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The effect of probiotics on immune regulation, acne, and photoaging☆,☆☆,★

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ABSTRACT

Probiotics are live micro-organisms that provide a health benefit to the host. The role of probiotics in the management of disease, as well as immune modification, has recently experienced a renewed interest in society, as probiotics can be found in products ranging from yogurt to facial creams. In this article, we discuss the role of probiotics in the development of the immune system, the treatment of acne and rosacea, and protection against aging and photodamage.

Introduction

The earliest report on probiotics dates back to 1907, when Elie Metchnikoff described a correlation between the ingestion of lactic acid–producing bacteria in yogurt and enhanced longevity (Gordon, 2008). During the past few decades, there has been renewed interest in probiotics not only in regards to digestive health, but also in the management of inflammatory diseases. The term *probiotic* has been defined as "living microorganisms which, when consumed in adequate amounts, confer a health effect on the host" (World Health Organization and Food and Agriculture Organization of the United Nations, 2001). *Lactobacillus* and *Bifidobacterium* have emerged as two of the most commonly used probiotics (Ouwehand et al., 2002), although newer strains such as *Bacillus coagulans* are being investigated with positive results (Benson et al., 2012).

Most commonly formulated as fermentation products, probiotics counter pathogenic bacteria, support barrier function, and contribute to the regulation of the innate and adaptive immune responses (Hacini-Rachinel et al., 2009). Probiotics can now be found in household items ranging from yogurt to children's popsicles to facial cream.

In this review, we discuss the role of probiotics in the development of the immune system, the treatment of acne, and protection against aging and photodamage.

Immune regulation

The concept of nature versus nurture is longstanding; however, we now understand how the environment, specifically the microbial environment, can influence the expression of our genes. While an individual may have a genetic predisposition to developing a condition, such as lupus or diabetes, an exposure to a specific environmental factor exerts pressure on the genome, determining if the disease ultimately develops and/or the disease severity.

Emerging insights into the interactions between probiotics and host receptors have demonstrated the ability of probiotics to modulate gene expression and cellular differentiation of the immune system. Given that the gastrointestinal tract houses the largest reservoir of commensal bacteria and acts as the body's largest immune organ, a significant body of research evaluates the influence of probiotics on the modification of the immune system in the gastrointestinal tract (Benyacoub et al., 2014; Savage, 1977). The communication among epithelium, macrophages, dendritic cells, and micro-organisms in the gastrointestinal tract results in T-cell differentiation (Sansonetti and Medzhitov, 2009), ultimately training the innate and adaptive immune systems to achieve immune homeostasis and tolerance for commensal microbiota (Bron et al., 2012). The immune system recognizes both pathogenic and commensal bacteria through the family of Toll-like receptors (TLR) (Hemmi et al., 2000). Proteins located on the surface of bacteria, including lipopolysaccharide (LPS), flagellin, and lipoproteins, as well as bacterial DNA within the cell interact with the TLRs, modifying the immune response (Benson et al., 2012). A study using germ-free mice demonstrated that specific strains of gut microbiota regulated the expression of genes involved with nutrient absorption, energy metabolism, intestinal barrier function, and immunity (Hemarajata and Versalovic, 2013). Similarly, in humans subjected to probiotic bacteria (*Lactobacillus* species), gene transcription profiles of immunity and intestinal barrier varied pre- and post-treatment with probiotics (Van Baarlen et al., 2010).

Although probiotics may exert their effect locally when applied or ingested, with their influence on immune regulation, their effects often extend to other organ systems. Evidence suggests that chronic inflammation and gut microbiota imbalance contributes to obesity, diabetes, cancer, depression, and inflammatory bowel disease (Hormannsperger and Haller, 2010; Karin et al., 2006; Kushner et al., 2006; Musso et al., 2011;

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Turnbaugh et al., 2006). A common thread underlying these conditions is the concept of chronic inflammation without a clear pathogenic threat. Short bursts of inflammation are required in certain circumstances—for instance, when a host encounters pathogens such as *Staphylococcus aureus* or Herpes Simplex Virus. However, chronic low levels of inflammation when no true threat is present contribute to many so-called "diseases of Western society," including but not limited to those listed above. An ideal probiotic would be capable of boosting the host's immune response to true threats, while inhibiting an ongoing immune reaction when no threat is present. We call this concept "immune regulation."

