Probiotics and Health 益生菌与健康

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摘　要：皮肤是人体最大的器官，也是机体防御外界各种物理、化学及病原微生物侵害的重要组织。皮肤系统若出现老化，则导致其功能衰退、防御功能下降，危害机体健康。日常生活中，各类光照时刻侵害着我们的皮肤，加速其老化的速度。研究指出，光照尤其是日光中的紫外辐射可通过直接损伤 DNA、产生活性氧、降解细胞外基质和诱发炎症等多种方式损伤皮肤细胞，导致皮肤功能的下降。近年来，越来越多的研究发现微生态对于皮肤健康有重要影响，而益生菌作为调节皮肤微生态平衡的手段，通过抗氧化、减少细胞外基质降解和抑制炎症因子的表达，延缓皮肤光老化。本文系统综述了皮肤光老化的机制与益生菌抵抗光老化的研究进展，进而探讨益生菌改善皮肤健康的应用模式，以期对益生菌在皮肤抗光老化应用提供参考。

关键词：皮肤；光老化；益生菌；氧化损伤；抗氧化

Research progress on the mechanism of the repair of skin photoaging by probiotics

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Abstract: The skin, the largest organ of the human body, is the first defense line of the immune system. Aging of the skin may lead to dysfunction and weakened protection for our body, causing a series of health problems. Lights, especially the ultraviolet, may accelerate skin aging and destroy our skin barrier. Researchers have demonstrated that ultraviolet can directly damage the DNA and RNA in the skin cells and induce the generation of reactive oxygen species, leading to lipid peroxidation, extra-cellular matrix degradation, and inflammation, all of which ultimately accelerate skin photoaging. Growing evidence has proved the importance of microbiome to skin health, and probiotics may modulate the skin ecology and postpone skin aging through generating anti-oxidative metabolites, inhibiting the activities of matrix metalloproteinases, and reducing inflammatory cytokines. In this review, we summarized the mechanisms of skin photoaging as well as the cutting-edge studies of probiotics against skin photoaging and discussed the potential application of probiotics, aiming to provide a reference for the application of probiotics in the alleviation of skin photoaging.

Keywords: skin; photoaging; probiotics; oxidative damage; antioxidation

皮肤是人体最大的器官,正常成年人皮肤表面积约 1.8 m²,重量约占体重的 10%–15%[1]。同时,皮肤也是人体与外界环境之间的第一道屏障,在保护、调节体温、感觉、分泌、排泄和免疫等多方面发挥作用[2]。

当皮肤器官功能出现衰老性损伤、难以适应内外环境变化、发生色泽及弹性下降的情况时,被称为皮肤老化(skin aging)。皮肤老化是人体衰老过程中的一个伴随症状,也是皮肤众多健康问题中最受关注的一个现象。皮肤老化的因素主要分为内因和外因。皮肤衰老的内因主要是遗传因素,当年龄逐渐增大,人体细胞分裂增殖能力下降,皮肤会随之出现变薄、干燥、皱纹细小、出汗不足以及对温度的敏感性增加等老化症状[3]。

皮肤衰老的外因主要与紫外辐射和香烟烟雾相关[4–5]。其中,紫外辐射(ultraviolet radiation,UV radiation)导致的皮肤老化又称为光老化(photoaging)[6–7]。光老化是导致皮肤老化的主要外因,80%以上的面部老化均由光老化引起[8]。与遗传所致的皮肤老化特征不同,光老化皮肤表皮层的角质形成细胞活性下降,更新速度减慢,表皮屏障功能减弱,导致皮肤干燥脱皮;真皮层的成纤维细胞数量减少,胶原和弹性蛋白合成减慢而分解加速[9]。光老化皮肤与自然老化皮肤最重要的组织学差异是光老化皮肤真皮组织内无定形弹性纤维呈现过度积累状态,胶原纤维出现明显的异常断裂和结构紊乱[10–11]。老化的皮肤除美观性下降外,其防御损伤的功能也明显受损:

