Chapter 5

The Role of Probiotics in Acne and Rosacea

Caitlin F. Porubsky, Alexandria B. Glass,
Victoria Comeau, Christopher Buckley,
Marcus B. Goodman and Mary-Margaret Kober

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.79044

Abstract

Through basic science as well as 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, *Propionibacterium acnes* colonization and an inflammatory cascade. The antimicrobial properties of probiotics as well as the modification of the skin microbiome may decrease levels of *P. acnes* on the skin. Additionally, successful acne outcomes are influenced by compliance with topical regimens, which can commonly cause skin barrier disruption, leading to dryness and irritation. Consequently, calming inflammation as well as maintaining skin hydration and barrier repair is of primary importance when treating acne. In this chapter, we discuss how probiotics affect several factors in the pathophysiology of acne development and can improve the treatment outcomes.

Keywords: acne, probiotics, pathogenesis, inflammation, therapy

1. Introduction

Acne is an inflammatory disorder involving the pilosebaceous unit. A multifactorial cascade including excess sebum production, follicular hyperkeratinization, and bacterial overgrowth conspire to incite an inflammatory response. Acne therapies have focused on modulating this inflammatory response as well as targeting components of this cascade. Probiotics is an emerging area of research that continues to gain momentum for the treatment of acne. A probiotic is defined as a "live microorganism which, when administered in adequate amounts, confers a health benefit on the host" [1]. Both oral and topical preparations of probiotics have shown promise in the treatment of acne.

2. The gut-brain-skin axis

The field of dermatology continues to investigate the interconnected relationships between the skin and other systems of the body. The unifying theory of the gut-brain-skin axis outlines the relationship between the skin, gastrointestinal (GI) system, and mental health. Notably, the role of the gastrointestinal (GI) system is an area of particular interest as it relates to inflammatory skin conditions. The gut microbiome reacts to various stimuli resulting in systemic responses. By altering the GI microbiome, it is possible to decrease systemic inflammation, and these results can improve the severity of inflammatory skin diseases such as acne.

2.1. History of the gut-brain-skin axis

The gut-brain-skin axis originated in 1930 when John H. Stokes and Donald M. Pillsbury reported their clinical observations and colleagues' studies. They linked emotional states with gastrointestinal (GI) disorders through various mechanisms, including diet and neuronal responses. Stokes and Pillsbury reported cases of individuals with colitis who also suffered from urticaria and dermatographism. They purported that alterations of microflora increase gut permeability and lead to systemic inflammation. Higher levels of systemic inflammation result in altered cutaneous physiology. This association was further supported by the observation that hypochlorhydria is associated with multiple dermatologic conditions such as rosacea, eczema, pruritus, psoriasis, dermatitis herpetiformis, neurodermatitis, and acne [2].

Similarly, other case studies support the connection between gut physiology and cutaneous and psychological pathology. A psychopathic institute administered *Bacillus acidophilus* to their patients and recorded improvement in their mental distress, gastrointestinal disturbances, and skin eruptions [3]. A 1916 study showed patients with acne exhibiting alterations in their intestinal permeability [4]. In 1937, novel therapies for acne included acidophilus cultures, which acted as "intestinal flora changers" and improved pustular acne [5].

Stokes and Pillsbury's early concept of the gut being linked with the brain and skin started with anecdotal evidence and preliminary studies. They discovered that alteration of gastric acid levels and fluctuation of the gut microflora could have further effects beyond the GI system. From this evidence, they even proposed a treatment of Bacillus and cod liver oil, which is similar to present day probiotics and omega-3 fatty acids, to restore homeostasis in the gut. This early research has led to larger animal and human studies on the GI system, its microbiome, and its relation to the skin.

2.2. Theory of the gut-brain-skin axis

The negative impact of acne and other cutaneous diseases on the quality of life has been well-documented [6–10], and can cause long-lasting personality changes [10]. It has been reported that 8.8% of patients with acne exhibit depression [11]. Apart from psychological distress, acne patients often suffer from gastrointestinal disturbances at higher rates compared to the normal population [12]. The gastrointestinal tract houses the largest population of commensal bacteria, and in this reservoir of bacteria lies the central theme to the gut-brain-skin axis.

Hypochlorhydria and small intestinal bacterial overgrowth (SIBO) are two conditions that demonstrate an association with cutaneous pathology and mental health. Alterations in gastric acid secretion, such as hypochlorhydria, increase the risk for SIBO. While increased rates of SIBO have long been associated with psychological disorders of anxiety, depression, and fibromyalgia, more recent evidence has demonstrated increased rates of SIBO in rosacea patients, as well, with one study reporting an SIBO rate of 50% in rosacea patients. Those patients were then treated for SIBO with the antimicrobial rifaximin, and most had significant improvement or clearance of their rosacea [13, 14]. Additionally, an Australian study used the probiotic *Lactobacillus casei* to successfully reduce SIBO [15]. The authors not only noted improvement in the GI symptoms but also in cutaneous and psychological symptoms [13, 16, 17].

Intestinal permeability has also been linked to cutaneous pathology. As far back at 1916, acne patients have shown reactivity to stool-isolated bacteria using a serum complement test [4]. Later, Juhlin and Michaelsson tested *Escherichia coli* polysaccharide endotoxin in the blood samples of acne patients. The patients with severe acne had reactivity while the control had none [18]. A second study of human subjects with IBS identified increased levels of *E. coli* lipopolysaccharide (LPS)-induced cytokines in patients with IBS compared to controls [19]. Increased intestinal permeability and heightened immune responses has also been associated with chronic constipation [20]. Several studies have noted a higher prevalence of constipation in those with acne vulgaris [12, 21]. These correlations suggest increased intestinal permeability and consequently higher levels of circulating endotoxin may contribute to acne formation [21].