Oral probiotics have been shown to improve insulin sensitivity in animal models (Hsieh et al., 2013) as well as regulate the release of inflammatory cytokines in the skin through their interaction with gut-associated lymphoid tissue (Hacini-Rachinel et al., 2009). The gut-brain-skin axis suggests a mechanism that links gastrointestinal health, influenced by interactions with oral probiotics, to the health and well-being of the skin (Bowe and Logan, 2011). Several strains of *Lactobacillus* have been shown to have systemic anti-inflammatory effects. Studies have shown that *Lactobacillus reuteri* 100–23 induces systemic anti-inflammatory cytokines, such as interleukin (IL)-10 (Livingston et al., 2009). Soluble factors from *L. reuteri* inhibit production of pro-inflammatory cytokines and culture supernatants of murine-derived *L. reuteri* 6798 inhibit tumor necrosis factor (TNF) production of activated macrophages (Livingston et al., 2009; Thomas et al., 2012; Van Baarlen et al., 2010).

Several strains of *Lactobacillus* also demonstrate anti-inflammatory properties. The addition of *Lactobacillus paracasei* NCC2461 has been shown to inhibit neutrogenic inflammation in a skin model, and the addition of *L. paracasei* NCC2461 to lymphocyte culture has been shown to strongly inhibit the proliferative activity of CD-4 + T-cells in a dose-dependent manner and to induce the anti-inflammatory cytokines IL-10 and TGF-beta (7). Mice who consumed the probiotic for 7 days demonstrated a significantly higher antibody response and in vivo T-cell-mediated immune response, indicating *L. paracasei* affects both B- and T-cell function (Benyacoub et al., 2014). Similarly, mice treated with *Lactobacillus casei* had an increased ability to produce IL-10 and promote T-regulatory cell function (Hacini-Rachinel et al., 2009). An increase in T-regulatory cells suggests that this probiotic may help to balance the immune system's response to stimuli (Hacini-Rachinel et al., 2009; Pellaton et al., 2012). Consequently, certain probiotic strains may potentially boost appropriate immune responses, for example to a harmful pathogenic threat, while dampening the unnecessary immune responses seen in chronic inflammatory states.

Similar to *Lactobacillus*, *B. coagulans* has been shown to display immunoregulatory effects that could potentially impact the health of the skin. The incubation of peripheral blood mononuclear cells (PBMCs) and polymorphonuclear (PMN) cells with the supernatant and cell wall fragments of *B. coagulans* promoted mature phenotypes of antigen-presenting cells and inhibited spontaneous and stress-induced reactive oxygen species (ROS) formation (Benson et al., 2012; Jensen et al., 2010). We are well aware that ROS and oxidative stress play a role in acne, making this an intriguing finding with potential benefit for the acne patient (Bowe and Logan, 2010).

Disruption of skin barrier function is a known side effect of many acne medications including topical retinoids and benzoyl peroxide. The irritation, stinging, and dryness resulting from these medications can negatively impact compliance with an acne regimen. Rosacea and atopic dermatitis are other skin conditions in which the skin barrier is impaired, and symptoms improve when the skin barrier is strengthened. Oral ingestion of certain probiotic strains has been shown to improve the skin barrier and affect skin hydration and transepidermal water loss. Gueniche et al. (2014) studied the effects of oral supplementation with *L. paracasei* NCC2461 versus placebo for healthy female volunteers via a randomized placebo-controlled clinical trial. A capsaicin test was used to monitor skin sensitivity, while transepidermal water loss and dermatological assessments were utilized to measure skin barrier function. Both skin sensitivity and skin barrier function improved in the probiotic group. The probiotic group also showed increases in the serum concentration of TGF-beta after 29 days compared to no increase in the placebo group. TGF-beta has been shown to play a significant role in skin integrity (Hashimoto, 2000; Pasonen-Seppanen et al., 2003).

