism and fatty acid biosynthesis), and pathogen resistance (antibiotic biosynthesis) were all negatively correlated with the degree of photoaging.[16–18] Additionally, UVR also acts as an important external factor in inducing skin microecological changes. Probiotics are active microorganisms that have beneficial effects on the host by altering the microbiota composition of a specific part of the host's flora.[19] Numerous studies have found a close relationship between the skin microbiome and skin

Received: 6 September 2022
Accepted: 3 November 2022
Published: 16 November 2022

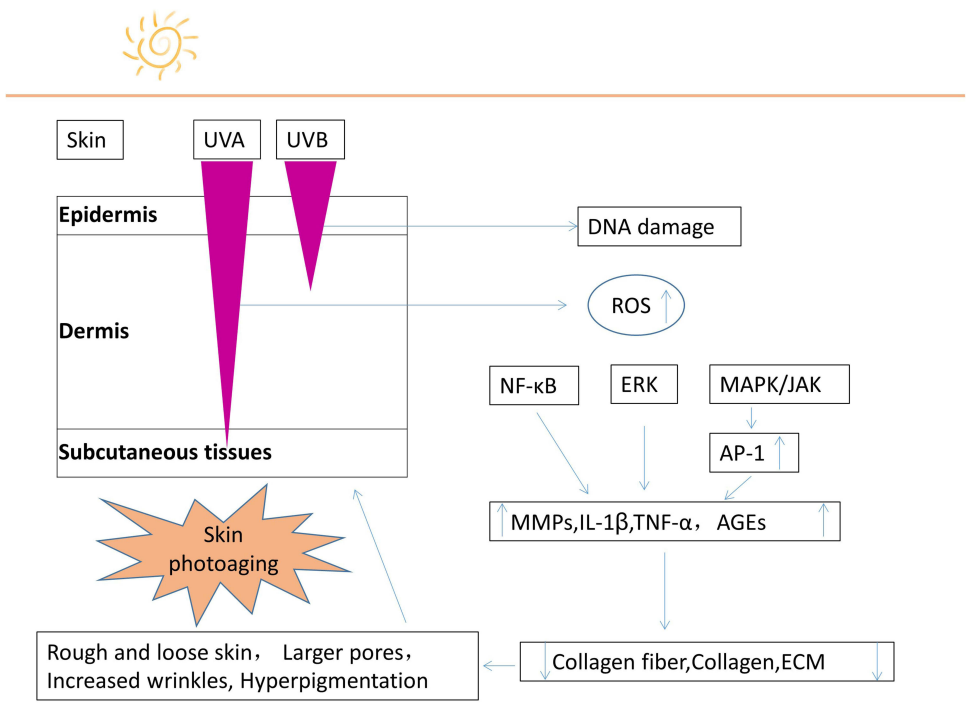

Figure 1 The mechanism of UV-induced skin photoaging.

health and stability.[20] The gut-skin axis indicates the relationship where the gut microbiome can also influence the skin health for its immunological properties. The positive regulation of the skin or gut microbiome by oral or topical probiotics has emerged as potential methods for preventing skin photoaging clinically. Oral probiotics are a group of living microorganisms that could change the gut microbiota that may induce a photoprotective effect on specific skin cells directly by modulating the immune response and inflammatory cytokines. Additionally, they can also increase serum levels of short chain fatty acid (SCFAs) and acetate, thereby inducing a series of immune and inflammatory response. Topical applications of probiotics have been studied as a means directly modifying the skin microbiome to prevent and treat the skin photoaging. Additionally, oral or topical probiotics are crucial in the management of other common cutaneous disorders such as atopic dermatitis,[21] acne,[22] rosacea,[23] and psoriasis[24–26] through modulating the skin microbiome and gut-skin microbial interactions. The role of oral and topical probiotics in photoaging and related mechanisms are discussed in this article Figure 2.