2.3. Impact of the gut microbiome

The gut microbiome is dynamic; it changes with the stress on its environment and reacts to feedback from other systems. As stated previously, changes in the microbiome may influence levels of systemic inflammation. Acne is an inflammatory disorder that has demonstrated its response to systemic inflammation and oxidative stress. A Russian study found that not only is the intestinal microflora of acne patients altered, but therapy for the GI disruption reduced the duration of acne treatment [22].

The gut's commensal bacteria can induce immune responses that ultimately reach T cells in the skin. Probiotics interact with the gastrointestinal mucosal immune system, altering levels of inflammatory cytokines in the blood [23]. For instance, the levels of gamma-aminobutyric acid (GABA) are modified by intestinal bacteria [24, 25]. Microbial-fermented food enriched with GABA has been shown to improve atopic dermatitis in mice through a Th-1 mediated-immune response [26].

Major histocompatibility cell (MHC) class II complexes are found on antigen presenting cells, such as dendritic cells and macrophages, and interact with immune-regulating T cells. Gastrointestinal bacteria, including strains of probiotics, have been shown to bind to the MHC II complex and modify their expressions [27]. A study that administered *Lactobacillus paracasei* NCC2461 (ST11) to mice found the probiotic to induce T regulatory cells and inhibited CD4+ T-cell proliferation, while increasing the secretions of anti-inflammatory cytokines, specifically IL-2, IL-10, and TGF-β [28]. Other strains of lactic acid bacteria continue to show that they induce T cell communication, decrease inflammatory response, and regulate antigen

presenting cells [29, 30]. The anti-inflammatory cytokines affect the differentiation of keratinocytes, while TGF-β has a considerable role in enhancement of the skin barrier [28, 31]. These findings were supported by a second study. Mice that were treated with *Lactobacillus casei* recruited T regulatory cells to inflamed skin and released higher levels of the anti-inflammatory cytokine IL-10 [32].

The composition of the gut microbiome can inhibit or promote the release of substance P in both the skin and intestinal tract [33, 34]. When a specific strain of *Lactobacillus paracasei* ST11 was orally administered, secretions of substance P decreased. Lower systemic levels of substance P enhanced skin barrier function and decreased local skin inflammation [35]. Inhibition of substance P directly affects acne pathogenesis, as substance P increases sebum production [36].

The interconnected relationship described by the gut-brain-skin axis illustrates the significant role of the gut microbiome, and its alteration, for instance by probiotics, may play in the development of acne. Modification of local and systemic inflammatory profiles by GI flora presents a target for potential therapy.

3. Pathophysiology of probiotics and acne

It is quite evident that the gut-brain-skin axis plays a theoretically significant role in the formation of acne lesions. In the following sections, we will discuss the pathophysiology behind probiotics and their ensuing potential impact in the arena of acne treatment. As previously discussed, the early theories introduced by Stokes and Pillsbury conceptualized the functional interdependence of the gut-brain-skin axis. It was further proposed that alterations in the neural axis result in gastrointestinal dysfunction, thereby disrupting the local normal flora, and resulting in widespread inflammatory response [37]. As we will see, the concept of systemic inflammatory response as well as oxidative stress is at the core of the rationale behind probiotics and their role in acne treatment.

3.1. Inflammation

The initial research during the era of Stokes and Pillsbury began with the discovery of concomitant hypochlorhydria in a significant portion of acne patients [37]. Additionally, the expanded SIBO theory suggested that an increased pH in the stomach resulted in a migration of bacteria proximally, increased gut permeability, and significant resultant inflammation [37]. This inflammation is the key starting point for the inflammatory cascade ultimately resulting in acne lesions.

The inflammatory state associated with acne has received much attention from dermatologic research studies and literature in recent years. While it was previously thought that events such as follicular keratinization and bacterial colonization preceded inflammation [38], it is now known that inflammation is actually the herald event [39].

The concept of acne as a result of inflammation is based upon the understanding that the immune system is designed to defend the human body against actual threats. However, in the acne patient, we are recognizing a chronic, low level of inflammation in the absence of threat [40]. Ideally, probiotics would eliminate this chronic inflammatory state, and in turn, halt the development of acne lesions.

Subclinical microcomedones are established as the earliest lesions of acne, and even at this early stage, inflammatory cells have been observed to be already present in these primary lesions. A modern research study was performed comparing immunohistochemistry and immunofluorescence of early, inflamed papules less than 6 h old in acne patients to both uninvolved skin of acne patients and a nonacne control group. In papules less than 6 h old, a remarkable increase in K16 and K67 activity is observed [39]. Uninvolved skin in acne patients exhibited increased expression of CD4+ T cells, and an even more significant upregulation of CD4+ T cells was observed in papules less than 6 h old [39]. The presence of macrophages was found to be higher in both uninvolved skin of acne patients as well as papules less than 6 h old of acne patients compared to nonacne controls [39].

One of the strongest pieces of evidence supporting the theory of baseline inflammation in acne patients is the increased presence of interleukin-1-alpha (IL-1), a well-known pro-inflammatory cytokine. In the above study, an increased level of IL-1-alpha was observed in both early lesional skin and uninvolved skin of acne patients in comparison with the control group [39]. IL-1 has been proposed as the signal that triggers the entire inflammatory cascade in the setting of a wound. In response to endothelial injury, IL-1 is the first cytokine to be produced, attracting lymphocytes to the area as well as activating endothelial cells to produce a hyperproliferative state [41]. It is further proposed that increased expression of K6 and K16, TNF-alpha, and endothelial growth factors then occur as a result [41]. Considering the above information, it may be deduced that IL-1 is a powerful inflammatory cascade that trigger in the setting of acne as well.