Overall, probiotics modulate the development of the immune system, often shifting the immune response toward regulatory and anti-inflammatory conditions. This ability of probiotics to modify chronic inflammatory states suggests that probiotics may have a role in treating chronic inflammatory conditions, ranging from inflammatory bowel disease to reactive airway disease to acne, rosacea, atopic dermatitis, and photoaging (Benyacoub et al., 2014; Bowe, 2013).

Acne

Through basic science and animal and human clinical trials, the evidence is growing for the use of probiotics in the treatment of acne. Acne formation is dependent upon several processes, including follicular hyperkeratinization, excess sebum production, *Propiobacterium acnes* colonization, and an inflammatory cascade (Baquerizo Nole et al., 2014). Successful acne outcomes are influenced by compliance with topical regimens that can commonly cause skin barrier disruption, leading to dryness and irritation. Consequently, calming inflammation as well as maintaining skin hydration and barrier repair are of primary importance when treating acne. Probiotics modify several factors in the pathophysiology of acne development and can potentially improve compliance as well.

At the basic science level, probiotics have been shown to directly inhibit *P. acnes* through the production of antibacterial proteins. In vitro *Streptococcus salivarius*, a prominent component of the oropharynx, has been shown to inhibit the growth of *P. acnes* and group A streptococci through the production of a bacteriocin-like inhibitory substance (BLIS-like substance) (Bowe et al., 2006). Similarly, strains of *Lactococcus* sp. HY 449 exhibit antimicrobial activity and inhibit the growth of *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Streptococcus pyogenes*, and *P. acnes* through the secretion of bacteriocins (Oh et al., 2006). Clinically, the topical application of probiotics has also been shown to modify the barrier function of the skin with a secondary increase in antimicrobial properties of the skin. Specifically, *Streptococcus thermophiles*, applied as a cream for 7 days, has been shown to increase ceramide production both in vitro and in vivo (Di Marzio et al., 1999, 2003, 2008). Not only do ceramides trap moisture in the skin, but certain ceramide sphingolipids, such as phytosphingosine (PS), exhibit direct antimicrobial activity against *P. acnes*. The clinical application of PS has been further substantiated by a 2-month pilot study showing an 89% reduction of acneiform papules and pustules after the application of 0.2% PS (Pavicic et al., 2007). By decreasing the counts of *P. acnes* on the surface of the skin, probiotics target one factor contributing to acne formation. By inducing the production of healthy ceramides, it helps restore healthy fats, which can benefit acne directly and counter common side effects resulting from acne therapies.

The immunomodulatory effects of probiotics on keratinocytes and epithelial cells suggest a physiologic mechanism to support the use of probiotics as an adjuvant treatment of acne. Strain K12 of *S. salivarius* inhibited production of the pro-inflammatory cytokine IL-8 in epithelial cells and keratinocytes, likely through the inhibition of the NK-kappaB pathway (Cosseau et al., 2008). This inhibition of multiple inflammatory pathways suggests that *S. salivarius* acts as an immune modulator when applied directly to the epithelium (Cosseau et al., 2008). Cultures of human skin treated with *L. paracasei* NCC2461 showed inhibition of substance-P–induced skin inflammation, as measured by reduction of vasodilation, edema, mast cell degranulation, and tumor necrosis factor alpha (TNF-alpha) release (Gueniche, Bastien et al., 2010; Gueniche, Benyacoub et al., 2010). As substance-P may amplify inflammation and sebum production, its inhibition lends itself toward therapeutic

application in acne treatment (Lee et al., 2008). A reduction on the inflammatory cascade again targets a factor in the pathogenesis of acne.

Two clinical trials of topical preparations of probiotics have assessed their effect on acne. The first trial applied *Enterococcus fecalis* lotion to the face for 8 weeks; a 50% reduction of inflammatory lesions was noted compared to placebo (Kang et al., 2009). A reduction in acne count, size, and associated erythema was again noted during a clinical study of *Lactobacillus plantarum* 5% extract, although these findings were not supported with the 1% extract (Muizzuddin et al., 2012), suggesting the effects may be dose dependent.