受过量 UV 照射后皮肤屏障的完整性被破坏、分泌功能明显下降,罹患皮肤炎症甚至皮肤恶性肿瘤的风险明显增加[12–13]。

皮肤老化除了与上述生理变化有关之外,还与在皮肤表面的庞大微生态群落系统息息相关[14]。皮肤微生态在防御入侵病原体、调整人体的免疫系统和分解代谢产物方面起着至关重要的作用,因此对皮肤乃至全身健康起到重要作用[15]。在机体衰老过程中,皮肤微生态也随之发生动态变化[16]。作者所在研究团队通过随访长寿家族成员,发现随着年龄的增长,皮肤微生态多样性急剧下降,芽孢杆菌丰度增多,粪球菌丰度减少;皮肤微生物的辅因子及维生素合成、糖原生成及代谢能力逐渐下降,而致癌微生物逐渐增多。Li 等发现随着紫外辐射剂量的累积,皮肤微生态也会在不同年龄阶段呈现不同的菌群特征[16]。蓝藻作为儿童组的优势菌群,被证实与防止紫外线损伤和色素沉着有关[17]。Li 等推测因为金黄色葡萄球菌、表皮杆菌和乳酸菌能够促进形成成熟而完整的免疫屏障,所以在光老化过程中起到保护作用[16]。不同年龄段的皮肤微生物群落功能预测分析结果显示在光老化过程中最主要的变化是代谢能力的变化、抗氧化能力(辅因子和维生素的代谢)[18]、膜完整性和细胞信号能力(甘油磷脂代谢)[19]、脂质代谢能力(甘油脂代谢、脂肪酸生物合成)[20]和对病原体抵抗能力(抗生素的生物合成)都与光老化程度呈负相关。上述结果表明在皮肤老化进程中皮肤微生态发挥着重要的作用,所以目前国内外对于抗皮肤光老化功能因子的研究从开发植物源性的多肽类、多糖类和黄酮类物质逐渐转向通过微生物手段维持皮肤健康微生态[21]。与此同时,化妆品市场也从植物提取物时代进入微生态护肤时代,通过益生菌调节皮肤微生态的平衡成为科学研究和市场应用的新热点。

益生菌(probiotics)是一类被世界卫生组织定义为通过摄取适当的量、对食用者的身体健康能发挥有效作用的活菌[22]。不同的研究表明,某些特定的益生菌能够积极影响机体微生物区系的组成[23],提升宿主局部器官状态。作者所在研究团队累积了超过两万株的健康功能微生物,建成了相应的菌种资源及基因组数据库并且对其进行功能挖掘,目前已证明益生微生物能通过调节肠道微生态从而在降糖降脂、抗氧化以及抑菌方面有显著的益生功能[24–26]。同样地,大量研究已证实皮肤的微生态系统与皮肤健康状况密切相关,通过益生菌调控皮肤微生态成为促进皮肤健康的新手段[14]。已有研究证实益生菌补充剂对特应性皮炎的治疗有作用[27–29],但在皮肤应用领域中,益生菌并没有被明确定义。虽然在中国化妆品行业国标中要求产品的菌落总数小于等于 1 000 CFU/g[30],但在一些欧美国家已经允许含有益生菌活菌成分的产品上架[31],这也印证了益生菌在日化行业广阔的开发前景。本文将从光老化损伤的病理机制及益生菌在皮肤领域的研究现状,系统综述益生菌抑制皮肤光老化研究取得的最新进展。

1　皮肤光老化的机制研究

根据波长不同,太阳光中的 UV 主要有 3 种类型:长波 UV (UVA 320–400 nm)、中波 UV (UVB 280–320 nm)和短波 UV (UVC 200–280 nm)[32]。UV 对皮肤的损害与波长密切相关:短波长 UVC 具有最强的诱变性,但会被臭氧层阻挡到地球表面;长波长 UVA 是一种微弱的诱变剂,但它具有很强的穿透能力,可以影响真皮甚至皮下组织区域;中波长 UVB 的诱变性很强,可以直接导致 DNA 和 RNA 损伤从而损伤皮肤细胞[6,33]。

1.1 紫外辐射对 DNA、RNA 和蛋白质的直接伤害

皮肤抵御 UV 辐射的第一道防线是通过构象和化学变化吸收 UV 能量的发色团[34−35]。DNA 是表皮中最丰富的发色团，对 UV 有最强的吸收作用。但过多的 UV 照射会产生激发电子态和有毒产物，引发 DNA 损伤[36]。吸收 UV 时，DNA 中的嘧啶碱基与相邻的嘧啶形成键，导致环丁烷-嘧啶二聚体和嘧啶-嘧啶酮(6-4)光产物的形成[37]。这两种光产物可导致功能基因碱基突变，发生复制转录错误，其中含损伤遗传信号的细胞不能得到有序凋亡，严重影响皮肤系统的健康[38]。

