Probiotics in Aging Skin

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© Springer-Verlag Berlin Heidelberg 2017
M.A. Farage et al. (eds.), Textbook of Aging Skin, DOI 10.1007/978-3-662-47398-6_78
Abstract

Health benefits of probiotics have been established recently and the scientific literature shows that the clinical uses of probiotics are broad and are open to continuing evaluation. The most common microorganisms used as probiotics are strains of lactic acid bacteria (LAB) including Lactobacilli and Bifidobacteria, which are part of the intestinal microbiota. Most probiotics are included in foods or dietary supplements and are aimed at functioning in the intestine. However, even if gastrointestinal tract has been the primary target, it is becoming evident that other conditions not initially associated with the gut microbiota might also be affected by probiotics.

Introduction

Health benefits of probiotics have been established by several studies in animals and humans, and the scientific literature shows that the clinical uses of probiotics are broad and are open to continuing evaluation. The most common microorganisms used as probiotics are strains of lactic acid bacteria (LAB), which are gram-positive, nonsporing, catalase-negative organisms that are devoid of cytochromes and of nonaerobic habit but are aero tolerant, acid-tolerant, and strictly fermentative; lactic acid is the major end product of sugar fermentation. Particular attention is paid to specific species of lactic acid bacteria (LAB), including Lactobacilli and Bifidobacteria, which are part of the intestinal microbiota. Most probiotics are included in foods or dietary supplements and are aimed at functioning in the intestine. However, even if gastrointestinal tract has been the primary target, it is becoming evident that other conditions not initially associated with the gut microbiota might also be affected by probiotics. It was speculated that the skin status could benefit from reinforced gut homeostasis. Nutritional intervention, particularly with dietary antioxidants, has been proposed to protect against UV-induced skin damage, and an increasing interest has been shown for new nutritional approaches using live microorganisms as probiotics. Moreover, the capacity of probiotics to modulate the systemic immune status, including the release of regulatory cytokines, might influence skin homeostasis. In addition, reports showing the efficacy of a selected probiotic extract in increasing ceramide levels in vivo, on stratum corneum (SC) of healthy young and old subjects, as well as in atopic dermatitis patients, thus reducing dryness, loss of tone, fullness, and water loss, opened new potential probiotic-based strategies against those pathophysiological skin alterations, including aging, associated with a reduced amount of the ceramide, major water-holding molecule in the extracellular space of the horny layer.

Overall, even if the potential use of probiotics for the skin has been hardly considered in the past, more recent experimental studies have suggested interesting, potential, new applications. The aim of the present review is to outline the main challenges associated with accumulating evidence in support of skin health claims for probiotics and to give a perspective of the scientific gaps that need to be addressed to advance the probiotic-based preventive or therapeutic approaches in aging skin, which is one of the most common dermatologic concerns.

