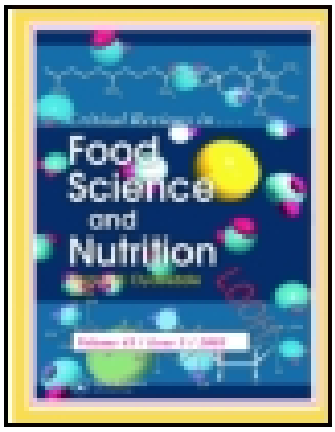

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Probiotic Lactic Acid Bacteria and Skin Health

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Abstract

Human skin is the first defense barrier against the external environment, especially microbial pathogens and physical stimulation. Many studies on skin health with Lactic acid bacteria (LAB) have been published for many years, including prevention of skin disease and improvement of skin conditions. LAB, a major group of gram-positive bacteria, are known to be beneficial to human health by acting as probiotics. Recent studies have shown that LAB and their extracts have beneficial effects on maintenance and improvement of skin health. Oral administration of *Lactobacillus delbrueckii* inhibits the development of atopic disease. In addition, LAB and LAB extracts are known to have beneficial effects on intestinal diseases, with *Lactobacillus plantarum* having been shown to attenuate IL-10 deficient colitis. In addition to intestinal health, *L. plantarum* also has beneficial effects on skin. pLTA, which is lipoteichoic acid isolated from *L. plantarum*, has anti-photoaging effects on human skin cells by regulating the expression matrix meralloprotionase-1 (MMP-1) expression. While several studies have proposed a relationship between diseases of the skin and small intestines, there are currently no published reviews of the effects of LAB for skin health through regulation of intestinal conditions and the immune system. In this review, we discuss recent findings on the effects of LAB on skin health and its potential applications in beauty foods.

Keywords Lactic acid bacteria, Probiotic, Skin, Beauty food

Introduction

Probiotics refer to microorganisms that have beneficial effects on host health. Interestingly, the most common focus of probiotics is modulation of immune system potency [1]. Lactic acid bacteria (LAB) have a number of beneficial effects and have formed the basis of the term probiotics. More specifically, *Lactobacilli* and *Bifidobacteria* species, the most common strains of LAB, are known to have the ability to regulate Th1:Th2 cytokine balance. In addition, many studies have shown that probiotics have beneficial effects on physical barrier function, mucosal immune system, metabolism, and systemic immunity [2, 3]. Further, probiotics have been used to successfully treat various diseases including atopic diseases, inflammatory bowel disease (IBD), irritable bowel syndrome, cardiovascular diseases, and pathogen infections [4-8].

Skin is an effective defense barrier between organisms and the external environment, playing an important role in preventing invasion of pathogens and detecting physical stimulation. Skin acts as protector and immune-surveillance mechanism, and is an extensively exposed organ that functions as a unique stimulator for immune sentinel and effector cells. Keratinocytes, the major cell type of the epidermis, can sense harmful pathogens and distinguish them from harmless commensal organisms. In addition, following exposure to intensive UV irradiation, keratinocytes are activated and induce an immune response by secreting key pro-inflammatory cytokines [9]. As a physical barrier, skin barrier function is a central event in various skin diseases. Specifically, impaired skin barrier function can lead to pathogen infection and atopic dermatitis (AD) [10, 11]. Several studies have shown that skin health is associated with the nutritional condition of the host. Interestingly, the probiotic *L. paracasei* was shown to decrease skin sensitivity and increase

the recovery rate of skin barrier function [12]. Thus, the purpose of this review is to provide an overview of the recent findings on the effects of LAB on skin health and its potential applications in beauty foods.