Collectively, several conclusions can be drawn from this information. These findings support the theory of acne as an inflammatory disease. Significant evidence reinforces the theory that inflammation precedes the overproduction of sebum, hyperproliferative state, and other physical manifestations of acneiform lesions. Taking into account the subtype of T cell activation observed, it is prudent to believe the inflammation is specific and antigenic in nature rather than an innate response [39].

Therefore, the anti-inflammatory actions of probiotics may be beneficial in the treatment of acne. Although the exact mechanism remains unclear, literature exists that suggests that *Lactobacilli* have been shown to modulate Th1/Th2 activity [42]. A separate study examined the Th1/Th2 inflammatory response of rats, when faced with an antigen challenge, in the setting of pretreatment with a combination of *Lactobacilli* and *Bifidobacterium* strains. It was found that the combination probiotic treatment did in fact alter both the Th1 and Th2 response [43]. As previously discussed in this section, a dysregulation of the T-cell response has been demonstrated in the skin of acne patients and it may be deduced that normalizing this response may be a critical step toward decreasing the baseline inflammatory state in this population.

Further solidifying this concept, in a study aimed at examining the immunomodulatory effects of probiotics in subjects with food allergies, it was determined that probiotics do in fact increase production of anti-inflammatory cytokines such as IL-10, TNF-α, and INF-γ [44]. This discovery may be re-enforced by looking back to the research involving rats and pretreatment with combined *Lactobacilli* and *Bifidobacterium*. In this study, significant reductions were also observed in the production of inflammatory cytokines, most notably IL-1α and IL-1β [43]. It should be noted that TNF-α production was decreased as well [43]. As previously discussed, the IL-1 cytokines play a key role upstream in the inflammatory cascade and altering the production of this cytokine via probiotics may prove advantageous in treating the acne patient.

Given the aforementioned research, it is once again reasonable to conclude that the addition of probiotics in the acne-prone patient would positively affect the causatory state of inflammation. It is clear that further research is needed to solidify the definitive effects of probiotics on the low-level inflammatory state and subsequent inflammatory cascade.

3.2. Oxidative stress

An alternative theory proposed by Allan L. Lorincz suggested that oxidative breakdown of lipids and squalene was a cause of acne rather than a consequence. The theory then goes on to suggest that this oxidative process is a trigger for the inflammatory condition seen in acne patients [38]. Subsequent studies reinforced this theory. In 1975, A Tappel also supported the theory of inflammation stemming from the damaging effects of lipid peroxidation [45].

This is both important and relevant in the setting of acne as squalene, a key component in the formation of the comedone, is sensitive to oxidative stress. In an independent study, squalene, when exposed to UV radiation (a source leading to oxidative stress), became increasingly comedogenic [46].

It has thus been proposed that alongside inflammation, oxidative stress may play a significant role in the development of acne lesions. Reactive oxygen species (ROS) are produced by environmental factors as well as cellular metabolism byproducts. Higher levels of ROS encourage an environment that is more hospitable to bacteria such as *P. acnes* [38]. In a study examining the activity of antioxidants defense enzymes in leukocytes, acne patients were found to have low levels of both superoxide dismutase and glutathione peroxidase [47].

Faulty antioxidant response seen in acne patients provides yet another role for probiotics in the treatment of acne. Probiotics have been proven to assist in antioxidant activity. In a study performed on the probiotic, *Bacillus coagulans RK-02*, evidence came to light that the bacteria produced a potent extracellular polysaccharide with significant antioxidant activity as well as superoxide radical scavenging activity and hydroxyl radical scavenging activity, even when measured against classic antioxidants including vitamin C [48].

In a separate study, researchers combined various strains of *Lactobacillus* with a gene encoding for superoxide dismutase. The *Lactobacilli* were found not only to successfully express the gene, but were also found to provide measurable defense against hydrogen peroxide species [49].

Probiotics provide a mechanism to counter free radical damage and increase antioxidant activity, resulting in an environment that is less attractive for *P. acnes* colonization.

http://dx.doi.org/10.5772/intechopen.79044

4. Probiotics used for the treatment of acne

4.1. Oral probiotics

The idea of treating acne with probiotics dates back to the 1930s. During that time, *Lactobacillus acidophilus (*a common probiotic found in foods such as yogurt) was a popular diet supplement for the treatment of acne among the public [5]. Although this trend was widely accepted, formal research had not been carried out proving its effectiveness. It was not until 1961 that the first official clinical trial regarding probiotics and its relationship to acne was published. The trial was performed by a physician from the Union Memorial Hospital in Baltimore, Maryland named Robert H. Siver. Dr. Siver followed 300 patients who were taking a commercially available oral probiotic tablet called "Latinex" (combination of *L. acidophilus* and *L. bulgaricus*). Subjects ingested this supplement for eight consecutive days followed by a two-week break and then repeated the process. Over time, he noticed that 80% of patients with acne experienced clearing of their skin, especially in those with inflammatory acne lesions. Despite this study lacking a placebo group to compare results and having an unconventional probiotic dosing regimen, the findings did suggest a promising linkage between the intestinal flora and acne [50].