Revisiting the gut–brain–skin axis, oral probiotics exert their effect on the skin through various potential mechanisms, including reduction of systemic inflammation and influence on absorption (Bowe et al., 2014). Oral administration of *L. reuteri* in stressed animals demonstrated significantly lower rates of perifollicular inflammation than controls, and the administration of oral probiotics has been shown to limit the major histocompatibility cell (MHC) class II surrounding hair follicles (Arck et al., 2010). Given that perifollicular inflammation appears to be one of the first steps in the acne process, impacting this early inflammation might have a preventative benefit in acne.

Insulin-like growth factor 1 (IGF-1) has also been shown to play a role in the pathogenesis of acne. This suggests that certain foods or probiotic strains may play a role in acne through their modulation of IGF-1. Low-fiber carbohydrates and dairy have been associated with an increased risk in acne development, likely driven by an increase in (IFG-1) (Adebamowo et al., 2006, 2008; Bowe et al., 2010). Supplementation of the probiotic *Lactobacillus* to the fermentation process of milk demonstrated a four-fold lower level of IGF-1 compared with nonfermented skim milk (Quadros et al., 1994). These findings suggest that probiotics may decrease systemic levels of IGF-1, improving acne from a systemic and mechanistic level.

The physician Robert H. Siver conducted the first clinical trial evaluating the effects of probiotics on acne in the 1960s. He studied the effects of an oral, commercially available probiotic (Lactinex composed *of L. acidophilus and L. bulgaricus*) in 300 patients (Bowe et al., 2014). Although the regimen he prescribed was unconventional, consisting of oral probiotics for 8 days followed by a 2-week break, then repeated, he observed that 80% of patients had some improvement, primarily in the inflammatory lesions (Bowe et al., 2014). However, a major limitation to his study was a lack of placebo controls. Despite this major limitation, he concluded that there might be an interaction between gut metabolic processes and manifestations on the skin (Siver, 1961).

More recent studies evaluating the role of oral probiotics on acne have largely been published in foreign journals. In an Italian study of 40 patients, one half received an oral supplement consisting of 250 mg of freeze-dried *L. acidophilus* and *Bifidobacterium bifidum* as an adjuvant to standard treatment (Marchetti et al., 1987). The group receiving the probiotic experienced improved clinical outcome and resolution of acneiform lesions compared to the nonsupplemented group, as well as demonstrated better tolerance for oral antibiotics (Marchetti et al., 1987). Similarly, a study out of Russia evaluated acne patients for impaired bacterial microflora, and patients received intestinal "microflora correcting agents" in addition to traditional acne therapy (Volkova et al., 2001). A more rapid clinical improvement was noted in those receiving the supplement (Volkova et al., 2001). Although the designs of these studies are more difficult to evaluate, they suggest a potential role for oral probiotics as an adjuvant in acne therapy.

A recent clinical trial demonstrated that oral antibiotics and probiotics might provide synergistic benefits, specifically for inflammatory acne (Jung et al., 2013). Forty-five females, aged 18 to 35 years, were randomly assigned to one of three arms: probiotic supplementation only, minocycline only, or both probiotics and minocycline. All patients showed a significant improvement in total lesion count at 4 weeks, with continued improvement throughout the 12-week study. However, the group taking both probiotics and minocycline had a significant decrease in total lesion count as compared to the other two groups. Furthermore, two patients from the minocycline-only group developed vaginal candidiasis. One randomized-controlled trial from Korea assigned acne patients to either receive fermented milk only or fermented milk with 200 mg of lactoferrin daily for 12 weeks (Kim et al., 2010). Lactoferrin, a glycoprotein, is a component of the innate immune system with bactericidal and fungicidal properties. The total lesion count and grade, as well as sebum content, were assessed monthly. The group receiving the lactoferrin-enriched fermented milk showed a greater decrease in total lesion count compared to fermented milk alone (56% versus 32.2%), largely through the decrease in triacylglycerols in skin surface lipids (Kim et al., 2010). Although the additional lactoferrin to the oral probiotic beverage demonstrated a greater decrease than the probiotic alone, the substantial decrease noted by the administration of an oral probiotic alone further supports the role of probiotics as an adjuvant in acne treatment.