Ⅰ. Probiotics and skin

The skin is a complex network of interactions between microbes and epidermis cells. In healthy skin, probiotics can be considered as innocuous or even beneficial. However, some skin diseases are caused by an imbalance of microorganisms, including dry skin and mild AD [13]. A number of recent studies have looked at the effects of probiotics and maintenance of healthy skin conditions. In one study, oral bacteriotherapy with probiotics was suggested to be useful for treating certain skin diseases. Likewise, a combination of *L. rhamnosus* 19070-2 and *L. reuteri* DSM 122460 was shown to be an effective therapy for AD [14], while the administration of *B. subtilis* was shown to prevent atopic lesions induced by mite antigen in NC mice [15].

Probiotics can also help to maintain skin homeostasis by protecting against UV-induced skin damage. Oral supplementation with the *L. johnsonii* La1 has a beneficial effect on cutaneous immune status after acute UV irradiation [16, 17]. Further, oral administration of *Lactobacillus paracasei* improves skin barrier function and prevents local skin inflammation by modulating the immune system in a disease-dependent manner [18]. Interestingly, in addition to live probiotics, heat-killed probiotics can effectively modulate the immune system. Heat-killed R-037 and *Lactobacillus delbrueckii* subsp. *lacti* have an inhibitory effect on the development of AD [19]. Thus, it is clear that there are numerous strains of probiotics that have diverse effects on skin health. The relationships between probiotics and their effects on the skin are summarized in

Table 1.

The majority of probiotics in the human body are found in the stomach and small intestines. Indeed, probiotic LAB are closely associated with beneficial effects on gastroenteritis and diarrhea. It has been suggested that probiotics systemically modulate immune responses in the gut, and other studies have considered the possibility that probiotics can have similar effects in human skin [20].

Ⅱ. Strategies to Improve Skin Health using Probiotics

1. Modulation of immune responses by probiotics

Lactobacilli, a major group of probiotics, can modulate the host immune response by binding to pattern recognition receptors (PRRs) expressed on a number of immune cells and other tissues including the intestinal epithelium. Probiotics, as microbe-associated molecular patterns (MAMPs), are recognized by PRRs, which in turn induce the production of cytokines and chemokines. PRR signaling receptors are divided into three families, namely, Toll-like receptors (TLRs), retinoic acid inducible gene-I (RIG-I)-like receptors, and nucleotide oligomerization domain-like (NOD) receptors (NLRs). Especially, TLR signaling is a major signaling pathway after MAMP binding and is activated according to the specific arrangement and sequence variations of extracellular leucine-rich repeat (LRR) domains. Dimerization of TLRs leads to the recruitment of adaptor molecules such as myeloid differentiation primary response gene 88 (MyD88). The TLR signaling pathway, through recruitment of MyD88, can subsequently activate the mitogen-activated protein kinase (MAPK) pathway and nuclear factor κB (NF-κB)

signaling cascade. Thus, TLR signaling is important for modulation of immune responses by probiotics [21].

LAB can induce different amounts and types of TLR signaling associated cytokines, namely, TNF-α, IFN-γ, IL-1β, IL-4, IL-6, IL-10, and IL-12. Further, LAB-ligation of TLRs induces translocation of NF-κB to the nucleus, resulting in production of proinflammatory cytokines. Similarly, *L. acidophilus* induces the release of high amounts of IFN-γ from natural killer (NK) cells and production of IL-12 in dendritic cells (DCs). However, not all species of LAB have a similar capacity for induction of IL-12 and IFN-γ production. For example, *B. bifisum* and *L. reuteri* inhibit *L. acidophilus*-induced secretion of IL-12 and IFN-γ secretion [22]. In addition, LABs are well known for their ability to modulate immune responses by altering the Th1/Th2 cytokine balance. Probiotic LAB modulates both protective Th1 type cytokines, such as IFN-γ, and immunosuppressive Th2 type cytokines, including IL-4. Both *L. rhammosus GG* and *Bifidobacterium bifibum MF20/5* improve Th1/Th2 polarization by decreasing IL-4 secretion in both unstimulated and *Mycobacterium tuberculosis* antigen-stimulated peripheral blood mononuclear cells (PBMCs) [23]. Likewise, lipoteichoic acid (LTA) isolated from *L. plantarum* has been shown to significantly inhibit LPS-induced TNF-α production [24]. Similarly, fermentation by *Lactobacillus* enhances inhibition of LPS-induced NO, PGE_2, TNF-α and IL-6 production by abrogating the activities of NF-κB and MAPK [25]. In addition, pre-treatment with *Lactobacillus acidophilus* has an anti-inflammation effect, reducing IL-8 and TNF-α secretion by inactivating the NF-κB pathway [26]. *Lactobacillus paracasei* KW3110 induces IL-12 expression and inhibits IgE secretion [27], while *L. rhamnosus* GR-1 increases levels of TNF and pro-inflammatory cytokine and decreases secretion of IL-6 and CXCL8. Lastly, the NF-κB