After Dr. Siver's research was published, other researchers became interested in a correlation between oral probiotics and acne. Two studies, both published in a non-English language journal, continued to demonstrate a connection. In 1987, an Italian article was published by Marchetti et al., 20 of the 40 patients with acne were given 250 mg of freeze-dried *L. acidophilus* and *Bifidobacterium bifidum* in addition to standard acne treatment. Subjects in the study group exhibited better compliance with their antibiotic regimen in addition to seeing improved clinical results in their acne [51]. In 2001, a similar investigation was performed in Russia by Vokova et al. using 114 subjects with acne. He found that 61% of the subjects had impaired bacterial microflora, and after probiotic supplementation in addition to combined acne therapy, their duration of treatment was greatly reduced to that of subjects without dysbacteriosis [22].

More recent studies have continued to confirm these results. In 2010, Kim et al. randomized 36 subjects with acne to receive either lactoferrin (a milk protein with anti-inflammatory, bactericidal, and fungicidal properties) added to fermented milk (experimental group) or fermented milk alone (control group). After 12 weeks, the experimental group experienced significant decreases in total lesion count (23.1%), inflammatory lesion count (38.6%), acne grade (20.3%), and sebum content (31.1%) compared to the control group. Although this study had the additional element of lactoferrin, both groups responded to the fermented milk and saw a reduction in total skin surface lipids. Furthermore, the addition of lactoferrin decreased a specific group of lipids called triacylglycerols, directly related to the decreased sebum content, acne lesion counts, and acne grade [52].

An interesting open-label study was published in 2013 by Jung et al. concerning probiotics versus antibiotics in 45 women between the ages of 18 to 35 years old. The females were randomized into one of three groups: probiotics only (a mixture of *L. acidophilus*, *L. delbrueckii*, and *B. bifidum*), oral minocycline only, or both probiotics and minocycline. After the first 4 weeks,

all patients observed significant improvement in their total lesion count; however, after 8 and 12 weeks, the group using both probiotics and minocycline experienced a significant decrease in their total lesion count compared to the other two groups. In addition, two subjects in the minocycline-only group developed vaginal candidiasis, an adverse event not observed in the group taking both. This study demonstrated that not only can probiotics augment antibiotic therapy, but they may also alleviate particular side effects experienced with chronic antibiotic use by suppressing the growth of unwanted organisms [53].

A 2016 clinical trial identified 57 patients with erythematous papulopustular facial rashes that were diagnosed as either acne, seborrheic dermatitis, or rosacea. The participants were started on a vegetarian diet and appropriate standard therapy for their disorder, including antibiotics, retinoids, and/or steroids. 37 patients of these patients were randomized to receive a daily oral probiotic supplement with *E. coli* Nissle. The group receiving probiotics showed an 89% improvement in their facial dermatoses compared to 56% improvement achieved with diet and standard therapy in the control group. In addition, white blood cell count via blood draw and immunoassays of IL-8, INF-α, and IgA levels were measured throughout the trial. After treatment, lymphocytosis disappeared by 78% in the probiotic group compared to 42% in the control group. Also, levels of INF-α, IL-8, and Ig-A normalized only in the probiotic group compared to no change seen in the control group [54].

4.2. Topical probiotics

With the growing body of evidence for the role of systemic probiotics in the treatment of acne, the efficacy of topical probiotics is also generating interest and investigation. Similar to oral probiotics, the use of topical probiotics dates back to the early 1900s [55]; however, proper clinical trials were not conducted until much later. In 1999, Di Marzio et al. completed the first clinical trial evaluating topical probiotics and their effects on ceramide production in the skin. Ceramides are waxy lipid molecules that comprise 50% of the lipid matrix within the intercellular spaces of the stratum corneum. Along with cholesterol and long-chain fatty acids, they are essential to maintaining the water permeability of the skin barrier. Ceramides have been found to be low in patients with aged skin, xerosis, atopic dermatitis, psoriasis, and even acne; therefore, increasing their production may significantly impact these disorders [56]. Initially, Di Marzio et al. conducted an *in vitro* study during which he added the bacterium *Streptococcus thermophilus* to human keratinocyte cell cultures and found an increase in the production of ceramides. He believed this was due to *S. thermophilus'* possession of sphingomyelinase, an enzyme that hydrolyzes sphingomyelin into ceramides. Many bacteria have been reported to produce extracellular sphingomyelinase including the genera *Bacillus, Listeria, Staphylococcus, Mycobacterium, Chlamydia, Pseudomonas, Leptospira,* and some species of *Helicobacter.* Although this enzyme primarily functions as a virulence factor for the bacteria, its ability to increase ceramide production may provide a benefit in treating skin diseases [57].

In the next phase of the study, Di Marzio tested this theory *in vivo* on 17 healthy subjects with normal skin. The subjects were instructed to apply 0.5 g of a topical probiotic formulation consisting of *Streptococcus thermophilus* twice a day to the volar surface of one of their forearms. They applied the vehicle alone to the contralateral forearm for comparison. An

additional four subjects were treated with sphingomyelinase purified from *Bacillus cereus* to ensure that the results produced were specific to the sphingomyelinase and not another component within the bacterium. After seven consecutive days of application, the probiotic formulation containing *S. thermophilus* caused an increase in the production of ceramides in the stratum corneum, which was comparable to the results seen using the sphingomyelinase extracted from *B. cereus.* These results demonstrated that the sphingomyelinase produced by *S. thermophilus* may improve skin barrier function [58].