The Pathogenesis of Photoaging Induced by UVR

UVR can be classified into three types based on wavelength: UVA (320–400 nm), UVB (280–320 nm), and UVC (280–320 nm).[27,28] Among them, UVC is completely absorbed by the ozone layer, and both UVA and UVB are major contributors to skin disorders.[29,30] There are obvious differences in the changes in skin structure and function caused by the different wavelengths of UV. UVA accounts for 90–95% of the total UV and has a high penetration ability. UVA can penetrate the dermal papillary layer and affect cell components in the dermis and even subcutaneous tissue areas, such as fibroblasts, vascular endothelial cells, and Langerhans cells, as well as activate the matrix metalloproteinases (MMPs), which promote the degradation of collagen (mainly type I and type III collagen) and elastic fibers, resulting in dermal structure disorder. This type of damage is difficult to repair and has long-term effects on dermal tissue, resulting in skin relaxation, sagging, abnormal increase in wrinkles, and other macroscopic photoaging damage.[31,32]

Cellular DNA, RNA, and Protein Damage

As the most abundant chromophore, DNA strongly absorbs UVR.[33–35] When the skin epidermis absorbs UVR, pyrimidine bases in DNA combine with adjacent pyrimidines, resulting in the formation of cyclobutane-pyrimidine dimers and pyrimidine-pyrimidine (6–4) photoproducts. The latter causes mutations in functional base genes, seriously

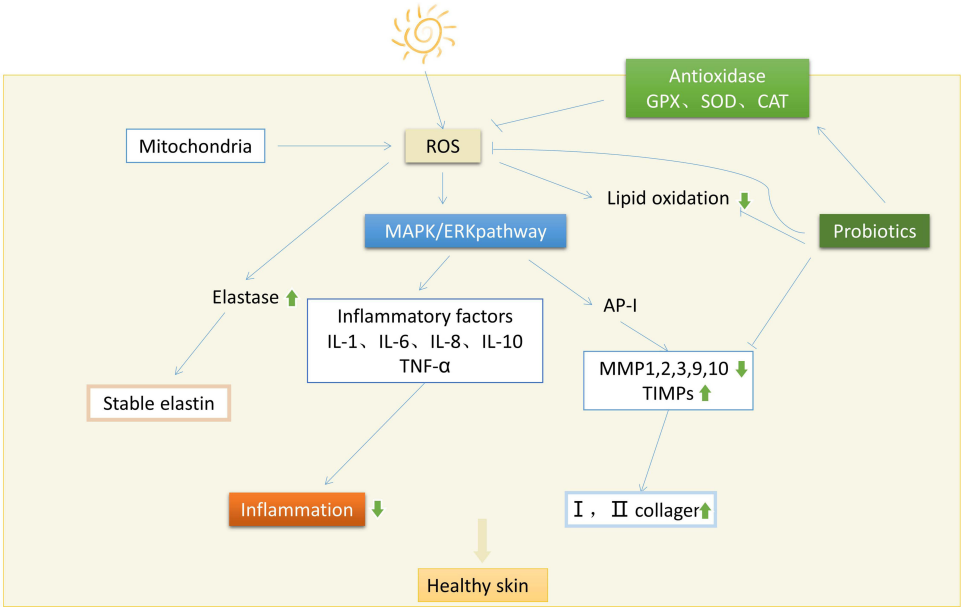

Figure 2 The role of probiotics against skin photoaging through multiple pathways.
Abbreviations: UVA, ultraviolet -A; UVB, ultraviolet -B; ROS, reactive oxygen species; NF-κB, nuclear factor-κB; ERK, extracellular regulated protein kinases; MAPK, mitogen-activated protein kinase; JAK, Janus kinase; AP-1, activator protein-1; MMP, matrix metalloproteinase; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor-α; AGEs, advanced glycation end products; ECM, extracellular matrix.