signaling pathway is also activated by the probiotic *L. rhamnosus GG* [28].

In summary, the immune modulatory effects of probiotics are coincident with their ability to stimulate PRR-associated cell signaling by acting as MAMPs. Interestingly, immune responses by probiotics are strain-specific, which has not been discussed in previous reviews.

2. Beneficial effects of probiotics for maintaining good skin condition

Recently, many researchers have studied the relationship between probiotics and skin health. The consensus of these studies is that probiotics have beneficial effects for improving skin health. Probiotics can improve skin conditions through two processes, either by acting as microflora on the skin or as probiotics in the intestines [29, 30]. In particular, resistant microflora of the skin, mainly Gram-positive bacteria, are regarded as "beneficial" to the "normal health" of the host. Indeed, such microflora can influence skin barrier function and the immune system [29]. Probiotics in the intestines can also have beneficial effects on skin health and can be used as a treatment by administration to the host. For example, *Bifidobaterium infantis* prevents skin disorders-associated immune abnormalities, while *Lactobaillus reuteri* protects epidermal keratinocytes from *staphylococcus*. Further, other LAB can act as probiotics by alleviating infantile eczema [30-32].

Blocking the release of pro-inflammatory cytokine is an important strategy for the treatment of skin inflammation [33]. Inhibition of pro-inflammatory cytokines is a well-known property of probiotics, especially LAB. Specifically, LAB including *L. plantarum* and *Lactobacillus acidophilus* strongly inhibit the potential activity of inflammatory mediators, inflammation associated cytokines, and related signaling pathways [22-26]. *L. paracasei* accelerates the

recovery of skin barrier function and inhibits P-induced skin inflammation by modulating reactive skin-associated inflammatory mechanisms. Specifically, *L. paracasei* was shown to abrogate the release of substance P-induced TNF-α expression [34]. In addition, probiotics have beneficial effects on the alleviation of AD lesions. Heat-killed *L. brevis* SBC8803 has been shown to have an inhibitory effect on development of AD by preventing increased IgE production [35]. Probiotic-mediated improvement of AD is also associated with Th1 and Th2 cytokines, and adults with AD treated with the probiotic *Lactobacillus salivarius* exhibit a statistically significant improvement of lesions that is associated with a significant reduction of Th1 cytokines (IL-12+IFNgamma) and the Th1/Th2 ratio (IL-12+IFNgamma/IL-4+IL-5) [36]. Another cytokine, IL-4, has been strongly implicated in skin diseases such as AD. The pathological features of AD are dependent on IL-4, in that they are a consequence of IL-4 overexpression in the skin. Importantly, several probiotics have been shown to decrease levels of IL-4 production [23, 37].

Keratinocytes are first responders to the external environment and serve as initiators in skin innate immune systems by modulating expression of cytokine/chemokines including IL-1β, TNF-α, IL-8, and granulocyte/macrophage colony-stimulating factor (GM-CSF) in the skin [38-40]. Indeed, the immune initiation potency of keratinocytes is facilitated through TLRs such as TLR1, TLR2, TLR3, TLR4, TLR5, TLR6 and TLR 10. Notably, TLR2, a major recognition receptor of LAB, is considered to be a key receptor in epithelial cells. Further, one research group has reported that TLR2 is the only such receptor expressed on the surface of cultured normal human keratinocytes [41, 42]. Cytokine/chemokines production via TLRs results in protection of the host from bacteria pathogens and fungi by stimulating skin inflammation [43].