Ceramides not only have a role in water permeability, but they also play a part in the antimicrobial and anti-inflammatory properties of the skin. The exact antimicrobial mechanism of ceramides has not been confirmed; however, there are many theories: reduction of bacteria adherence to epithelial cells, inhibition of bacterial protein kinases, and/or damage to the cell wall of the bacteria [59, 60]. Aware of their antimicrobial properties, Pavicic et al. performed a study in 2007 to evaluate the role of ceramides in patients with acne. The study consisted of both an *in vitro* and *in vivo* phase. *In vitro*, he found that phytosphingosine (PS), one of the four types of sphingoid bases that make up ceramides, inhibited growth of *Propionibacterium acnes*, an important contributor to acne formation. From these findings, he performed a two-part *in vivo* pilot study testing a 0.2% PS formulation on subjects with acne. In the first part, 30 subjects with acne applied a topical medication containing PS with benzoyl peroxide (PS-BPO) to half of their face versus benzoyl peroxide (BPO) alone to the contralateral side of their face two times per day. After 2 months, comedones were reduced by 72% and inflammatory papules and pustules by 88% in the PS-BPO group versus 22 and 32%, respectively, in BPO only group. In another arm of the trial, 10 subjects applied PS alone to half of their face and a placebo cream alone to the other side of their face twice a day. After 2 months, the placebo increased comedones by 43% compared to only 6% in the PS group. More significant results were seen in inflammatory acne numbers with an 89% reduction observed in the PS group compared to no change in the placebo group [61].

Topical probiotics may also help with stress-induced acne. It is known that acne can be exacerbated due to stress, primarily due to a release of a chemical called substance P. Sebocytes stimulated by substance P show higher levels of proinflammatory cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6) tumor necrosis factor-alpha (TNF-alpha), and peroxisome proliferators activated receptors-gamma (PRAR-gamma), compared to a control [36]. Studies by Gueniche et al. in 2010, using both *in vitro* and clinical trials, have shown that two bacteria, *Lactobacillus paracasei* and *Bifidobacterium longum,* may improve inflammatory skin conditions by inhibiting substance P [33, 62]. As an adjunctive to current acne therapy, these two bacteria in topical formulations may provide relief for individuals suffering from inflammatory and/or stress-induced acne not responding to conventional treatment methods.

4.3. Future directions

Studies of topical and oral probiotics have demonstrated the beneficial anti-inflammatory and antibacterial properties of probiotics in the treatment of acne. Newer research is focusing on yet another treatment mechanism—the production of antimicrobial peptides (AMPs). AMPs are molecules produced by the innate immune system of a wide range of organisms, including

humans, plants, and insects, that act as a first line of defense against natural antimicrobial agents [63]. These peptides are extremely small, are anti-inflammatory, and have been shown to exhibit properties against bacteria, fungi, viruses, and tumors. They have even shown the ability to overcome bacterial resistance because it is difficult to develop complete resistance to AMPs, making them potential candidates for future therapeutic medications [64, 65]. Besides being produced by many eukaryotic organisms, numerous bacteria have been found to produce AMPs. These bacterial AMPs, called bacteriocidins, have been isolated from about 50 various bacterial species, especially lactic acid-producing bacteria [66–68]. Some researchers refer to bacteriocidins as only those produced by Gram-positive bacteria, which are further classified into two subgroups: lantibiotics (class I) and nonlantibiotics (class II). Many of the lactic acid bacteria produce AMPs in the nonlantibiotics group. AMPs produced by Gram-negative bacteria are sometimes referred to as microcins and classified further into two groups: class I and class II [68]. For simplicity, the general term "bacteriocidins" will be used here.

Compared to AMPs produced by eukaryotic organisms, bacteriocidins have a narrower spectrum of activity, only capable of targeting a few species but have the advantage of being more potent. Bacteriocidins are active at pico- to nanomolar concentrations compared to micromolar concentrations required when produced by eukaryotes. Bacteriocidins are bactericidal, causing pore formation in cell membranes [69].

There have been multiple studies performed observing the effects of AMPs on many disorders, including acne vulgaris. In 2006, Bowe et al. discovered that a normal oral flora bacterium, *Streptococcus salivarius,* was capable of inhibiting the growth of *P. acnes* by producing a bacteriocidin called bacteriocin-like inhibitory substances (BLIS). While BLIS is responsible for inhibiting group A streptococcus (GAS), a pathogenic bacterium responsible for causing many upper respiratory infections, its activity against *P. acnes* had not previously been evaluated. In this *in vitro* study, oral swabs were taken from 106 subjects and cultured for the growth of *S. salivarius.* Out of 106, 33 specimens yielded growth of *S. salivarius* and were available for assays of *P. acnes* and GAS. Results found 11 (33.3%) inhibited the growth of *P. acnes* and 13 (39.4%) inhibited the growth of GAS. Although these results focused only on *in vitro* activity, this study demonstrated the potential use of BLIS or BLIS-producing bacteria in future as acne topical treatment formulations [70].

A similar study in 2009 by Kang et al. demonstrated the effects of the bacterium, *Enterococcus faecalis* SL-5 (a very common inhabitant of the human gastrointestinal tract) and its effect on *P. acnes*. He conducted *in vitro* and *in vivo* studies. In the *in vitro* aspect of the study, *E. faecalis* proved to be bacteriocidal to *P. acnes* due to a bacteriocidin named ESL5. In the clinical trial, 70 subjects with mild-to-moderate acne were enrolled in an 8-week double-blind, randomized, placebo-controlled phase III study. Subjects were randomized into the probiotic or placebo group. Those in the experimental group applied a lotion containing ESL5 to the areas of the face involved with acne twice per day, and the control group applied a placebo lotion twice daily. After 8 weeks of application, a decrease in the number of comedones was seen in the probiotic group compared to the placebo group; however, these results were not statistically significant. In the inflammatory lesion counts, a statistically significant reduction of greater than 50% was observed in the *E. faecalis* group compared to placebo [71].

While these findings suggest that probiotics and the AMPs produced may benefit patients with acne, larger randomized controlled clinical trials are needed. Further studies will elucidate the most efficacious strains, preparations, and treatment regimens for the treatment of acne and potential uses in other conditions.

