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Title

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Journal

Dermatology Online Journal, 20(9)

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Publication Date

2014

DOI

10.5070/D3209023918

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Commentary

Future perspective of probiotics in dermatology: an old wine in new bottle

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Dermatology Online Journal 20 (9): 11

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Abstract

Probiotics are live microbial food supplements that are beneficial to the host health when administered in adequate amounts. Probiotics do have an exciting concept in digestive functions, but these live microbes have wider applicability as evidenced by gut-brain-skin axis theory given 80years back. However, the details regarding use of probiotics for dermatological indications ranging from atopic dermatitis to acne and sexually transmitted infections is dispersed in the literature, herein we have tried to focus all under one heading. Overall, probiotics seem to be promising and safe therapeutic modality, but the evidence as of now, from the available published data is low. This review will stimulate readers to carry out well designed, larger population based trials, so as to validate its use in dermatology practice.

Keywords: probiotics, atopic dermatitis, acne, bacterial vaginosis.

Introduction

The word probiotic comes from the Greek word 'for life'. The United Nations Food and Agricultural Organization defines probiotics as "live microorganisms, which, when administered in adequate amounts, confer a health benefit to the host"^[1]. Probiotics are defined as non-digestible oligosaccharides, that selectively stimulate the growth of bifidobacteria and lactobacilli, thus producing a probiotic effect^[2]. Synbiotics is a term referring to the use of both probiotics and prebiotics simultaneously. Symbiotic treatment also contains the metabolites secreted by *L. rhamnosus* Lcr35, these metabolites can be defined as eubiotics^[2].

The most widely used bacteria as probiotics, are the *Lactobacilli* and *Bifidobacteria* but products incorporating other organisms such as Gram positive cocci, bacilli, yeasts, and *E.coli* have also been applied^[3]. Probiotic preparations are widely available to consumers as powders, tablets, drinks and fermented dairy products.

The first generation of probiotics (also called bacterial therapeutics) refers to the non-engineered, naturally occurring strains, while the second generation bacterial therapeutics are genetically engineered, and based on naturally occurring lactobacilli strains, where genes that produce potent antiviral compounds (for instance, single chain antibodies or antiviral compounds like cyanovirin) are inserted into the *Lactobacillus* genome^[4].

Probiotics and prebiotics offer an exciting and challenging concept in digestive functions. By selectively stimulating the growth of beneficial bacteria in the large bowel, they have been shown to improve calcium bioavailability, reduce the risk of development of precancerous lesions in the colon, ameliorate mucosal inflammation in numerous gastrointestinal disorders, and induce hypotriglyceridemia and hypoinsulinemia.

To date virtually all probiotic applications have been targeted at the gastrointestinal tract. The evolution of the definition of probiotics from one focused on the intestine to the current one 'live microorganisms which when administered in adequate amounts confer a health benefit on the host', reflects the broader applicability of microbes to the host. This paper elucidates the role of probiotics in the dermatological sector for boosting skin health.

Indications of Probiotics in Dermatology:

Data analysed from peer-reviewed journals demonstrates a wide range of dermatological indications as enumerated in Table 3.

Atopic dermatitis:

Immune response in neonates is dominated by Th2 cytokines but during the first year of life, immune response shifts to the Th1-based ones as a result of the repeated exposure to different infectious antigens^[12]. The hygiene hypothesis is based on finding that the prevalence of allergic diseases is inversely related to high-standard hygienic and sanitary conditions and have contributed to reduce childhood contact with pathogens, decreasing the Th1 driven immune response^[13]. More recently, another hypothesis has been proposed. The host's primary microbial stimulation occurs with the establishment of the gut microflora, and exposure to commensal microflora or to specific bacterial strains may represent a key modulator of the immune system which may prevent the development of atopic diseases^[14, 15]. The developing microflora in the early postnatal period is involved in the activation of innate and adaptive immunity and the continuous microbial stimulus from the developing microflora is required for the successful maturation of the gut mucosal immune system. As a consequence, a lacking or inadequate microbial stimulus results in reduction of the intestinal surface area, alteration of mucosal enzyme patterns, mucosal barrier and mucosal IgA system and abrogation of oral tolerance^[16,17]. It has been observed that gut microflora of atopic children is characterized by a reduced neonatal bifidobacteria to clostridia ratio^[18, 19]. Thus, if unbalanced microflora may favor the development of atopic diseases, probiotics may be helpful because of their capacity of balancing the gut microecology, restoring the normal intestinal permeability, improving immunological gut barrier function and downregulating the production of pro-inflammatory cytokines. Numerous studies have evaluated the potential benefits of probiotics in children affected by atopic dermatitis, with contrasting results. [Table 4]

Acne vulgaris:

Over 70 years have passed since dermatologist John H. Stokes and Donald M. Pillsbury first proposed a gastrointestinal mechanism for the overlap between depression, anxiety and skin conditions such as acne. They hypothesized that emotional states might alter the normal intestinal microflora, increase intestinal permeability and lead to systemic inflammation^[20]. The theoretical value of oral probiotics as adjuvant care in acne vulgaris seems sound. Recent studies [Table 4] have shown that orally consumed pre and probiotics can reduce systemic markers of inflammation and oxidative stress^[21, 22]. Since the local burden of lipid peroxidation in acne is high, such that it appears to place a great demand upon blood-derived antioxidants, the ability of probiotics to limit systemic oxidative stress may be an important therapeutic pathway^[23, 24]. Oral probiotics can regulate the release of inflammatory cytokines within the skin and a specific reduction in interleukin-1 alpha, would certainly be of potential benefit in acne^[25]. Also probiotics have been postulated to improve insulin sensitivity thus linking the role of high glycaemic diets in exacerbation of acne. An additional mechanism whereby probiotics might influence acne is via regulation of glycemic control. In recent years it has become evident that there may indeed be a connection between dietary components, most notably low-fiber carbohydrates, and the risk of acne^[26]. This is of relevance because emerging research shows that the gut microbiota contributes to glucose tolerance^[27], and that orally administered *Bifidobacterium lactis* can improve fasting insulin levels and glucose turnover rates, even in the presence of a high-fat diet^[28]. While much more research is necessary, the mechanisms appear to involve the ability of *bifidobacteria* to prevent the efflux of lipopolysaccharide (LPS) endotoxins into systemic circulation. Specifically, the loss of *bifidobacteria* by poor dietary choices - high fat, sugar - leads to increased intestinal permeability, encroachment of LPS endotoxins through the intestinal barrier, which in turn leads to low-grade inflammation, oxidative stress and insulin resistance^[29,30]. In humans, probiotic administration may diminish systemic access of gut-derived LPS endotoxins and reduce reactivity to such endotoxins^[33]. This entire picture takes on greater meaning when considering recent international studies showing that acne is associated with increased consumption of highly palatable, sweet, fried, calorie-rich foods with low nutrient density^[31, 32] and that it is well documented that a period of insulin resistance occurs during puberty, one coinciding with the development of acne. Therefore, it seems reasonable to ask, to what degree might the gut microbiota influence these processes and disease risk during puberty?

Topical probiotics:

The ability of ingested probiotics to alter distant microbial residents suggests that topical probiotics too may have a role. The first report that topical bactriotherapy' (via local *Lactobacillus bulgaricus* application) may be helpful in acne and seborrhea was published in 1912^[34]. However, it was not until 1999 that proper scientific technique was used to evaluate some of the potential skin-specific benefits of lactic acid bacterial application. Specifically, researchers showed that lactic acid bacteria, *Streptococcus thermophilus*, a species found in most yogurts, can increase ceramide production when applied to the skin for 7 days as a cream^[35]. This work, which has since been replicated, is of relevance to acne, particularly when considering that

some of the ceramide sphingolipids, most notably phytosphingosine (PS), provide both antimicrobial activity against *P. acnes* and direct anti-inflammatory activity. Sphingolipids have been noted to be low in acne, and the seasonal loss of ceramides may be driving force for exacerbation of acne in winters^[36, 37]. Indeed, topical application of 0.2% PS reduced papules and pustules by 89% in a recent 2-month pilot study^[38]. Studies hinting at the value of topical probiotics in acne include recent reports that strains of *Bifidobacterium longum* and *Lactobacillus paracasei* can attenuate skin inflammation mediated by substance P^[39, 40]. This is of relevance because substance P may be a primary mediator of stress-induced amplification of inflammation and sebum production in acne. Certain substances secreted by bacterial strains, such as antimicrobial peptides, have been shown to inhibit growth of *P. acnes*. *Streptococcus salivarius*, a prominent member of the oral microbiota of healthy humans, has been shown to secrete a bacteriocin-like inhibitory substance (BLIS-like substance) capable of inhibiting *P. acnes*. In addition to the antimicrobial activity, *S. salivarius* bacterial cells themselves inhibit a number of inflammatory pathways, thus acting as immune modulators.

Bacterial vaginosis:

Bacterial vaginosis is the most commonly diagnosed cause of vaginitis. The classic signs and symptoms are abnormal discharge and amine odour, which is the result of volatile byproducts of the anaerobic metabolism produced by glycosidase activity of anaerobe pathogens. The normal vaginal environment is dominated by lactobacilli species that are critical for maintaining a fairly acidic pH (<4.7) by producing lactic acid. Cultivation methods identified the major species of human lactobacilli to be *L. crispatus* and *L. jensenii*. In the early stages of BV research, BV used to be called Gardnerella vaginitis, because a substantial amount of *Gardenella vaginalis* were found in all women with BV. Other bacteria identified in cultivation studies, like *Mobiluncus*, *Mycoplasma hominis* and various anaerobes (*Porphyromonas*, *Prevotella*, *Peptostreptococcus*, *Veillonella*) are also important players in BV. The Lactobacilli exist in abundance in the normal vaginal flora, they produce hydrogen peroxide, lactic acid and other bacteriocins, which inhibit pathogens and function as antiretroviral or antibacterial compounds^[41, 42, 43].

Early clinical trials from 1986-1996 investigated probiotics used without adjacent antibiotic treatment. The outcome measures of these early studies were often fairly undefined, but used vague terms like flora improvement^[44].