Indeed, LAB are known to function as immune modulators, with this property having been achieved through regulation of pro-inflammatory cytokine production through TLR signaling. Further, many studies have shown that LAB have a beneficial effect on skin inflammation, with some studies suggesting that T cells are important for mediating the effects of probiotics on skin. *L. casei* has been shown to alleviate allergic skin inflammation by inhibiting both effector and regulatory T cells, and treatment with *L. casei* reduces recruitment of CD8+ effector T cells into the skin, enhances the frequency of $FoxP3^+$ Tregs, and increases production of IL-10 by $CD4^+CD25^+$ regulatory T cells in the skin [44].

While recent research has demonstrated a strong relationship between skin health and probiotics, the mechanisms by which probiotics facilitate improved skin health remains unclear. Here, we propose a mechanism to explain how skin health is improved by probiotics (Fig. 1). As described above, skin function is closely tied with inflammation. Modulation of skin immunity and inflammation responses are associated with common cell signaling, NF- kB. Here between the skin immune and inflammatory responses in the presence of a common signal transduction factors to the NF-kB signal [45]. Aspects of the skin immune, ROS (reactive oxygen species) is expressed by certain internal or external stress in skin keratinocytes. This ROS activate the cellular signaling through regulate inflammatory signal, NF-kB [46]. Then activated NF-kB enters the nucleus and induces expression of MMPs, factor that affect skin function through degradation of extracellular matrix proteins. In a perspective of inflammation reaction, NF-kB influences the expression of inflammatory cytokines such as TNF-α, induce MMP expression. It means specific factor associated with skin is regulated through the NF-kB signal [45, 47, 48]. In the previous studies, probiotic is well known the expression of inflammatory cytokines via the

NF-kB signal [25]. Thus, we suggest that probiotics can affect skin and intestine health through regulation of inflammatory signals such as NF-κB.

3. Skin health reflects the effect of probiotics on intestinal health

Until now, research groups have studies the beneficial effects of probiotics by focusing on their ability to maintain intestinal health and prevent diseases of the gut [49]. However, the current focus of probiotic studies has moved from looking only at intestinal health to studying relationships between the internal immune system and other immunological tissues in the host, such as intestine-skin and intestine-brain interactions. Importantly, the notion that intestinal microflora and inflammatory skin conditions are physiologically intertwined is not a new one. Stokes-Pillsbury previously suggested in 1930 that the skin is influenced by emotional states and microbial flora, reporting that gut microflora can influence the degree of acne by a systemic effect on inflammation as well as by controlling oxidative stress through direct and indirect mechanisms [50]. In addition, Fry defined the association between the small intestines and skin diseases to three subgroups, namely, i) a non-specific relationship, ii) a specific relationship, and iii) a generalized disease process [51].

As previously mentioned, probiotics enhance skin conditions by improving gut health (Fig. 1). The majority of the beneficial effects of probiotics on skin via intestines are facilitated through systemic immune responses [3, 20, 50]. In particular, probiotics regulate specific T-cells such as Th1 cells and modulate activity of Th1-type cytokines in the gut mucosa, which may influence immune responses in other tissues for which they play an important role [34-37]. Indeed, orally administrated *Lactobacillus casei* has been shown to alleviate skin inflammation by reducing the