除此之外，UV 辐照也会损伤细胞内的 RNA 碱基，导致 mRNA 不能正常翻译、转录，影响细胞信号的转导[39]。而 UV 也会导致皮肤细胞内氨基酸发生各种突变，并且影响蛋白质的合成，甚至导致细胞周期停滞和凋亡，这些突变也可以消除细胞的凋亡能力，从而促进皮肤恶性肿瘤的形成[40]。

1.2 紫外辐射对细胞皮肤成分的间接光损伤

1.2.1 活性氧的形成

活性氧(reactive oxygen species，ROS)是机体内含氧并且性质活泼的物质的总称，参与细胞损伤和分子信号传递[41]。ROS 包括超氧阴离子、羟基自由基和 O_2 衍生的非自由基物种如 H_2O_2 等[42]。研究指出，在有氧环境中，被激发的光敏剂可将能量转移到分子氧(O_2)上，从而产生 ROS[39]。线粒体内产生的 ROS 约占细胞总 ROS 的 90%[43−44]。而当细胞受到 UV 辐射后，线粒体中的电子转移不能发生有序的转移，不少电子直接逃逸到氧气中，在线粒体呼吸链的复合体Ⅰ和复合体Ⅲ形成 ROS[45−46]，造成细胞的损伤及能量代谢的紊乱。

人体可通过自身细胞产生抗氧化剂维持氧稳态，从而抵抗 ROS 带来的细胞损伤。目前已知的清除体内 ROS 的抗氧化酶是谷胱甘肽过氧化物酶(glutathione peroxidase，GSH-Px)、超氧化物歧化酶(superoxide dismutase，SOD)和过氧化氢酶(catalase，CAT)[47]。人体通过对氧的动态平衡调控实现氧的能量利用最大化及损伤修复，但在强度过高的 UV 辐照后，ROS 的产生将超越机体系统的调节能力，如高水平的 ROS 将累积破坏细胞的结构和功能，并介导炎症反应[48−49]。ROS 可激活多条细胞信号通路，导致胶原生成减少、基质金属蛋白酶(matrix metalloproteinase，MMPs)合成增多，最终促进皮肤衰老[40]。

1.2.2 脂质过氧化

过量 UV 辐照将产生大量的 ROS，而 ROS 在体内可与不饱和脂肪酸链进行脂质过氧化反应，形成过氧化脂质。过氧化脂质一方面会扰乱磷脂双分子层的结构，影响细胞膜的完整性[50]；另一方面，脂质过氧化物可以进一步分解成许多反应醛，与 DNA 碱基发生反应，产生无法修复的聚合物，最终导致各种皮肤疾病[51−52]。

1.2.3 对蛋白质的损伤

长期的 UV 照射将对真皮细胞外基质(extracellular matrix，ECM)造成明显的损伤。真皮 ECM 最重要及含量最高的物质是胶原、弹性蛋白和糖胺聚糖，这些蛋白的主要功能是维持皮肤的强度、弹性和水分[53]。光老化导致的皮肤粗糙、松弛、起皱与皮肤中 MMPs 的增加密切相关。MMPs 的是一类锌依赖的内肽酶家族，其主要生理作用是降解 ECM 中的各种蛋白质成分[54]。在光老化皮肤中，不仅 MMPs 的表达增加，其拮抗因子——金属蛋白酶组织抑制因子(tissue inhibitor of matrix metalloproteinases，TIMPs)的表达也降低[55−56]。