Probiotic Microorganisms and Health Benefits

The history and evolution of the definition of “probiotic microorganism” has been extensively reviewed by Fioramonti et al. [1]. The concept of probiotics was most likely derived from a theory first proposed by Nobel Prize-winning Russian scientist Elia Metchnikoff, who suggested in 1908 that long life of Bulgarian peasants resulted from their consumption of fermented milk products. The term “probiotic,” which literally means “for life,” was first used by Lilly and Stillwell (1965) [1] to describe “substances secreted by one microorganism, which stimulate the growth of another.” A powerful evolution of this definition was coined by Parker (1974), who proposed that probiotics are “organisms and substances which contribute to intestinal
microbial balance [1].” Fuller (1989), then modified the definition in 1989 to “a live microbial feed supplement, which beneficially affects the host animal by improving its microbial balance [1].” Afterwards, Salminen et al. in 1998 defined probiotics as “foods which contain live bacteria, which are beneficial to health,” whereas Marteau et al. in 2002 defined them as “microbial cell preparations or components of microbial cells that have a beneficial effect on the health and well-being.” In these definitions, the concept of an action on the gut microflora, and even that of live microorganisms disappeared. In 2001, a new and complete definition of probiotic has been presented by the Food and Agriculture Organization of the United Nations-World Health Organization (FAO-WHO) and approved by the International Scientific Association for Probiotics and Prebiotics and best exemplifies the breadth and scope of probiotics as they are known today: “Live microorganisms, which when administered in adequate amounts, confer a health benefit on the host.” This definition retains the historical elements of the use of living organisms for health purposes but does not restrict the application of the term only to oral probiotics with intestinal outcomes [2]. Probiotics represent a large variety of bacterial genera, species, and strains. Several criteria have been proposed for considering a given microorganism as probiotic. These include the ability to adhere to cells; exclude or reduce pathogenic adherence; persist and multiply; produce acids, hydrogen peroxide, and bacteriocins antagonistic to pathogen growth; be safe, noninvasive, noncarcinogenic, and nonpathogenic; and coaggregate to form a normal balanced flora. Different strains have different actions in different clinical situations, and moreover, it is important to stress that each probiotic microorganism displays its own properties and so data obtained from one strain cannot be extrapolated to another. The most common microorganisms used as probiotics are strains of lactic acid bacteria such as Lactobacillus, Bifidobacterium genera, other bacterial genera including Enterococcus and Streptococcus. Moreover, VSL#3, a patented bacterial preparation including four strains of Lactobacilli, three strains of Bifidobacteria, and one strain of Streptococcus salivarius subsp. thermophilus, also possesses properties that make it a probiotic agent.

With the first publication in 1987 on the general properties of the Lactobacillus GG and its antimicrobial substance [3], a new era was initiated in which research laboratories from many countries began serious investigations on a variety of probiotic strains.

Probiotics provide an attractive alternative to antibiotics in the treatment of inflammatory bowel disease (IBD) [4]. In addition, there is considerable evidence that the highly concentrated cocktail of probiotics, VSL#3 is efficacious in preventing onset and relapse of pouchitis, a nonspecific inflammation of the ileal reservoir after ileo-anal anastomosis, which appears to be associated with bacterial overgrowth and dysbiosis [5]. Probiotics have also been implicated in the prevention and decreased recurrence of colon and bladder cancer [6, 7]. Antitumoral effects of selected strains of probiotics in vitro and in vivo have also been reported [8–10].

Probiotics have been demonstrated to have an adjuvant effect on immunological responses; their interaction with mesenteric lymph nodes can result in an up-regulation of plgA against intestinal pathogens and food antigens [11].

Promising applications include the prevention of respiratory infections in children, prevention of dental caries, elimination of nasal pathogen carriage, prevention of relapsing Clostridium difficile-induced gastroenteritis. Proposed future applications include the treatment of rheumatoid arthritis, treatment of irritable bowel syndrome, prevention of ethanol-induced liver disease, treatment of diabetes, and prevention or treatment of graft versus host disease [10].

**Probiotics in Aging Skin**

Aging has been defined as the accumulation of molecular modifications, which manifest as macroscopic clinical changes. Human skin, unique
among mammalians insofar as it is deprived of fur, is particularly sensitive to environmental stress. Major environmental factors have been recognized to induce modifications of the morphological and biophysical properties of the skin. Factors as diverse as ultraviolet radiation, atmospheric pollution, wounds, infections, traumatisms, anoxya, cigarette smoke, and hormonal status have a role in increasing the rate of accumulation of molecular modifications and have, therefore, been termed “factors of aging.” Aging of the skin is commonly associated with increased wrinkling, sagging, and increased laxity, but when considering the underlying reasons for these changes, it is important to distinguish between the effects of true biological aging (intrinsic aging) and environmental factors, such as exposure to the sun (extrinsic aging). Generally, the molecular changes of photoaging are considered to be as augmentation and amplification of the molecular changes associated with chronological skin aging [12]. In terms of biochemical and molecular mechanisms, skin aging is a really complex process, which involves a variety of changes and a lot of molecules. This section highlights certain aspects of the properties of probiotics that could have interesting implications in the skin aging treatment, even if future investigations will be indispensable. In Fig. 1, a scheme is reported, which summarizes the main biochemical, molecular, and cellular changes underlying skin aging process that include alterations of skin-associated microflora, skin pH increase, reduced stratum corneum lipid levels, abnormal oxidative stress, collagen level reduction, and altered immune responsiveness. The possible sites of action of probiotics useful to slow down or inhibit the process of cutaneous aging are also highlighted.