affecting the health of the epidermal system.[33,36,37] Longwave and shortwave UVR can both cause DNA damage but in different ways. Shortwave UVB and UVC can directly cause pyrimidine dimerization, inhibit plasmid DNA replication, or induce mutations after error repair. Long-wave UVA generally does not directly cause DNA damage but causes gene mutations via the production of excessive reactive oxygen species (ROS).[38,39] Additionally, UVR also damages cellular RNA. The mRNA would not be properly translated and transcribed, affecting signal transduction.[40] UVR can also induce cellular amino acid mutations, affect protein synthesis and even lead to cell cycle arrest and apoptosis. These mutations can eliminate the apoptotic capacity of cells, promoting the occurrence and development of cutaneous malignancies.[41]

Abnormal Photooxidative Stress Pathway

The major regulatory pathways of photooxidative stress consist of mitogen-activated protein kinase (MAPK), nuclear factor-κB (NF-κB), Janus kinase (JAK), and nuclear respiratory factor-2 (Nrf-2). The MAPK signaling pathway activates the expression of MMPs by activating activator protein-1 (AP-1) via the receptor tyrosine kinase signaling pathway, which is regulated by extracellular signal kinase 1/2, c-Jun N-terminal Kinase (JNK), and p38 protein.[42–44] JNK and p38 signaling pathways play key roles in UVR-mediated increase in expression of AP-1 and cyclooxygenase-2 (COX-2), which are both targets for anti-skin photoaging and carcinogenesis therapy.[45] Nrf-2 is a target of UV radiation. Nrf-2 regulates the expression of endogenous antioxidants such as glucose-6-phosphate dehydrogenase, thioredoxin reductase, glutathione-S-transferase, and peroxidases.[46] Oxidative stress also activates the NF-κB by activating the cytoplasmic inhibitor of NF-κB (I-κB) kinase, which phosphorylates and degrades I-κB. Activation of NF-κB is related to UVR-mediated oxidative modification of cell membrane components. NF-κB was released from its inhibitor I-κB, contributing to translocation of activated NF-κB to the nucleus and the activation of inflammatory cytokines and prostaglandins.[47,48]

UVR-Induced Mitochondrial Dysfunction

Mitochondria play an important role in oxidative reactions. UVR can induce mitochondrial DNA mutation, impair mitochondrial function, and decrease O_2 consumption and ATP production, thereby affecting cell migration and division.[49] UV-induced mitochondrial dysfunction and toxicity mechanisms include activation of cysteine-containing aspartate proteolytic enzyme, membrane depolarization, and cytochrome C release.[50] Above all, mitochondrial

dysfunction not only affects activities required for cellular energy expenditure, such as DNA repair but also increases oxidative stress levels, causing the production of ROS. When mitochondria damage and ROS production exceed a certain threshold, cell senescence and even death may occur.[51] Nrf-2 also plays a role in maintaining cellular redox balance by regulating mitochondrial respiration.[52]

Inflammatory Cascade Induction

UVR induces the expression of proinflammatory genes. Inflammatory mediators play an important role in skin photoaging.[53] They are released from keratinocytes, fibroblasts, tumor cells, leukocytes, and vascular endothelial cells, including plasma mediators (bradykinin, plasmin, and fibrin), lipid mediators (prostaglandins, leukotrienes, and platelet-activating factors), and inflammatory cytokines (interleukin-1 [IL-1], IL-6, and tumor necrosis factor-α [TNF-α]).[54,55] ROS-activated COX-2 and prostaglandin E2 (PGE2) are involved in the activation of ornithine decarboxylase and regulate cell proliferation.[56–58] UVR activates subcutaneous inflammatory cytokines, which trigger ROS and reactive nitrogen to produce peroxynitrite, leading to DNA deletion and recombination.[59,60] UVR alters the expression of transforming growth factor-β (TGF-β), which causes extracellular matrix (ECM) remodeling by regulating MMPs and thus promotes skin photoaging.[61]