number of CD8+ effector cells such that only CD4+ T-cells are present [52]. The clinically relevant improvement of acne following administration of a mixture of *L. acidophilus* and *L. bulgaricus* provides further clinical evidence of the skin-gut connection of probiotics [53]. In addition, probiotics have been shown to attenuate release of biologically active peptides, including substance P release in both the intestinal tract and skin [32, 54]. Interestingly, the influence of probiotics through the inhibition of substance P production has been suggested as a mechanism of communication between the gut and skin [55]. Another study reported amelioration of skin homoeostasis by oral administration of probiotics following stress-induced skin inflammation. Together, these observations strongly support the existence of a probiotic link in the gut-brain-skin axis [58]. This concept is supported by a number of studies, including identification of peptide-containing cells in skin [59]. In addition, the association of inflammatory bowel diseases and skin diseases provides further evidence to strengthen the relationship between the gut and skin [58, 59].

Ⅲ. Probiotic extracts, including LTA, and skin health

Previous studies have suggested that live probiotics are the most effective for modulating the immune response of the host [60-62]. However, extracts of probiotics have been demonstrated to have similar or even more effective activity for stimulating and modulating immune response compared to live probiotics. Specifically, *Lactobacillus casei* extract is a potent inducer of NF-κB through the TLR-2/MyD88 signaling pathway [63]. Likewise, heat-killed *Lactobacillus casei* generate an enhanced adaptive immune response when administered nasally with a pneumococcal antigen or live bacteria [64]. A clinical trial of a probiotic lysate of

Bifidobacterium longum sp. used a non-replicating bacteria extract applied to the skin, rather than live probiotics, and was shown to improve sensitive skin. Following this study, a test cream containing a 10% bacterial extract was shown to have a clinically relevant effect on skin dryness, and was shown to increase skin resistance against physical and chemical aggression. Together, these results suggest that specific bacteria extracts have beneficial effect on reactive skin [65]. In addition, many published studies have demonstrated that specific bacterial extracts, including those of *Lactobacillus johnsonii*, *Lactobacillus casei*, *Lactobacillus plantarum*, and *lactobacillus acidophilus* have beneficial effects on anti-adhesion and anti-microbial potency on cutaneous and mucous surfaces, respectively [66, 67].

As mentioned above, regulation of TLR signaling pathways and skin immune responses are important to protect skin from immune associated skin disease, such as AD [41, 42, 68]. Specific elements of probiotics modulate immune responses triggered by TLR ligands. In particular, lipoteichoic acid (LTA), a major component of the Gram-positive bacteria cell wall, is important for modulating the activity of the innate immune response [69]. LTA is well known for its potent immune modulatory activity. For example, pLTA (isolated from *Lactobacillus plantarum*) has been shown to have an inhibitory effect on LPS-induced TNF-α production [24]. Research on the inhibition of TLR3-dependent inflammation by probiotic bacteria through a TLR2-dependent mechanism in skin injury suggests that LTA may be effective for treating skin inflammation [70]. Further, several research groups have consistently demonstrated the relationship between LTA and skin health by showing that purified LTA from *Lactobacillus rhamnosus* GG has an immune modulatory effect against UV radiation and inhibition of skin tumor development [71]. In addition, our research group has shown that pLTA has an anti-photoaging effect on UV-

irradiated human skin through regulation of MMP-1 expression (not published). Thus, we propose that LTA, which is a component of many probiotic extracts, is an important element of probiotics for maintenance of skin health.

Ⅳ. Conclusion

The international cosmetic market for beauty foods is expanding, and similarly the interest for probiotic LAB is growing very fast. LAB is a remarkable group of probiotics that have anti-inflammatory properties and are capable of improving skin health. Although the precise mechanisms by which LAB improve skin health is unknown yet, its beneficial effects on skin health have been demonstrated by numerous studies, and the literature continues to grow. LAB have been shown to modulate the expression of MMPs and their extracts, rather than live whole LAB, can have beneficial effects on immune modulation, including skin health. Probiotics directly influence human skin. In addition, modulation of immunity in the gut may be relevant for maintaining the health of human skin through a systemic mechanism. Recent years have witnessed a proliferation of published clinical studies involving probiotic foods and beverages. At the same time, the global market for nutricosmetics is growing rapidly due to changes in lifestyle, aging population and increased consumer awareness. Therefore, academic and industry interests on probiotic lactic acid bacteria on skin health are expected to grow rapidly.