Fig. 1 Skin aging-associated biochemical, molecular, and cellular changes and possible sites of action of probiotics
Probiotics and Skin Aging-Associated Microflora Changes

The probiotic principle is likely to be applicable to any environment where a normal microflora exists. The skin also has a normal microflora [13], albeit less complex than the intestinal microflora because of the harsh environment provided by the human skin. The normal microflora of the skin is composed of a limited number of microbial types, mainly gram-positive species. A number of physiological conditions such as hydration, pH, O₂, and growth substrates are the major factors in determining the limited number of microbial species that colonize human skin. Cutaneous microflora defends the skin against premature aging, inflammation, and dehydration and is involved in competitive exclusion of pathogens and increases the acidic nature of the skin, thereby making it even more inhospitable to many pathogens [14]. Some microflora are able to breakdown the fatty acid molecules (from the natural oils) in the skin and thereby increase its acidity. Skin microflora is different depending on the site of the body. The most common genera found in the microflora of the skin are Propionibacteria, Staphylococcus, Micrococcus, Corynebacterium, and the yeast Malassezia [13]. Based on the proposed probiotic therapy to positively modulate the intestinal microflora, the use of probiotics is postulated to also change the composition of the skin microflora from a potentially harmful composition towards a microflora that would be beneficial for the host [15]. Due to competition for adhesion sites and nutrients, and possibly the production of antimicrobial substances, levels of certain less desirable genera can decrease. However, because the skin has an entirely different environment than the intestine, some different selection criteria for probiotics would be applied. Acid and bile resistance are prime selection criteria for intestinal probiotics, obviously these are not relevant for application to the skin. On the other hand, adhesion is important for the skin as well, to improve transient colonization and colonization resistance toward potential pathogens. Also, production of antimicrobial substances is important for an application on the skin, which, together with inhibition of pathogen adhesion, provides colonization resistance. Of interest, Ouwehand et al. [15] have investigated the possibility of applying probiotics to the skin [15]. Propionic acid bacteria (PAB) were chosen as potential probiotics because they are members of the normal microbiota [16] and have been observed to exhibit antifungal activity [17]. All tested probiotic strains were found to inhibit the growth of some of the target strains, the Candida albicans strains being mainly sensitive. All of the tested potential probiotic strains were found to exhibit some adhesion to keratin, the main protein of the skin. Two of the tested strains were, in fact, found to adhere well: 16 % and 20 % of the applied cells, Propionibacterium freudenreichii ssp. freudenreichii 20271 and Lactobacillus rhamnosus 5.5a, respectively. The results of this study strongly encourage the use of skin probiotics even if further studies are needed and should focus on the identification and assessment of strains that also exhibit activity in vivo against potential skin pathogens and will indeed persist on the skin in vivo and be active there.