In vivo Immune Suppression

UVR primarily reduces cellular immunity but can also affect humoral immunity.[62] UVR depletes epidermal Langerhans cells, which have been identified as important mediators of cellular immune response that are involved in antigen presentation.[63] UVR not only reduces the number of Langerhans cells but also disrupts their functions, such as lymphocyte migration and surface antigen expression. Long-term UVR reduces the expression of costimulatory molecules on the Langerhans cells, which inhibits the synthesis of membrane-associated antigens B7 (B7-1, B7-2).[64] UVR causes Langerhans cell depletion, which increases macrophage levels in the epidermis, activates regulatory T cells (Tregs), dysregulates the immune balance of T helper 1/2 cells (Th1/ Th2), and polarizes the Th1/ Th2 response to Th2.[65] The immunosuppressive effect of Th2 response polarization may be related to IL-12 because IL-12 depletion causes T cell activation in favor of Th2 and promotes Treg activation.[66–68]

Induction of ECM Remodeling

Collagen and elastin are both functional structural proteins of the ECM that promote angiogenesis and metastasis through remodeling. Damaged collagen and elastin are always the sensitizers of photooxidative stress. The specific properties of various collagens are dependent on the length of the triple helical segments, triple helical breaks, and amino acid modifications. Elastin fibers consist primarily of an elastin core (90%) surrounded by fibrillar microfibrils. The elastic fibers in the skin lose their normal structure and function when exposed to UVR. UVR also depletes the microfiber network in the epidermis-dermis and dermis, generating abnormal elastic fibers.[69,70] During the process of ECM remodeling, ECM proteolytic enzymes (MMPs and elastase) are generated by epidermal keratinocytes and fibroblasts. Their basal levels rise with age and further increase due to environmental pollutants and UVR as a result of the breakdown of collagen and elastin.[71–73] The transcription factor AP-1 is mainly activated by the MAPK signaling pathway, which can stimulate the transcription of a variety of MMPs, including MMP-1, MMP-2, MMP-9, and MMP-3, thereby degrading the ECM. Furthermore, AP-1 suppresses the transcription of the type I collagen gene.[74,75] The enhanced degradation of ECM by MMPs and the decreased expression of ECM structural proteins further damage the ECM and tissue integrity. Tissue inhibitors of MMPs (TIMPs) inhibit the affinity of MMPs. The remodeling of collagen and elastin in angiogenesis, metastasis, and tissue destruction is mainly due to increased MMP expression and decreased TIMP expression.[76,77]

Mechanism of Probiotics in Photoaging

Positive Modulation of Gut-Skin Microbial Interaction by Oral Probiotics

Oral probiotics act directly on the gut microbiota and rapidly restore the homeostasis of gut microbiome, which play a vital role in the skin homeostasis. That depends on the important structural basis, gut-skin axis (GSA).[78] The disrupted

GSA is associated with various dermatologic condition, including skin photoaging. Despite that the exact mechanism of gut-skin microbial interactions has not been clarified, it has been postulated that changes to the gut microbiota could trigger the systemic inflammation and abnormal immune response that disrupt the skin health.[79] Gut microbiota or its metabolic products could migrate from gut into the circulation and accumulate in the skin owing to the increased intestinal permeability, which may damage the skin barrier and make its susceptible to inflammation.[80] Thereby, oral probiotics could reverse these dermatologic conditions through the positive modulation of gut-skin microbial interaction.