另外，导致 ECM 结构损伤的主要因素就是 ROS 水平的上升。UV 照射后皮肤细胞内 ROS 增加，DNA、脂质和蛋白质的氧化产物增多，这

些产物能激活细胞因子，使细胞内凋亡相关信号转导通路如 MAPK、ERK 等激活[57]，然后激活转录因子 AP-1 和 NF-κB。一方面，AP-1 和 NF-κB 上调 MMPs 的转录水平、下调 TIMPs 的转录水平，引起胶原蛋白被降解[58]；另一方面，皮肤细胞的 AP-1 和 NF-κB 可下调转化生长因子-β (transforming growth factor-β，TGF-β) II 型受体的表达，导致下游 Smad/TGF-β 信号通路受损，降低编码 I 型和 II 型胶原前体的 *COL3A1* 和 *COL1A1* 基因的转录，减少胶原的生物合成[59−60]。同时，也有研究提出 ROS 可诱导皮肤组织的弹性蛋白酶活性升高、导致胶原纤维蛋白的异常合成，最终导致 ECM 内的无定形弹性蛋白增多，皮肤弹性下降。因此，在光老化的皮肤中，可观察到异常弹性蛋白的沉积、弹性物质聚集体的弯曲、紊乱和高度分支的弹性纤维[61]。

1.2.4　炎症反应

　　UV 辐照除了通过 DNA、RNA 及蛋白损伤外，也会诱发皮肤炎症，导致皮肤光老化。UV 通过引起皮肤细胞内 ROS 产生，导致细胞释放白细胞介素家族 IL-1、IL-6、IL-8、IL-10 和 TNF-α 等系列炎症介质[62]，从而使局部皮肤的炎症发生。

2　益生菌的抗光老化作用

2.1　益生菌的抗氧化作用

　　益生菌是一类对人体有益的活性微生物，具有维持肠道菌群结构平衡、调节机体免疫力、提高机体抗氧化水平等功能。其中，益生菌的抗氧化功能与皮肤系统的健康密切相关。益生菌的抗氧化机制可以分为 4 种：清除活性氧和自由基系统、增强抗氧化酶系统、还原调控系统和氧化损伤修复系统[63]。由于益生菌可以通过多种途径协助机体抗氧化，因此不少研究者试图将益生菌

应用于皮肤抗光老化的治疗中(表 1)。

　　部分益生菌菌株可以增加抗氧化酶活性或清除 ROS，减轻皮肤在 UV 辐照后的氧化损伤(图 1)。作者所在研究团队发现植物乳杆菌 GDMCC61123 具有较强的自由基清除能力和抗脂质过氧化能力，体内实验结果证明该菌株可以增加小鼠体内谷胱甘肽过氧化物酶和超氧化物歧化酶活性，缓解体内氧化应激作用明显[26]。Im 等发现嗜酸乳杆菌 IDCC 3302 通过增加皮肤抗氧化酶如超氧化物歧化酶和过氧化氢酶的活性防止 UVB 引起的氧化应激损伤[64]。Lim 等通过 ABTS 自由基清除试验发现嗜酸乳杆菌 KCCM12625 具有较好的抗氧化作用，且能显著降低 UVB 辐射后 HaCaT 细胞中升高的 ROS 水平，减轻氧化损伤导致的光老化现象[65]。Ishii 等通过体内实验证明口服短双歧杆菌 Yakult 可防止 ROS 的产生，减弱 UV 引起的皮肤屏障扰动和氧化应激[66]。说明益生菌产品在抗氧化、抗皮肤光老化治疗中有良好的开发前景。

　　由于含活菌的制剂在日化用品中受到一定的限制，所以有不少研究者尝试验证益生菌的发酵产物是否同样具有抗氧化作用。作者所在研究团队发现发酵乳杆菌 GDMCC 61827 的发酵上清具有良好的抗 UV 诱发的皮肤光损伤能力，采用比较基因组学及靶向代谢组证实该发酵乳杆菌具有良好的烟酰胺合成功能，发酵液中含较高的烟酰胺。发酵乳杆菌 GDMCC 61827 的发酵上清作用于 UV 损伤的皮肤细胞后能明显减少细胞内活性氧的产生、高效稳定线粒体膜电位，在体外及体内均展现良好的抗光老化作用[67]。瑞士乳杆菌 NS-8 发酵液具有显著的清除自由基的功能，可降低 UV 诱导生成的 ROS，改善皮肤过氧化酶的活性水平，缓解皮肤细胞光损伤作用[68]。