Probiotics and Skin Aging-Associated pH Changes

Normal skin pH is somewhat acidic and in the range of 4.2–5.6 and has been attributed largely to endogenous agents including the Na⁺/H⁺ antiporter, NHE1, and one or more secretory phospholipase/s A2 (sPLA₂) enzymes, which hydrolyses membrane phospholipids, thereby generating free fatty acids (FFAs) that contribute to the acidification of the stratum corneum [18, 19]. The acid mantle, the combination of sebum (oil) and perspiration, on the skin’s surface protects and renders the skin less vulnerable to damage. It also protects from attack by environmental factors, such as the sun and wind, and leaves it less prone to dehydration. The acidic skin pH keeps the resident bacterial flora (see above) attached to the skin, whereas an alkaline pH promotes its dispersal from the skin [20]. The natural pH varies from one part of the body to the other and, in general, the pH of a man’s skin is lower than a
woman's skin. This acidic environment is very important, as it discourages bacterial colonization and provides a moisture barrier through absorption of moisture by amino acids, salts, and other substances in the acid mantle and in addition regulates the activity of many of the enzymes in the stratum corneum [21]. For example, the activities of both β-glucocerebrosidase and acidic sphingomyelinase are optimal at or below pH 5.5. If the pH of the stratum corneum is increased, the activities of β-glucocerebrosidase and acidic sphingomyelinase are reduced and the extracellular processing of glucosylceramides and sphingomyelins to ceramides is impaired, leading to abnormalities in the structure of the extracellular lipid membranes and decreased permeability barrier function [22–24]. On the other hand, many of the proteases in the stratum corneum have, instead, an optimum pH of 7 or higher; therefore, their activity is low at the usual stratum corneum pH. Thus, increases in stratum corneum pH stimulate protease activity, resulting in increased corneocyte desquamation [22–24]. Skin pH is relatively constant from childhood to approximately age 70 and then rises significantly, the increase being especially pronounced in lower limbs, possibly related to impaired circulation and, consequently, to stasis and reduced oxygen supply [25]. Recently, a decreased NHE1 expression that accounts for the pH abnormality in moderately aged epidermis in mice and human has been reported [26]. The reduced NHE1 expression could account the impairment of lipid processing and epidermal barrier homeostasis in aged skin even if further studies will be required to delineate whether altered sPLA₂ activity also contributes to the functional abnormalities in moderately aged epidermis. An interesting property of probiotics is the fermentative metabolism that involves the production of acid molecule, thus acidifying the surrounding environment. Moreover, Yadav and Sinha [27] have recently reported the ability of probiotic Lactobacilli to increase the production of free fatty acids (FFAs) by lipolysis of milk fat and to produce conjugated linoleic acid (CLA) by using internal linoleic acid, which may confer nutritional and therapeutical value to probiotic treatment [27].

These evidences suggest that the oral assumption and/or the topical application of probiotic preparation on the aged skin could cause a pH decrease thus coming back near the physiological acid pH. Consequently, the most important cutaneous enzymes that have been impaired by aging could again function.

Probiotics and Skin Aging-Associated Altered Stratum Corneum Lipid Composition

Several studies have demonstrated that ceramides play an essential role in both the barrier and water-holding functions of healthy stratum corneum (SC), suggesting that the dysfunction of the stratum corneum associated with aging as well as that observed in patients with several skin diseases could result from a ceramide deficiency [28]. A previous study reported a significant increase in skin ceramide levels in healthy subjects, after a treatment in vivo with a cream containing sonicated S. salivarium ssp. thermophilus [29]. The presence of high levels of neutral sphingomyelinase activity in this organism was responsible for the observed increase of stratum corneum ceramide levels, thus leading to an improvement in barrier function and maintenance of stratum corneum flexibility. There is also evidence that the treatment with a sonicated preparation of a S. salivarium ssp. thermophilus S244 was able to induce an increasing ceramide levels in vivo, on stratum corneum of atopic dermatitis patients [30]. Considering the role of the ceramides in regulating the water-holding capacity and in maintaining skin integrity, the possibility that the topical application of a probiotic formulation, representing a source of exogenous SMase able to hydrolyze skin SM and consequently to generate ceramides, may lead to reduce dryness, loss of tone, fullness, and water loss, thus slowing the process of skin aging [31], has been recently investigated. The skin barrier and the water-holding capacity are the other most important functions of the SC and these functions are related to the composition and structure of SC intercellular lipids [32, 33], including cholesterol.
ceramides, and fatty acid. Therefore, the capacitance and ceramide levels as markers of epidermal hydration were determined. The findings indicated that the barrier improvement, resulting in a prompt increase in the water-holding capacity, was observed when the aged subjects were applied *S. thermophilus*-containing cream. In fact, at the end of the treatment a statistically significant increase in hydration values was shown when compared with the values observed at the beginning. An amelioration in hydration skin could be attributed to the increase of the stratum corneum ceramides levels. Topical application of a sonicated *S. salivarium* ssp. *thermophilus* preparation lead to increased nonhydroxy and hydroxy fatty acid ceramides levels in stratum corneum. These results could be again explained with the presence of high levels of neutral SMase in *S. thermophilus*. Altogether, the findings suggest that there are two eventual possibilities by which topical application of a sonicated *S. thermophilus* preparation may contribute to the improvement of lipid barrier and a more effective resistance against aging-associated skin xerosis. One possibility would be that the presence of high levels of neutral SMase in *S. thermophilus* hydrolyses skin SM thus generating ceramides, with structural function in the stratum corneum lipid bilayers. The other eventuality is that *S. thermophilus* SMase-produced ceramides are involved in epidermal differentiation and proliferation signaling pathway as important second messenger, as previously described [34]. Thus, although the mechanism of action of topical application of a sonicated *S. thermophilus* preparation needs to be further elucidated, the results obtained with this experimental cream consist in a relevant increase of skin ceramide levels, which was associated to a more effective resistance against aging-associated skin xerosis.