5. Conclusion

In summary, oral and topical probiotics are emerging as an exciting treatment option or adjuvant treatment for acne. Although additional research needs to be performed, the clinical trials conducted so far have continued to provide evidence that probiotics can improve acne, along with multiple other inflammatory disorders, with very limited adverse effects. In the upcoming years, probiotic formulations have the potential to be a fundamental component of acne treatment and may augment the efficacy of current treatments today.

Conflict of interest

No conflict of interest to be reported by the authors.

Author details

Caitlin F. Porubsky[2], Alexandria B. Glass[2], Victoria Comeau[2], Christopher Buckley[1,2], Marcus B. Goodman[2] and Mary-Margaret Kober[1]*

*Address all correspondence to: mmkober@gmail.com

1 Riverchase Dermatology, Naples, FL, USA

2 Department of Dermatology, Philadelphia College of Osteopathic Medicine, Roswell, GA, USA

References

[1] Morelli L, Capurso L. FAO/WHO guidelines on probiotics: 10 years later. Journal of Clinical Gastroenterology. 2012;**46**(Suppl):S1-S2

[2] Stokes JH, Pillsbury DM. The effect on the skin of emotional and nervous states: I II. Theoretical and practical consideration of a gastro-intestinal mechanism. Archives of Dermatology and Syphilology. 1930;**22**:962-993

[3] Saunders A. The bacillus acidophilus treatment. Institution Q. 1924;**15**:85-88

[4] Strickler A, Kolmer JA, Schamberg JF. Complement fixation in acne vulgaris. Journal of Cutaneous Diseases. 1916;**34**:166-178

[5] Ereaux LP. Facts, fads and fancies in the treatment of acne vulgaris. Canadian Medical Association Journal. 1938;**39**(3):257-261

[6] Mallon E, Newton JN, Klassen A, Stewart-Brown SL, Ryan TJ, Finlay AY. The quality of life in acne: A comparison with general medical conditions using generic questionnaires. The British Journal of Dermatology. 1999;**140**(4):672-676

[7] Thomas DR. Psychosocial effects of acne. Journal of Cutaneous Medicine and Surgery. 2004;**8**(Suppl 4):3-5

[8] Loney T, Standage M, Lewis S. Not just 'skin deep': Psychosocial effects of dermatological-related social anxiety in a sample of acne patients. Journal of Health Psychology. 2008;**13**(1):47-54

[9] Rapp DA, Brenes GA, Feldman SR, Fleischer AB Jr, Graham GF, Dailey M, et al. Anger and acne: Implications for quality of life, patient satisfaction and clinical care. The British Journal of Dermatology. 2004;**151**(1):183-189

[10] Magin P, Adams J, Heading G, Pond D, Smith W. Psychological sequelae of acne vulgaris: Results of a qualitative study. Canadian Family Physician. 2006;**52**:978-979

[11] Uhlenhake E, Yentzer BA, Feldman SR. Acne vulgaris and depression: A retrospective examination. Journal of Cosmetic Dermatology. 2010;**9**(1):59-63

[12] Zhang H, Liao W, Chao W, Chen Q, Zeng H, Wu C, et al. Risk factors for sebaceous gland diseases and their relationship to gastrointestinal dysfunction in Han adolescents. The Journal of Dermatology. 2008;**35**(9):555-561

[13] Parodi A, Paolino S, Greco A, Drago F, Mansi C, Rebora A, et al. Small intestinal bacterial overgrowth in rosacea: Clinical effectiveness of its eradication. Clinical Gastroenterology and Hepatology. 2008;**6**(7):759-764

[14] Ghoshal UC, Ghoshal U. Small intestinal bacterial overgrowth and other intestinal disorders. Gastroenterology Clinics of North America. 2017;**46**(1):103-120

[15] Barrett JS, Canale KE, Gearry RB, Irving PM, Gibson PR. Probiotic effects on intestinal fermentation patterns in patients with irritable bowel syndrome. World Journal of Gastroenterology. 2008;**14**(32):5020-5024

[16] Addolorato G, Mirijello A, D'Angelo C, Leggio L, Ferrulli A, Abenavoli L, et al. State and trait anxiety and depression in patients affected by gastrointestinal diseases: Psychometric evaluation of 1641 patients referred to an internal medicine outpatient setting. International Journal of Clinical Practice. 2008;**62**(7):1063-1069

[17] Pimentel M, Chow EJ, Lin HC. Eradication of small intestinal bacterial overgrowth reduces symptoms of irritable bowel syndrome. The American Journal of Gastroenterology. 2000;**95**(12):3503-3506

[18] Juhlin L, Michaelsson G. Fibrin microclot formation in patients with acne. Acta Dermato-Venereologica. 1983;**63**(6):538-540

[19] Liebregts T, Adam B, Bredack C, Roth A, Heinzel S, Lester S, et al. Immune activation in patients with irritable bowel syndrome. Gastroenterology. 2007;**132**(3):913-920

[20] Khalif IL, Quigley EM, Konovitch EA, Maximova ID. Alterations in the colonic flora and intestinal permeability and evidence of immune activation in chronic constipation. Digestive and Liver Disease. 2005;**37**(11):838-849

[21] Bowe W, Patel NB, Logan AC. Acne vulgaris, probiotics and the gut-brain-skin axis: From anecdote to translational medicine. Beneficial Microbes. 2014;**5**(2):185-199

[22] Volkova LA, Khalif IL, Kabanova IN. Impact of the impaired intestinal microflora on the course of acne vulgaris. Klinicheskaia Meditsina (Mosk). 2001;**79**(6):39-41