表 1 文献中报道的具有抗光老化特性的益生菌

Table 1 Probiotics with anti-photoaging effects reported in the article

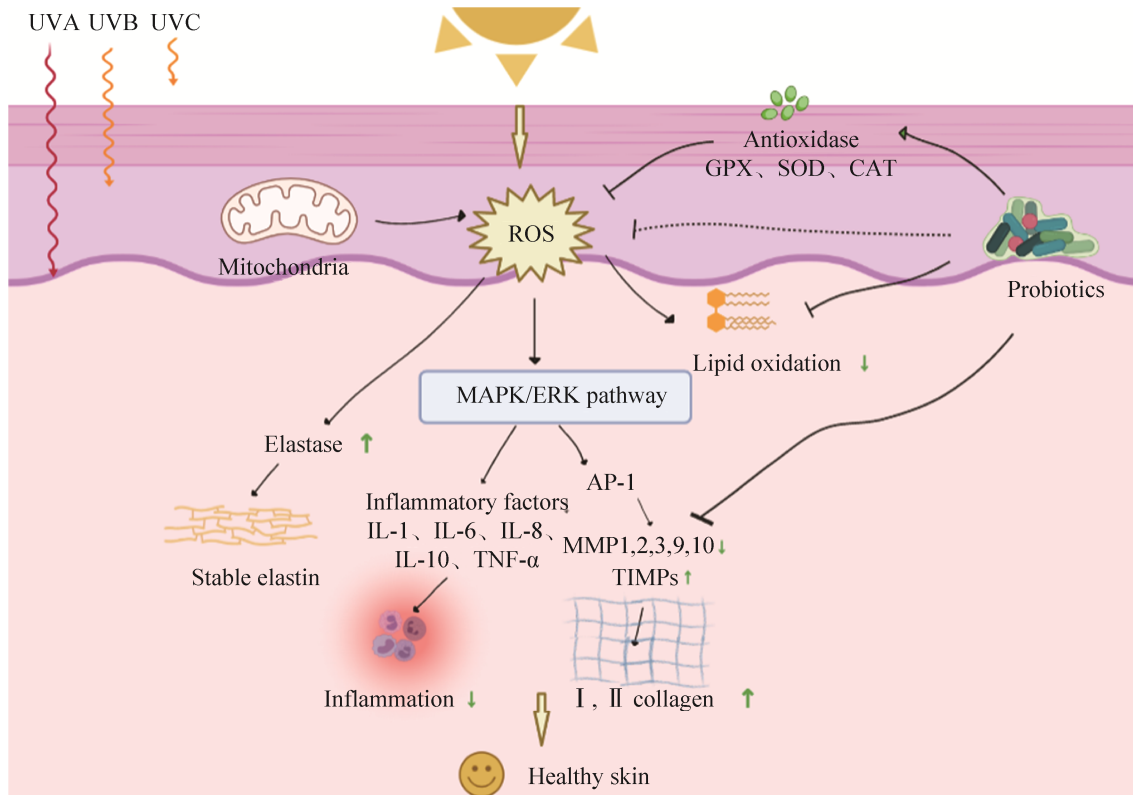| Strains	Form	Test sample and quantity	Mechanism	Effect
Lactobacillus plantarum GDMCC61123	Live bacteria	C57 mice: 10 controls *vs* 10 models *vs* 10 tests	Increased the activities of GSH-Px and SOD in mice	Strong free radical scavenging ability and anti-lipid peroxidation ability[26]
Lactobacillus acidophilus KCCM12625	Inactivated microorganisms	HaCaT/HDF Cells	Increase the activity of skin antioxidant enzymes such as SOD and CAT; reduce the expression levels of MMP-1 and MMP-9 produced in the process of skin aging, and increase the expression of procollagen	Reduced the loss of collagen in the dermis and prevented skin oxidative stress damage caused by UVB[65]
Bifidobacterium breve Yakult	Live bacteria	female hairless mice (Hos: HR-1 strain): 6 controls *vs* 6 models *vs* 6 tests	Reduced the production of ROS; reduced the activity of elastase in the skin	Reduced skin barrier disturbance and oxidative stress caused by UV[66]; resistant to skin damage caused by UV[75]
Limosilactobacillus fermentum GDMCC 61827	Cell-free metabolites	HaCaT Cells/Dunkin Hartley Guinea pig: 6 controls *vs* 6 models *vs* 6 tests	Reduce the production of ROS in cells and stabilize mitochondrial membrane potential; down-regulate the transcription levels of MMP-1, MMP-3, IL-1β, IL-6, and IL-8 in skin cells damaged by UVB	Reduced collagen degradation *in vitro* and *in vivo*; relieved mild cell death and inflammatory cell infiltration in the skin of guinea pigs irradiated by UV[67]
Lactobacillus helveticus NS-8	Fermented milk	SKH-1 hairless mice: 10 controls *vs* 10 models *vs* 10 tests	Scavenged free radicals, reduced UV-induced ROS; improved the activity level of skin peroxidase	Alleviated the photoaging effect of skin cells[68]
Lactobacillus rhamnosus HK-9	Fermented plant extract	HaCaT Cells	Significantly inhibited the production of ROS in HaCaT Cells; improved the anti-MMP-2 and MMP-9 formation ability of agastache leaves	Improved the anti-photoaging activity of natural products[69]