**Probiotics and Skin Aging-Associated Oxidative Stress**

The epidermis of skin possesses an extremely efficient antioxidant activity that is superior to most tissues [35], and it has been proposed that the reduction in efficiency of this system during aging is an important factor in skin aging. There are many reports describing the reduction of antioxidant enzymes in skin with age, while others suggest that skin aging is not due to a general decline in antioxidant capacity. However, all agree that the accumulation of free radicals throughout life most likely promotes cellular aging. Generation of reactive oxide species (ROS) is thought to play a major role in skin aging. All the biological structures, as human skin, undergo the detrimental action of ROS. The free radical theory of aging proposes that aging results from accumulation of oxidative damage over a lifetime due to excess ROS, which result from aerobic metabolism [36]. ROS generation is increased in aged skin and represents a key step in molecular pathways, which eventually lead to increased collagen breakdown. ROS cause damage to lipids, proteins, and DNA and also influence cellular senescence [37]. In addition, free radicals also cause damage to connective tissue components of the dermis, particularly collagen [38], which again is likely to influence cell behavior via cell-matrix interactions. Indeed, poorly maintained cellular redox levels lead to elevated activation of nuclear transcription factors such as NF-κB and AP-1, which are involved in several aging-associated degenerating processes, including extracellular matrix degradation [39]. Probiotics have been demonstrated extracellularly to produce effective bioactive molecules exerting several beneficial effects as antioxidative effects by different mechanisms, including the release of exopolysaccharides (EPSs), a class of such effective biomolecules that probiotic bacteria release into the surroundings to protect themselves under starvation conditions and also at extreme pH and temperature conditions [40]. These EPSs are long-chain, high-molecular-mass polymers, which are used in food and dairy industries as texturizers, viscosifiers, and syneresis-lowering agents [41, 42]. They have also been reported to show antiulcer, immunomodulatory, antiviral, antioxidant, and various other biological activities. Recently, studies have demonstrated that microbial EPS has significant
antioxidant and free radical scavenging activities, and also have numerous potential applications as pharmaceutical formulations [43].

A widespread mechanism for protection against oxidative stress is provided by the antioxidant enzyme superoxide dismutase (SOD). Bruno-Bàrcena et al. [44] showed that heterologous expression of an SOD gene in intestinal Lactobacilli provides protection against peroxide toxicity [44]. Indeed, the authors suggest that it may be possible to use these SOD-rich species in the biotherapy for treatment of peptic ulcers or ulcerative colitis. Using a similar approach, the cumulative oxidative damage could also be reduced in the aged skin.