[23] Fuchs-Tarlovsky V, Marquez-Barba MF, Sriram K. Probiotics in dermatologic practice. Nutrition. 2016;**32**(3):289-295

[24] Schafer DF, Fowler JM, Jones EA. Colonic bacteria: A source of gamma-aminobutyric acid in blood. Proceedings of the Society for Experimental Biology and Medicine. 1981;**167**(3):301-303

[25] Bravo JA, Forsythe P, Chew MV, Escaravage E, Savignac HM, Dinan TG, et al. Ingestion of lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. Proceedings of the National Academy of Sciences of the United States of America. 2011;**108**(38):16050-16055

[26] Hokazono H, Omori T, Ono K. Effects of single and combined administration of fermented barley extract and gamma-aminobutyric acid on the development of atopic dermatitis in NC/Nga mice. Bioscience, Biotechnology, and Biochemistry. 2010;**74**(1): 135-139

[27] Arck P, Handjiski B, Hagen E, Pincus M, Bruenahl C, Bienenstock J, et al. Is there a 'gut-brain-skin axis'? Experimental Dermatology. 2010;**19**(5):401-405

[28] Benyacoub J, Bosco N, Blanchard C, Demont A, Philippe D, Castiel-Higounenc I, et al. Immune modulation property of lactobacillus paracasei NCC2461 (ST11) strain and impact on skin defences. Beneficial Microbes. 2014;**5**(2):129-136

[29] Livingston M, Loach D, Wilson M, Tannock GW, Baird M. Gut commensal lactobacillus reuteri 100-23 stimulates an immunoregulatory response. Immunology and Cell Biology. 2010;**88**(1):99-102

[30] Benson KF, Redman KA, Carter SG, Keller D, Farmer S, Endres JR, et al. Probiotic metabolites from Bacillus coagulans GanedenBC30 support maturation of antigen-presenting cells in vitro. World Journal of Gastroenterology. 2012;**18**(16):1875-1883

[31] Hashimoto K. Regulation of keratinocyte function by growth factors. Journal of Dermatological Science. 2000;**24**(Suppl 1):S46-S50

[32] Hacini-Rachinel F, Gheit H, Le Luduec JB, Dif F, Nancey S, Kaiserlian D. Oral probiotic control skin inflammation by acting on both effector and regulatory T cells. PLoS One. 2009;**4**(3):e4903

[33] Gueniche A, Benyacoub J, Philippe D, Bastien P, Kusy N, Breton L, et al. *Lactobacillus paracasei* CNCM I-2116 (ST11) inhibits substance P-induced skin inflammation and accelerates skin barrier function recovery in vitro. European Journal of Dermatology. 2010;**20**(6):731-737

[34] Verdu EF, Bercik P, Verma-Gandhu M, Huang XX, Blennerhassett P, Jackson W, et al. Specific probiotic therapy attenuates antibiotic induced visceral hypersensitivity in mice. Gut. 2006;**55**(2):182-190

[35] Philippe D, Blum S, Benyacoub J. Oral lactobacillus paracasei improves skin barrier function recovery and reduces local skin inflammation. European Journal of Dermatology (France). 2011;**21**:279-280

[36] Lee WJ, Jung HD, Lee HJ, Kim BS, Lee SJ, Kim DW. Influence of substance-P on cultured sebocytes. Archives of Dermatological Research. 2008;**300**(6):311-316

[37] Bowe WP, Logan AC. Acne vulgaris, probiotics and the gut-brain-skin axis—Back to the future? Gut Pathogens. 2011;**3**(1):1

[38] Bowe WP, Logan AC. Clinical implications of lipid peroxidation in acne vulgaris: Old wine in new bottles. Lipids in Health and Disease. 2010;**9**:141

[39] Jeremy AH, Holland DB, Roberts SG, Thomson KF, Cunliffe WJ. Inflammatory events are involved in acne lesion initiation. The Journal of Investigative Dermatology. 2003;**121**(1):20-27

[40] Kober MM, Bowe WP. The effect of probiotics on immune regulation, acne, and photoaging. International Journal of Women's Dermatology. 2015;**1**(2):85-89

[41] Freedberg I, Tomic-Canic M, Komine M, Blumenberg M. Keratins and the keratinocyte activation cycle. The Journal of Investigative Dermatology. 2001;**116**(5)

[42] Ghadimi D, Folster-Holst R, de Vrese M, Winkler P, Heller KJ, Schrezenmeir J. Effects of probiotic bacteria and their genomic DNA on TH1/TH2-cytokine production by peripheral blood mononuclear cells (PBMCs) of healthy and allergic subjects. Immunobiology. 2008;**213**(8):677-692

[43] Cazzola M, Tompkins TA, Matera MG. Immunomodulatory impact of a synbiotic in T(h)1 and T(h)2 models of infection. Therapeutic Advances in Respiratory Disease. 2010;**4**(5):259-270

[44] Flinterman A, Knol E, van Leperen-van Dijk A, TImmerman H, Knulst A, Bruijnzeel-Koomen C, et al. Probiotics have a different immunomodulatory potential in vitro versus ex vivo upon oral administration in children with food allergy. International Archives of Allergy and Immunology. 2007;**143**(3)

[45] Tappel A. Lipid peroxidation and fluorescent molecular damage to membranes. Pathobiology of Cell Membranes, edited by B.F. Trump and A.U Arsila. New York Academic; 1975. pp.145-170

[46] Mills OH, Porte M, Kligman AM. Enhancement of comedogenic substances by ultraviolet radiation. The British Journal of Dermatology. 1978;**98**(2):145-150