Lactobacillus plantarum C2	Fermented plant extract	Mouse fibroblasts Cells Balb3T3	Increased the content of antioxidants such as total phenols, flavonoids and anthocyanins	Enhanced the scavenging ability of free radicals and inhibit the peroxidation ability of linoleic acid[70]
Lactobacillus plantarum HY7714	Inactivated microorganisms	Hs68 HDF Cells	Inhibited the activation of JNK/AP-1 signaling pathway and reduced the excessively high MMP-13 transcription level and MMP-2 and MMP-9 activities in UVB damaged cells	Reduced collagen degradation[72]
Lactobacillus sakei KCCM 11175P	Microbial structure composition	HNDF Cells	Blocked MAPK signal and inhibited the expression of MMP-1 transcription factor AP-1	Increased the content of collagen in dermal cells and relieved photoaging damage[73]
Lactobacillus casei B9-1	Microbial structure composition	Normal primary human fibroblast	Extracellular polysaccharides down-regulated the expression levels of MMP-1, MMP-2, MMP-3, MMP-9 and MMP-10, and up-regulated TIMPs; enhanced the anti-collagenase and anti-elastase activities in skin cells	Effectively reduce collagen degradation by UV[74]
Lactobacillus brucei JCM1115	Fermented plant extract	CCD-986sk fibroblasts and HaCaT Cells	Effectively inhibit UVB-induced elastase activity and MMPs expression	Promoted the synthesis of type I procollagen[76]
Lactobacillus acidophilus IDCC 3302	Inactivated microorganisms	HaCaT Cells	Inhibited the production of pro-inflammatory cytokines mediated by MAPK signaling pathway	Reduced skin inflammation caused by UVB[64]
Lactobacillus reuteri DSM17938	Live bacteria/microbial lysates	Reconstructed human epidermis	Reduced the expression level of pro-inflammatory factors IL-6 and IL-8; increased the level of laminin A/B	Anti-inflammatory and improve skin barrier function[83]
Bifidobacterium breve B-3	Live bacteria	Hairless mice (Hos: HR-1 strain): 8 controls *vs* 8 models *vs* 8 tests	Reduced UV-induced interleukin-1β production in the skin	Reduce inflammation in mice irradiated by UV[85]