Probiotics and Skin Aging-Associated Collagen Level Reduction

The processes associated with intrinsic skin aging are thought to result from a combination of events including decreased proliferative capacity of skin-derived cells, decreased matrix synthesis in the dermis, and increased expression of enzymes that degrade the collagenous matrix. Collagen is one of the main building blocks of human skin, providing much of the skin’s strength. Dermal fibroblasts make precursor molecules called procollagen, which is converted into collagen. There are two important regulators of collagen production: transforming growth factor (TGF)-β, a cytokine that promotes collagen production, and activator protein (AP)-1, a transcription factor that inhibits collagen production and up-regulates collagen breakdown by up-regulating enzymes called matrix metalloproteinases (MMPs) [45, 46]. In aged skin, there is elevation of AP-1 as compared to young skin [47]. MMP activity is increased in aged human skin and is associated with dramatic increased levels of degraded collagen [12]. In addition, synthesis of types I and III procollagen is reduced in aged human skin [48]. The combination of increased breakdown of collagen and decreased synthesis of new collagen results in an overall decrease in collagen levels in the dermis. The MMPs are a large family of degradative enzymes and four in particular are thought to be important in matrix degradation in the skin. The combined actions of collagenase (MMP1), 92 kDa gelatinase (MMP2), 72 kDa gelatinase (MMP9), and stromelysin 1 (MMP3) can fully degrade skin collagen and components of the elastic network. Coupled with these changes, elastin gene expression is markedly reduced after the age of 40–50, as determined by mRNA steady state levels in cultured fibroblasts, and there is a progressive disappearance of elastic tissue in the dermis. In aged skin there is an increase of MMP activity and reduced collagen I expression. Moreover, an irradiation of human skin with just a single dose of UV light has been shown to increase the activities of MMPs, and this has been associated with significant degradation of collagen fibers. In presenescent dermal fibroblasts, metalloproteinase activity is relatively low with MMP1 and MMP3 shown to be expressed at very low levels. In contrast, levels of matrix metalloproteinase inhibitors TIMP1 and TIMP3 are high, further reducing degradative capacity. In senescent fibroblasts, however, this is reversed with an increase in matrix metalloproteinase expression and a reduction in the expression of tissue inhibitors of metalloproteinase (as a review, see [49]). Ulisse et al. [50] demonstrated the capacity of an oral VSL#3 treatment to decrease MMP activity at the tissue level in the maintenance treatment of patients with pouchitis [50]. Further insights into the molecular basis of periodontitis have identified the potential clinical significance, giving the experimental ground for a new innovative, simple, and efficacious therapeutical approach of periodontal disease [51]. In particular, the anti-inflammatory effects of L. brevis extracts on periodontitis patients, which were associated to a significant decrease of MMP levels in saliva samples, were assayed by zymogram and Western blotting. Moorthy et al. [52] evaluated the effect of L. rhamnosus and L. acidophilus on neutrophil infiltration and lipid peroxidation during Shigella dysenteriae 1-induced diarrhea in rats demonstrating a reduction of levels of myeloperoxidase, lipid peroxidation, alkaline phosphatase, and the expression of MMP2 and MMP9 [52]. Together, these data suggest that probiotic treatment could decrease skin aging-
associated MMP activity and may represent a new, promising, and inexpensive approach to treat the cutaneous laxity.