Aging skin and protection from ultraviolet light

Aging skin involves a complex interplay between intrinsic aging, including genetic and hormonal influences, and extrinsic aging, which is subject to environmental factors such as ultraviolet (UV) light, trauma, pollution, infections, and cigarette smoking. At the molecular level, alterations in aging skin include an increase in skin pH, a decreased ability to quench reactive oxygen species, and increased matrix metalloproteinase activity (Cinque et al., 2010). UV radiation is considered the strongest precipitator of extrinsic aging. As public knowledge has increased regarding the link between sun exposure and photoaging, interest in preventing and treating the adverse effects of UV radiation has escalated. Early studies suggest that probiotics and their metabolites might alter several aspects of skin aging.

Healthy, normal skin exhibits a slightly acidic pH in the range of 4.2-5.6, which aids in the prevention of pathogenic bacterial colonization, regulation of enzyme activity, and maintenance of a moisture-rich environment (Mauro, 2006); however, after the age of 70, the pH of skin rises significantly, stimulating protease activity (Hachem et al., 2003). Probiotic metabolism frequently produces acidic molecules, lowering the pH of the surrounding environment (Cinque et al., 2010), as seen with *Lactobacilli* producing free fatty acids (FFAs) and conjugated linoleic acid (CLA) during the fermentation process (Yadav et al., 2007). Theoretically, therefore, the use of probiotics may work to restore the normal skin pH and consequently return protease activity levels closer to those seen in young, healthy skin.

Free radicals form as a result of normal metabolic processes, but their production increases in the face of certain environmental factors, including UV light, pollution, and cigarette smoke. As we age and experience multiple such assaults in our environment, our own antioxidant defense system can become overwhelmed, allowing free radicals and ROS to damage cellular structures including DNA, lipids, and proteins such as collagen (Cinque et al., 2010). In vitro *B. coagulans* RK-02 produces extracellular polysaccharides, high-molecular-weight polymers composed of four monosaccharides. These extracellular polysaccharides have demonstrated significant antioxidant and free radical scavenging properties (Kishk and Al-Sayed, 2007; Kodali and Sen, 2008). Interestingly, by providing a heterologous superoxide dismutase to *Lactobacilli* that do not ordinarily produce this antioxidant enzyme, researchers were able to demonstrate that these *Lactobacilli* could produce superoxide dismutase and offer protection against peroxide free radicals (Bruno-Barcena et al., 2004). These studies suggest probiotics in their natural state, or after genetic modification, may slow aging of the skin by helping to restore the balance between free radical scavengers and the free radical production.

Probiotics have been shown to influence and alter the immune system. The question then arises whether probiotics may exert their influence on cutaneous homeostasis and regulation of the immune system in the setting of UV light exposure. Ultraviolet radiation (UVR) has long been known as a major contributor to aging skin, a term now widely

Table 1
Probiotics and Ultraviolet Light.