图 1　益生菌对皮肤光老化的修复通路

Figure 1　The repair pathway of probiotics on skin photoaging.

　　此外，亦有研究者尝试将益生菌用于植物天然成分的提取中，以增加植物提取物的抗氧化特性。Lim 等通过比较未发酵和鼠李糖乳杆菌 HK-9 发酵的龙舌兰叶提取物的皮肤抗氧化特性，发现采用 HK-9 发酵后的龙舌兰叶提取物能显著抑制角质形成细胞中活性氧如 NO 和 iNOS 的产生，证明采用益生菌能提高天然产物的抗光老化活性[69]。Curiel 等发现采用植物乳杆菌 C2 发酵桃金娘浆可明显提高匀浆中的抗氧化物质如总酚、黄酮和花色苷的浓度，增强其对自由基的清除力和抑制亚油酸的过氧化能力[70]。

　　益生菌可通过菌体自身、发酵上清以及发酵其他天然成分发挥抗氧化作用，在协助机体防御光老化中有良好的应用前景。

2.2　益生菌减少 UV 对真皮细胞外基质的破坏

　　真皮 ECM 损伤如胶原蛋白流失和弹性蛋白下降是皮肤光老化过程中一个重要的病理特征。在光老化的皮肤中，UV 辐照后会使皮肤细胞内的 ROS 增多，诱发 MMPs 水平增高，导致皮肤的胶原蛋白和弹性蛋白被降解，皮肤变得粗糙、松弛和起皱。益生菌除了能显著降低紫外辐射诱导的 ROS 水平之外，还能通过影响多个信号通路直接调节皮肤细胞 MMPs 的表达水平，减少 UV 辐照后胶原蛋白和弹性蛋白的降解[71]。作者所在研究团队发现发酵乳杆菌 GDMCC 61827 可下调 UVB 损伤导致的皮肤细胞中 MMP-1、MMP-3 转录水平上升，从而缓解皮肤光老化症状。Lim 等发现嗜酸乳杆菌 KCCM 12625 可以

通过影响皮肤细胞 AP-1 信号通路，减少皮肤衰老过程中产生的 MMP-1、MMP-9 的 mRNA 的表达，同时增加前胶原蛋白的表达，减少真皮层胶原蛋白流失[65]。Kim 等也证明了植物乳酸菌 HY7714 通过抑制 JNK/AP-1 信号通路的激活而降低了 UVB 损伤细胞内过高的 MMP-13 转录水平和 MMP-2、MMP-9 活性[72]。有学者推测，益生菌的结构多糖是其发挥抗光老化作用的主要功效成分。脂磷壁酸(lipoteichoic acid，LTA)是革兰氏阳性菌细胞壁的一种成分，You 发现清酒乳杆菌 LTA 可通过阻断 MAPK 信号抑制 MMP-1 转录因子 AP-1 的表达，增加真皮细胞胶原蛋白的含量，延缓光老化损伤[73]。Shirzad 等应用干酪乳杆菌 B9-1 的胞外多糖作用于 UV 损伤的皮肤细胞，同样发现其具有下调 MMP-1、MMP-2、MMP-3、MMP-9 和 MMP-10 表达水平、上调 TIMPs 的作用，发现干酪乳杆菌 B9-1 可增强皮肤细胞中抗胶原酶、抗弹性蛋白酶活性，有效减少光照后胶原蛋白的降解[74]。益生菌的抗光老化效果除了在细胞水平上得到验证之外，在动物水平上也同样得到验证。Kano 等发现无毛小鼠口服短双歧杆菌 Yakult 后能显著抵抗 UV 辐射引起的皮肤损伤，表现为皮肤中弹性蛋白酶的活性下降，皮肤弹性较不服用益生菌的小鼠明显增加[75]。

益生菌发酵其他植物可提高天然产物的抗光老化活性。Kang 等在泡菜中发现采用布氏乳杆菌发酵植物获得的提取物，可有效抑制 UVB 诱导的弹性蛋白酶活性和 MMPs 的表达，促进Ⅰ型前胶原的合成[76]。Shin 等采用乳酸菌发酵藿香叶，证明能明显提高藿香叶抗 MMP-2 和 MMP-9 形成的能力[77]。

综上所述，益生菌可通过多种途径减少光老化过程中胶原蛋白和弹性蛋白的流失，继而达到延缓光老化的效果。

2.3 益生菌抑制炎症因子的表达

除了上述造成光老化组织学差异的因素之外，炎症因子的累积也是光老化过程中皮肤损伤的一个不可忽视的因素，皮肤炎症因子的增多会导致屏障功能受到破坏，表皮水分失衡、皮肤通透性增加，引起更多的过敏原及化学物质的异常吸入，引起或加重皮肤疾病状态[78]，加速皮肤老化。而益生菌在缓解肠道炎症上已有广泛的应用，如作者所在研究团队发现戊糖片球菌 IM96 能显著缓解并降低机体在感染大肠杆菌 O157:H7 后的炎症水平[79]。同样地，益生菌缓解炎症的功能在调控皮肤免疫平衡上也有良好的疗效，如益生菌在特应性皮炎的治疗上已被广泛应用，证明益生菌可有效降低患者皮肤炎症水平，恢复免疫稳态[80]。