**Probiotics and Skin Aging-Associated Altered Immune Response**

Aging is accompanied by a reduction in the functional capacity of all the organs in the body, and accordingly, the activity of the immune system also declines with age (as a review, see [53]). The senescence of the immune system especially affects cell-mediated as well as humoral immunity. A decrease has also been observed in the ratio of mature to immature T lymphocytes and an increase in proinflammatory cytokine and ROS production [54]. Age-related alterations in immune function also affect the skin and may account for the increased susceptibility in the elderly to cutaneous infections and malignancies and decreased or variable contact hypersensitivity reactions [55]. Perhaps associated with these immunological changes and certainly with other physiological and environmental factors, the bifidobacteria numbers in the gut decrease markedly after 55–60 years of age [56]. The immune system of the elderly is a potential target for probiotics, as it is known to be affected adversely by the aging process, leading to decreasing resistance to diseases [56]. Several studies have reported the capacity of probiotics to counteract the immunosenescence process and to protect against infection [57, 58]. Probiotics have been demonstrated to induce an adjuvant effect on immunological responses, and this evidence suggests that the use of probiotics could also be effective in enhancing the skin barrier function, even if not all probiotics have the same immunological properties (as a review, see [59]). Immune regulation by probiotics is thought to be mediated through the balancing control of pro- and anti-inflammatory cytokines. Some strains of the genus *Bifidobacterium* exhibit powerful anti-inflammatory properties and thus may be able to restore an unbalanced cytokine production [60]. The efficacy of probiotic organisms in the treatment of pouchitis is also reported, an effect that could be in part attributed to nitric oxide synthase (NOS)-II activity decrease [50]. Nitric oxide (NO) is a paracrine regulator of various biological functions and is known to be involved in the physiology and pathophysiology of many systems, including the skin. It is synthesized from L-arginine by NOS. Of interest, the expression of NOS-II is also strongly implicated in several inflammatory skin conditions [61]. A recent study aimed to investigate the beneficial effects of *L. brevis* extracts on periodontitis patients reported that the relevant anti-inflammatory effects of *L. brevis* extracts could be attributed to the presence of high levels of arginine deiminase, which, also in this inflammatory model, metabolizing arginine to citrulline and ammonia, indirectly leads to nitric oxide (NO) generation inhibition, by competing with NOS for the same substrate, arginine [51]. The association between the composition of the *Bifidobacterium* microbiota and the different levels of proinflammatory cytokine TNF-α as well as anti-inflammatory cytokine TGF-β and regulatory cytokine IL-10 has been recently investigated [62]. The results showed that *Bifidobacterium* microbiota of the elderly may be modified through a probiotic intervention, and that even modest changes in the levels of specific *Bifidobacterium* species may be associated with changes in the cytokine levels, indicating that modulation of the intestinal *Bifidobacterium* microbiota may provide a means of influencing the inflammatory responses in the elderly. Nutritional intervention, particularly with dietary antioxidants, has been proposed to protect against UV-induced skin damage, and during recent years, an increasing interest has been shown for new nutritional approaches using live microorganisms as probiotics. UV radiation is known to alter the cutaneous and systemic immune systems implicated in the development of skin tumors. Of note, findings suggest that ingested probiotic bacteria (*L. johnsonii* La1) can maintain in a mouse model as well as in humans a normal cutaneous immune capacity after UV exposure [63, 64]. The presented evidence would suggest that La1, via priming the immune system in the gut, may be considered an immunoprotector against the predicted
The immunosuppressive effect of UV on the skin immune system. In particular, probiotic ingestion was able to allow a protective cutaneous hypersensitivity reaction, a normal epidermal Langerhans cell density, as well as to maintain or restore the systemic IL-10 production to levels equivalent to non-UV-exposed conditions, thus confirming the ability of La1 to preserve the capacity of the organism to respond to immunological changes.

Of note, the ingestion of probiotics has been associated with a diminution in the severity of autoimmune, particularly intestinal inflammatory, diseases as well as allergic disorders [65, 66].

In conclusion, the scientific literature strongly supports the ability of probiotics to modulate the immune response as well as their capacity to counteract the immunosenescence process and to protect against infection [57, 58].