[47] Basak PY, Gultekin F, Kilinc I. The role of the antioxidative defense system in papulopustular acne. The Journal of Dermatology. 2001;**28**(3):123-127

[48] Kodali VP, Sen R. Antioxidant and free radical scavenging activities of an exopolysaccharide from a probiotic bacterium. Biotechnology Journal. 2008;**3**(2):245-251

[49] Bruno-Barcena JM, Andrus JM, Libby SL, Klaenhammer TR, Hassan HM. Expression of a heterologous manganese superoxide dismutase gene in intestinal lactobacilli provides protection against hydrogen peroxide toxicity. Applied and Environmental Microbiology. 2004;**70**(8):4702-4710

[50] Siver R. Lactobacillus for the control of acne. The Journal of the Medical Society of New Jersey. 1961;**59**:52-53

[51] Marchetti F, Capizzi R, Tulli A. Efficacy of regulators of the intestinal bacterial flora in the therapy of acne vulgaris. La Clinica Terapeutica. 1987;**122**(5):339-343

[52] Kim J, Ko Y, Park YK, Kim NI, Ha WK, Cho Y. Dietary effect of lactoferrin-enriched fermented milk on skin surface lipid and clinical improvement of acne vulgaris. Nutrition. 2010;**26**(9):902-909

[53] Jung GW, Tse JE, Guiha I, Rao J. Prospective, randomized, open-label trial comparing the safety, efficacy, and tolerability of an acne treatment regimen with and without a probiotic supplement and minocycline in subjects with mild to moderate acne. Journal of Cutaneous Medicine and Surgery. 2013;**17**(2):114-122

[54] Manzhalii E, Hornuss D, Stremmel W. Intestinal-borne dermatoses significantly improved by oral application of Escherichia coli Nissle 1917. World Journal of Gastroenterology. 2016;**22**(23):5415-5421

[55] Peyri J. Topical bacteriotherapy of the skin. The Journal of Cutaneous Diseases. 1912;**30**: 688-689

[56] Breiden B, Sandhoff K. The role of sphingolipid metabolism in cutaneous permeability barrier formation. Biochimica et Biophysica Acta. 2014;**1841**(3):441-452

[57] Flores-Díaz M, Monturiol-Gross L, Naylor C, Alape-Girón A, Flieger A. Bacterial Sphingomyelinases and phospholipases as virulence factors. Microbiology and Molecular Biology Reviews. 2016;**80**(3):597-628

[58] Di Marzio L, Cinque B, De Simone C, Cifone MG. Effect of the lactic acid bacterium Streptococcus thermophilus on ceramide levels in human keratinocytes in vitro and stratum corneum in vivo. The Journal of Investigative Dermatology. 1999;**113**(1):98-106

[59] Bibel DJ, Aly R, Shinefield HR. Antimicrobial activity of sphingosines. The Journal of Investigative Dermatology. 1992;**98**(3):269-273

[60] Bibel DJ, Aly R, Shah S, Shinefield HR. Sphingosines: Antimicrobial barriers of the skin. Acta Dermato-Venereologica. 1993;**73**(6):407-411

[61] Pavicic T, Wollenweber U, Farwick M, Korting HC. Anti-microbial and -inflammatory activity and efficacy of phytosphingosine: An in vitro and in vivo study addressing acne vulgaris. International Journal of Cosmetic Science. 2007;**29**(3):181-190

[62] Guéniche A, Bastien P, Ovigne JM, Kermici M, Courchay G, Chevalier V, et al. Bifidobacterium longum lysate, a new ingredient for reactive skin. Experimental Dermatology. 2010;**19**(8): e1-e8

[63] Lehrer RI, Ganz T. Antimicrobial peptides in mammalian and insect host defence. Current Opinion in Immunology. 1999;**11**(1):23-27

[64] Bals R. Epithelial antimicrobial peptides in host defense against infection. Respiratory Research. 2000;**1**(3):141-150

[65] Zhang Z, Mu L, Tang J, Duan Z, Wang F, Wei L, et al. A small peptide with therapeutic potential for inflammatory acne vulgaris. PLoS One. 2013;**8**(8):e72923

[66] Lüders T, Birkemo GA, Fimland G, Nissen-Meyer J, Nes IF. Strong synergy between a eukaryotic antimicrobial peptide and bacteriocins from lactic acid bacteria. Applied and Environmental Microbiology. 2003;**69**(3):1797-1799

[67] Harder J, Tsuruta D, Murakami M, Kurokawa I. What is the role of antimicrobial peptides (AMP) in acne vulgaris? Experimental Dermatology. 2013;**22**(6):386-391

[68] Hassan M, Kjos M, Nes IF, Diep DB, Lotfipour F. Natural antimicrobial peptides from bacteria: Characteristics and potential applications to fight against antibiotic resistance. Journal of Applied Microbiology. 2012;**113**(4):723-736

[69] Nissen-Meyer J, Nes IF. Ribosomally synthesized antimicrobial peptides: Their function, structure, biogenesis, and mechanism of action. Archives of Microbiology. 1997;**167**(2/3): 67-77

[70] Bowe WP, Filip JC, DiRienzo JM, Volgina A, Margolis DJ. Inhibition of propionibacterium acnes by bacteriocin-like inhibitory substances (BLIS) produced by Streptococcus salivarius. Journal of Drugs in Dermatology. 2006;**5**(9):868-870

[71] Kang BS, Seo JG, Lee GS, Kim JH, Kim SY, Han YW, et al. Antimicrobial activity of enterocins from *Enterococcus faecalis* SL-5 against *Propionibacterium acnes*, the causative agent in acne vulgaris, and its therapeutic effect. Journal of Microbiology. 2009;**47**(1):101-109