Study	Probiotic strain	Model	Findings
Kim et al., 2014	*Lactobacillus plantarum* HY7714	Human dermal fibroblasts and hairless mice	*L. plantarum* inhibited UVB-induced matrix metalloproteinase 1 (MMP-1) expression to preserve procollagen expression in human fibroblasts. Oral administration of *L. plantarum* reduced the number and depth of wrinkles in hairless mice compared to control. Histologic samples from the hairless mice demonstrated that *L. plantarum* inhibited MMP-13, MMP-2, and MMP-9 expression in dermal tissue.
Weill et al., 2013	*Lactobacillus rhamnosus* GG	Female hairless mice	Hairless mice administered *L. rhamnosus* produced higher levels of interferon-gamma in lymph nodes and numbers of total, helper, and cytotoxic T-cells compared to controls. A delay in ultraviolet radiation–induced tumors was noted in mice receiving *L. rhamnosus*. An increase in IgA antibodies in the small intestine was noted.
Sugimoto et al., 2012	*Bifidobacterium breve* strain Yakult (BBY)	Hairless mice	BBY suspensions and fermented milk containing BBY administered for 9 and 14 days, respectively, suppressed the production of UV-induced elastase and IL-1beta and prevented a loss of elasticity associated with ultraviolet light exposure.
Peguet-Navarro et al., 2008	*Lactobacillus johnsonii* (La1)	Randomized, double-blind controlled trial of 54 healthy volunteers	Oral administration of La1 demonstrated restoration of CD1a Langerhans cell markers compared to placebo at day 4 post-ultraviolet radiation (UVR). No difference in immunostains was noted 1-day post UVR.
Gueniche et al., 2009	*Lactobacillus johnsonii* NCC 533 (La1)	Randomized, double-blind controlled trial of 54 healthy volunteers	Oral administration of La1 for 8 weeks did not prevent early UV-induced activation of Langerhans cells after exposure to 2 × 1.5 MED UV radiation. However, La1 increased recovery of allostimulatory function compared to placebo.

accepted as photoaging. Photoaging is manifested as wrinkling, increased skin fragility, and the presence of solar lentigos. Acute effects of UVR result from the direct effect of UVR on DNA and the modulation of the immune system through the release of inflammatory cytokines and, ultimately, immunosuppression (Kock et al., 1990; Schwarz and Schwarz, 2002).

Probiotics are emerging as a therapy to mitigate or prevent the effects of UV-induced skin damage. In hairless mice, the oral administration of *Bifidobacterium breve* prevented UV-induced transepidermal water loss compared to mice receiving placebo. Additionally, the administration of *B. breve* suppressed the UV-induced increase in hydrogen peroxide levels, oxidation of proteins, and xanthine oxidase activity in the skin (Ishii et al., 2014). These findings suggest that oral administration of probiotics may at least partially alleviate UV-induced barrier changes and oxidative stress in the skin.

Human studies have substantiated the role of oral probiotics in attenuating UV-induced photodamage. The probiotic *Lactobacillus johnsonii* and 7.2 mg of carotenoids were administered to healthy women for 10 weeks, then subjects were exposed to either simulated or natural sunlight. Compared to placebo, dietary supplementation prevented the UV-induced decrease in Langerhans cell density and accelerated the recovery of immune system homeostasis after exposure to UVR (Bouilly-Gauthier et al., 2010). Comparison of the minimal erythema dose (MED) showed that in those receiving supplementation, the MED rose by 20% (Bouilly-Gauthier et al., 2010). These results suggest that oral probiotic supplementation might play a role in mitigating the detrimental effects of UV exposure; however, without control groups to delineate the effects of probiotics versus carotenoids independently, it is difficult to attribute the findings to one compound in the dietary supplement. This represents a significant limitation to the study.

Refer to Table 1 for the complete list of probiotics and photoprotection.

Future Directions

While the evidence supporting the use of probiotics for acne and anti-aging is clearly mounting, several questions remain. First, which will ultimately benefit the skin to a greater extent: oral ingestion or topical application? Alternatively, will a combination approach of oral and topical prove to be the most effective? Will live probiotic strains offer an advantage to using probiotic derivatives, metabolites, or supernatants? Will live strains be capable of surviving on the skin, and if so, for how long? What is the minimal dose or concentration necessary of each probiotic required to see a benefit, and is a mixture of probiotics synergistic as compared to use of one particular strain?

As our understanding of the human microbiome grows, we deepen our appreciation of how individualized and complex each person's microbial environment is. We envision a need to ultimately custom tailor an oral and skin care regimen to each and every patient after sampling that patient's unique microbial "fingerprint." A one-size-fits-all approach is very unlikely to achieve optimal results when it comes to altering an individual's microbiome. Although we are only now skimming the surface of this exciting field, early studies suggest that oral and topical probiotics hold potential in the treatment of acne as well as in photoprotection and slowing the signs of aging skin.

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