Oxidative Stress Level Reduction

The pathophysiology of skin photoaging is closely associated with ROS-induced damage, including the activation of the MAPK and NF-kB signaling pathways, reduction in MMP synthesis, and production of collagen, thereby leading to skin photoaging. Shin et al[81] demonstrated that topical fermentation of *Agastache rugosa*-fermented extract *(ARE-F)* with a probiotic *Lactobacillus* enhances UVB-induced levels of total glutathione and superoxide dismutase activity while decreasing UVB-induced ROS, MMP-2, and MMP-9 levels in UV-B-irradiated Hacat keratinocytes. Im et al[82] found that topical *Lactobacillus acidophilus IDCC 3302* protected against UVB-induced photodamage to epidermal cells by enhancing the activity of skin antioxidant enzymes, hydration factors and suppressing the MMP levels through the inhibition of MAPK signaling pathway. Lim et al[83] found that topical *Lactobacillus acidophilus KCCM12625* has a good antioxidant effect, and can significantly reduce the elevated ROS level in HaCaT cells following UVB irradiation, and alleviate skin photoaging caused by oxidative damage. Ishii et al[84] proposed that oral administration of *Bifidobacterium breve Yakult* could prevent ROS production and attenuate UV-induced skin barrier damage and oxidative stress in animal experiments. Kang et al[85] demonstrated that a topical plant extract fermented with *Lactobacillus buchneri* alleviated the effect of ROS in a UVB-induced photoaging in vitro model by increasing the synthesis of type I procollagen, inhibiting elastase activity, and increasing the expression of UVB-induced MMPs on HaCaT keratinocytes and dermal fibroblasts. Chen et al[86] found that topical *Limosilactobacillus fermentum XJC60* was able to stabilize mitochondrial function, reduce ROS production in UVB-injured skin cells, and thereby maintain the skin health. Additionally, recent studies have demonstrated oxidation resistance as the major mechanism by which *Lacticaseibacillus rhamnosus GG (ATCC 53103, LGG)*[87] and *Lacticaseibacillus casei strain Shirota* attenuate skin photoaging.[88]

Inflammatory Cascade Inhibition

Increased skin inflammatory factors cause destruction of the barrier function, transepidermal water loss (TEWL), increased epidermal permeability, and accelerated skin photoaging. Satoh et al demonstrated that oral administration of *Bifidobacterium breve B-3* in UV-irradiated mice effectively reduced UV-induced IL-1β production in the skin. Resultantly, TEWL, skin hydration, and epidermal thickening were suppressed.[89,90] Besides the antioxidant properties, topical *Lactobacillus acidophilus IDCC3302* can also inhibit the production of pro-inflammatory cytokines mediated by the MAPK signaling pathway and reduce skin inflammation induced by UVB radiation.[82] To manage skin photoaging, Khmaladze et al found that topical *Lactobacillus reuteri DSM 17938*[91] had anti-inflammatory activity against the IL-6 and IL-8 induced by UVR. Keshari et al[92] found that butyric acid from a new generation of topical probiotic *Staphylococcus epidermidis* could down-regulate the UV-induced pro-inflammatory IL-6 cytokine via short-chain fatty acid receptor. Hong et al[93] demonstrated that orally administered oligosaccharides modulate inflammatory immune responses induced by UVR to reduce the TEWL and sunburn erythema, thereby preventing skin photoaging.

Maintaining the Immune Homeostasis

Some specific probiotics like *Lactobacillus paracasei* promote immune responses to eliminate pathogens.[94] Additionally, they can suppress unnecessary immune responses to maintain immune balance against chronic inflammatory conditions. This could be attributed to the regulation of the number of Tregs by probiotics. The Tregs play a significant role in the immunosuppression resulting from skin photoaging. *Lactobacillus johnsonii* prevents UVR-induced reduction in the density of epidermal Langerhans cells and accelerates the restoration of cutaneous immune homeostasis after UV-induced immunosuppression. Additionally, probiotics play different roles in different immune conditions. Under physiological conditions, probiotics can reduce chemotaxis of cytotoxic T cells to attacked skin, increase Treg recruitment, increase

Treg differentiation, induce functional impairment of CD8+ T cells, and quiescent dendritic cell activation, all of which regulate the activation and function of T cell subsets. Gauthier et al[95] conducted three clinical trials to assess the effect of a dietary supplement (DS) containing *Lactobacillus johnsonii* and nutritional carotenoids on early UVR-induced skin damage. The findings reveal that DS intake has a beneficial effect on the long-term and repeated effects of UV exposure, and is more targeted on photoaging. Kim et al[96] found that dietary supplements containing *Bifidobacterium. Longum* and galacto-oligosaccharide protected the skin from UVB-induced photoaging due to their anti-inflammatory and antioxidant properties. Additionally, they increased serum levels of short chain fatty acid (SCFAs) and acetate, which have been proven to increase and activate skin-resident Tregs that are dependent on histone acetylation.