在 UV 辐射下，表皮层的角质形成细胞通过释放白细胞介素 IL-1、IL-6、IL-8、IL-10 和 TNF-α 等炎症介质，诱发局部的炎症，导致皮肤通透性增加，屏障功能下降[81-82]。嗜酸乳杆菌 IDCC 3302 可以抑制 MAPK 信号通路介导的促炎细胞因子的产生，减少 UVB 辐射引起的皮肤炎症[64]。Khmaladze 等发现罗伊氏乳杆菌可缓解 UV 辐照诱导的皮肤炎症[83]。Satoh 等证实口服益生菌同样能减少炎症、抵抗光老化：受 UV 辐照的小鼠在服用短双歧杆菌 B-3 后，能有效减少皮肤中紫外线诱导的白细胞介素-1β 的产生[84]。作者所在研究团队发现发酵乳杆菌 GDMCC 61827 可下调 UVB 损伤导致皮肤细胞中 IL-1β、IL-6、IL-8 表达水平的上升，并且外敷发酵乳杆菌 GDMCC 61827 发酵上清液能有效缓解紫外辐照豚鼠皮肤中轻度细胞死亡和炎症细胞浸润情况。Keshari 等发现新一代益生菌表皮葡萄球菌能通过发酵代谢产物中的丁酸介导短链脂肪酸受体 2 表达，调节 UVB 诱导的促炎细胞因子 IL-6 的产生[85]。

因此，益生菌可通过抑制 UV 辐照后皮肤异常免疫作用的形成，减少皮肤的光老化损伤。

3　皮肤应用益生菌的潜在形式

随着人们对皮肤微生物区系了解的不断加深，我们相信会有更多针对个体特征定制的皮肤护理方案出现。但是在益生菌的皮肤应用中还存在很多待解决的问题：口服和外涂哪种才是最好的应用方式？活性微生物应用效果会比灭活微生物要好吗？如果是，应如何安全和持久地植入益生菌？活菌存活时间有多久？多种益生菌混合物应用是否具有协同作用？

人们通常认为活性益生菌比灭活益生菌更有可能具有生物活性，因为活性益生菌比灭活细胞更容易附着在宿主黏膜和细胞上，并且可对有害微生物产生更好的抗菌活性[86]。因此，最理想的皮肤益生菌治疗方案应该为让有活性的益生菌在皮肤上保持活性，并在皮肤上定居[87]。但很少有研究表明局部使用的益生菌可以在皮肤上增殖、定居，并融入宿主正常皮肤微生物区系的成员。如果采用口服摄入益生菌，则难以保证益生菌的长期定植，停用益生菌后功效将很快消失[88]。因此，如何维持益生菌活菌的持久性将是研究者们关注的新方向。

至今，大多数皮肤益生菌产品并不真的含有活菌，而是由灭活微生物、菌体成分或益生菌的无细胞代谢物组成。目前国内化妆品行业国标要求对产品的菌落总数进行控制，是因为在皮肤上直接应用活菌菌体存在一定风险，例如在皮肤存在伤口的情况下，应用活菌可能会导致细菌移行到血液中，产生菌血症[89]。另外，由于益生菌的保藏和运输方式比较严格，保持活菌在皮肤上存活及生长仍是难以解决的技术问题[31]。目前的科学研究仅从灭活微生物、菌体成分或益生菌的无细胞代谢物对皮肤疾病(如光老化)的分子

作用机制和表型进行探讨，而未进一步探究其与皮肤微生态之间的关系。灭活的益生菌、菌体成分或益生菌的无细胞代谢物依然是目前在皮肤上应用益生菌产品首选的应用模式[90]。

4　结论

综上所述，UV 辐射对皮肤中的 DNA、RNA 及蛋白质产生直接损伤，影响细胞存活状态；UV 同时诱导细胞内 ROS 累积，导致脂质过氧化发生，进一步损伤 DNA 和 RNA、导致细胞外基质胶原蛋白和弹性蛋白降解；另外 UV 还诱发皮肤局部炎症，降低皮肤对外界有害物质的防御；这些共同促进了皮肤光老化的发生。而通过应用具有抗氧化功能的益生菌，可以清除活性氧、调节基质金属蛋白酶表达水平，实现缓解细胞外基质损伤，减轻皮肤炎症。益生菌在保护皮肤免受 UV 损伤方面具有良好的应用前景，随着科学研究的不断深入，研究者们将进一步验证益生菌在维护皮肤健康上的应用价值。因此，在目前的研究基础上，我们还需要从皮肤微生态、益生菌、益生元及后生元的抗光老化分子机制等多方面深入探索益生菌对皮肤系统的作用机制，开发更多新型微生态策略来保护受 UV 辐射的皮肤，延缓光老化。

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