**New Frontiers in Probiotic Research and Concluding Remarks**

As the elderly population increases, the prevalence of aging-related diseases will increase and functional foods that provide health benefits to control aging and prolong health span will become more desirable. The experimental evidences summarized in the present review strongly encourage the treatment with selected probiotic strains as sun protector, in ameliorating the aging skin condition, in improving dermocosmetic treatments, in recovering skin properties after an injury, as well in preparing skin to cutaneous laser resurfacing. Laser procedures for the aging face are numerous and emerging rapidly. Ablative laser resurfacing is considered to be the gold standard to improve clinical features of the aging face and generally refers to treatment with a carbon dioxide laser (10,600 nm) [67]. It improves fine and some coarse wrinkles and overall dyspigmentation, lightens dark under-eye circles, and generally improves the texture of skin; it can also be used to ameliorate old acne scarring. Side effects include increased erythema immediately following the treatment, slight discomfort, swelling, and potential bruising. Pretreatment clinical assessment and consultation are critical before prescribing or performing the treatments and procedures to review the risks and complications [39]. The potent anti-inflammatory effects exerted by selected strains of probiotics could render them good candidates to prevent or reduce, at least partially, the side effects associated to ablative laser resurfacing. Moreover, considering that most of the topically applied cosmetic products have only a short-term effect on superficial structures, the oral supplementation can be integrated with topical products to obtain an even more effective result.

Since probiotics are intrinsically benign bacteria and they appear to implant, at least temporarily, in the gastrointestinal tract of nearly everyone who consumes them, they can be used as vehicles for transporting genes of medical importance to the host [68]. This approach is also helpful to slow the process of skin aging.

Advances in the field of probiotic research provide new delivery systems, creation of disease-targeted recombinant strains, and isolation and characterization of signaling molecules that can modulate microbial biofilms and infectious processes [2] (Fig. 2). Moreover, the development of new delivery mechanisms could provide encapsulating probiotics, such that they rehydrate at specific sites, and encasing prebiotics in nanoaggregates that could protect against...
stomach acid and deliver their payload when the pH reaches 7.4 [69]. Potentially, such nanoencapsulation will also allow probiotic delivery in foods, such as biscuits [2]. At the macromolecular level, it will be possible to coat capsules with biosensors that detect the optimal conditions for release of probiotic contents as suggested by Hopper [70]. An alternative approach to improving probiotic efficacy is to enhance a strain’s ability to cope with stress at the genetic level. This approach has been successfully employed to increase the stress tolerance profile of two probiotic strains: L. salivarium UCC118 and Bifidobacterium breve UCC [71, 72]. Cloning the betL gene into L. salivarium resulted in a significant increase in the ability of the transformed strain to accumulate betaine, which confer increased salt tolerance and osmotolerance, thus improving the clinical efficacy of the probiotic.

The growing rates of antibiotic resistance and the realization that biofilm formation makes it more difficult for antibiotics to eradicate infections have led to studies of new approaches for managing infectious biofilms using probiotics. These include disruption or penetration of biofilms by beneficial microbes or alteration of the environment to restore a noninfectious biofilm. An in vitro study has shown that Gardnella vaginalis species biofilms can be penetrated by L. rhamnosus GR-1, leading to rapid disruption and death of the pathogens [73]. Other studies have shown that this Lactobacillus strain can also prevent the formation of C. albicans biofilms, and it can kill the yeast in vitro [2]. Moreover, fluorescent in situ hybridization and confocal laser microscopy, used successfully to study complex oral biofilms, could be used to better understand how gram-negative and gram-positive bacteria interact in biofilms and are affected by different nutrients, as suggested by Thurnheer [74]. In summary, biotechnology holds the key to future advances in the clinical application of probiotic product.

An additional message, supported by scientific evidence, strongly emerges that probiotics can enhance health in a more holistic manner, by improving the balance of the intestinal flora, preventing disease, reducing allergic events, interdicting the introduction of harmful microorganisms, and suppressing intestinal enzyme activity that could have detrimental effects. Probiotics must be viewed as healthy additions to everyone’s diet. The discovery of new probiotics has been based on a calculated strategy of considering the characteristics of an ideal strain and then asking nature to provide it within the diversity of the microbial world. Now the objective should be to define the appropriate uses of probiotics and to discover new applications, which will bring benefit to human health including ameliorating the aging skin condition.

Cross-References

▶ The Potential of Probiotics and Prebiotics for Skin Health

References