ECM Remodeling Inhibition

ROS levels increase following UVR exposure, resulting in elevated levels of MMPs, degradation of skin collagen and elastin, as well as skin roughness, sagging, and wrinkling. In addition to directly reducing ROS levels, probiotics can indirectly modulate MMP expression in skin cells, reducing collagen and elastin degradation after UVR exposure.[97] Topical *Lactobacillus acidophilus KCCM12625* can also reduce the mRNA expression of MMP-1 and MMP-9 during skin photoaging by disrupting the AP-1 signaling pathway of skin cells while increasing procollagen expression and reducing dermal collagen protein loss.[83] Kim et al[98] also demonstrated that oral *Lactobacillus plantarum HY7714* reduced the excessive MMP-13 transcription level and the activities of MMP-2 and MMP-9 in UVB-damaged cells by inhibiting the activation of the JNK/AP-1 signaling pathway. You et al[99] found that oral *Lactobacillus sakei* can inhibit the expression of AP-1 by blocking the MAPK signaling pathway to increase collagen in dermal fibroblasts and delay skin photoaging. Shirzad et al[100] found that extracellular *Lactobacilli* exopolysaccharides *(LEPS)* can downregulate the expression levels of MMP-1, MMP-2, MMP-3, MMP-9, and MMP-10, and upregulate TIMPs. It was found that *LEPS* of B9-1 from *L. casei* can enhance the anti-collagenase and anti-elastase activities in skin cells, and effectively reduce the degradation of collagen after UVR exposure. Kang et al[85] found that topical extracts obtained from *Lactobacillus brucei*-fermented plants in kimchi could effectively inhibit UVB-induced elastase activity and expression of MMPs, and promote the synthesis of type I procollagen. Negari et al[101] demonstrated that the metabolites from the topical probiotic *Staphylococcus epidermidis* of Cetearyl isononanoate (CIN) as a potential carbon source could repair impaired collagen and induced the synthesis of collagen through phosphorylated extracellular signal regulated kinase (p-ERK) activation, thereby preventing the skin photoaging.

Conclusion

Above all, UVR can induce skin photoaging in various ways. It can directly damage the cellular DNA, RNA, and proteins, disrupting skin homeostasis and health. UVR can also induce the production of intracellular ROS, further damaging the DNA. Additionally, UVR can induce the abnormal expression of the photooxidative stress pathway, mitochondrial dysfunction, inflammatory cascade, and immune suppression in vivo. These factors together promote kin photoaging. Oral and topical probiotics have been proven to be effective in protecting the skin from UV damage and might emerge as an excellent potential treatment option for skin photoaging. The associated mechanisms mainly include positive modulation of gut-skin microbial interaction, reduction of oxidative stress level, inhibition of the inflammatory cascade, maintenance of immune homeostasis, and inhibition of ECM remodeling. With the advancement of scientific research, a growing amount of evidence will confirm the significance of oral and topical probiotics in skin photoaging. Based on the current study, there is a need to further explore the role of probiotics in skin photoaging from multiple perspectives, including probiotic categories, application method, application conditions, and anti-photoaging molecular mechanisms to develop more novel and effective microecological strategies to protect UVR-irradiated skin and delay photoaging.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by the National Science Foundation of China (82073453), the Zhejiang Provincial Natural Science Foundation of China (LY20H110002), the General Project Funds from the Health Department of Zhejiang Province (2020KY446), the outstanding Young People Fund in Zhejiang Provincial People's Hospital (ZRY2018C004, ZRY2020C008).

Disclosure

The authors declare that there are no conflicts of interest in this study.

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