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Tables and Figures Lagend

Table 1. Various therapeutic effect on skin health by probiotics

Probiotics	Associated actions	Reference
Bifidobacteria species	Prevention of skin disorders – associated with immune abnormalities & improve sensitive skin	(32)
Bacillus subtilis	Prevention of atopic lesions	(15)
Lactobacillus acidophilus	Clinical improvement of acne	(50)
Lactobacillus bulgaricus	Clinical improvement of acne	(50)
Lactobacillus casei	Alleviation of skin inflammation	(45)
Lactobacillus delbreuckii	Inhibition of atopic dermatitis development	(19)
	Decrease of skin sensitivity	(12)
Lactobacillus paracasei	Acceleration of skin barrier function recovery	(35)
	Therapy for atopic dermatitis	(14)
Lactobacillus rhamnosus	Prevention against UV-induced skin damage	(16)
	Therapy for atopic dermatitis	(14)
Lactobacillus reuteri	Protection of epidermal keratinocytes	(31)
Lactobacillus salivarius	Therapy for atopic dermatitis	(37)

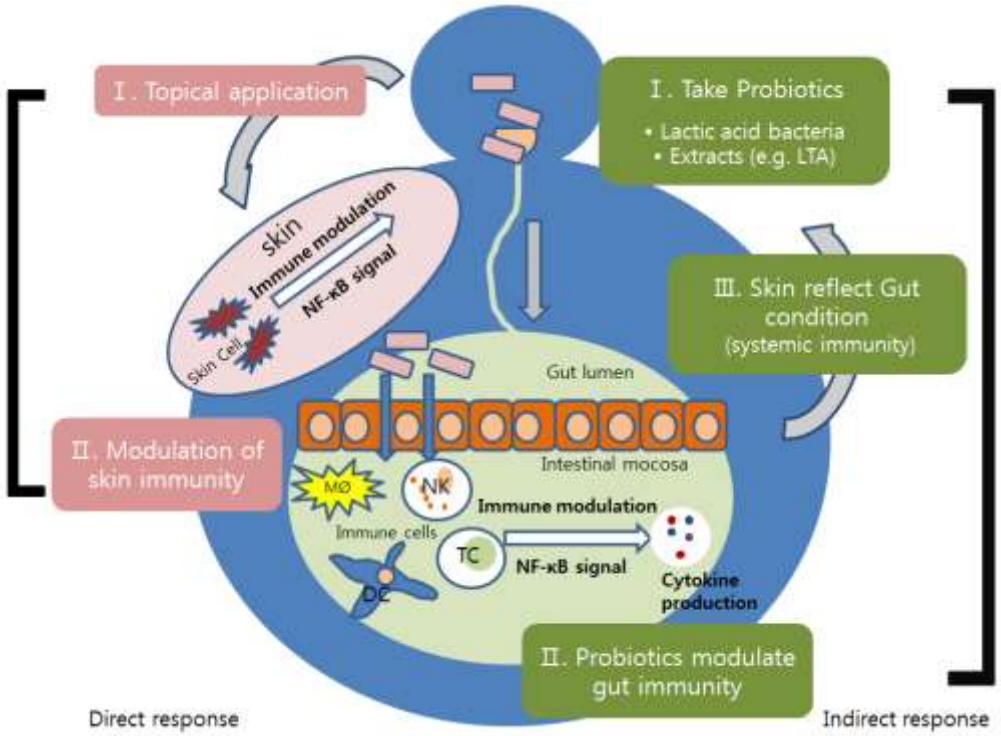

Figure 1. Probiotics can regulate the skin immunity through the inflammatory signals, NF-κB