In the last decade, fewer trials still investigated the use of probiotics without adjacent antibiotic therapy and often tested combination strains (*L. rhamnosus/fermentum* and *L. reuteri/casei*) and others [Table 4]. Measuring protocol adherence is a crucial addition for future study designs. Future clinical trials will also have to include at risk populations like pregnant women, who could greatly benefit from a product preventing bacterial vaginosis which is highly associated with preterm labor^[45].

Vulvovaginal candidiasis:

Vulvovaginal Candidiasis affects 75% of sexually active women at least once in their lifetime. It is reported that five percent of females who have suffered an acute infection of VVC will experience a recurrence. The mainstay of conventional treatment for VVC is an antifungal medication. However, this appears to be unsuccessful in preventing recurring infections. A number of studies [Table 4] have evaluated the effectiveness of yogurt consumption as a preventive measure for VVC and to allow their wide use for this indication. Although the pathogenesis of VVC remains a controversial issue, it seems that when the balance between the microorganisms existing in the vaginal microbiota is disrupted, the overgrowth of *Candida* is facilitated.

It has been suggested in some studies, that lactobacilli are quite common even in the vaginal epithelium of women with VVC. However, the composition of lactobacilli species and/or strains was different between healthy women and those with VVC. The vaginal microbiota of healthy women was more frequently dominated by *Lactobacillus salivarius*, while the vagina of women with VVC was more commonly dominated by *Lactobacillus cateniforme*^[46]. The results of some studies associated VVC either with a reduced number of lactobacilli or with a species of lactobacilli not producing H₂O₂ [Figure 1]. The results of some clinical trials support the effectiveness of lactobacilli, especially *Lactobacillus acidophilus*, *Lactobacillus rhamnosus* GR-1 and *Lactobacillus fermentum* RC-14, administered either orally or intravaginally in colonizing the vagina and/or preventing the colonization and infection of the vagina by *C. albicans*, while the results of a small number of clinical trials do not corroborate these findings^[47]. However, the empirical use of probiotics may be considered in women with frequent recurrence of VVC (more than three episodes per year), especially for those who have adverse effects from or contraindications for the use of antifungal agents, since the adverse effects of probiotics are very rare.

Oral mucositis:

Oral mucositis is the painful inflammation with necrosis and ulceration of the oral cavity and it is usually a consequence of chemotherapy or radiotherapy or a combination of those, especially in patients treated for head and neck cancer. Often an interruption of the cancer therapy becomes necessary, reducing the number of administering courses of chemotherapy and negatively impacting the effectiveness of the treatment. Trefoil Factor 1 (TEF1) is a protein secreted by human salivary glands and contributes to the structural density of the mucus layer covering the oral mucosa. LL-TFF promotes protection and healing

of mucosal tissues. In animal models it has been successfully demonstrated that *Lactococcus lactis* delivering TFF1 can cure ruptured epithelial lining when given orally to mice^[48]. A randomized, double-blind placebo-controlled study demonstrated the effectiveness of *Lactobacillus brevis* CD 2 lozenges in reducing incidence and severity of chemo- and radiotherapy induced mucositis in patients with head and neck carcinoma^[49].

Safety issues related to probiotics

Theoretical safety concerns for probiotics involve risk of infection, adverse metabolic effects, immune reactions and gene transfers. Worldwide use of probiotics is extensive. Many of the *Bifidobacterium*, *Lactobacillus*, and *Streptococcus* probiotics have been used for millennia. Probiotics are very safe. There are no documented cases of translocation of probiotics from the gut even when intestinal mucosal ulcerations are present. A study showed that only in a mean of 0.2% of positive blood cultures in Finland during 1995–2000 were *Lactobacillus* isolates reported^[68]. Apart from lactobacillaemia, infectious endocarditis, liver abscess and fungaemia are some infections, which have been associated with probiotics^[69, 70, 71]. These cases appear mainly in patients with serious underlying diseases and/or immunosuppression. Probiotics are widely used in very-low-birth-weight and premature infants to prevent necrotizing enterocolitis. No probiotic safety issues in infants and children have ever arisen. Probiotics are safe in immunosuppressed patients and patients undergoing chemotherapy or radiation with whom they can prevent and treat diarrhea.

Conclusion

Though probiotics are widely used for digestive functions their use in dermatology sector is still in infancy. In the era of growing antibiotic resistance and overwhelming adverse reactions, probiotics serve as valuable and exciting alternatives for treating various dermatoses as documented by various studies. With paucity of clinical trials more randomized, double-blind, placebo controlled trials are required for documenting greater effectiveness and safety so that probiotics can be widely used and, life delicately treated with microbiota.

Appendices

Table 1. Desirable properties of probiotic bacteria^[5]

Human origin, if intended for humans
Acid and bile stability
Adherence to human intestinal cells and intestinal mucin
Competitive exclusion and colonization of the human intestinal tract
Production of antimicrobial substances
Antagonism against carcinogenic and pathogenic bacteria
Safety in food and clinical use
Clinically validated and documented health effects

Table 2. Health benefits of Probiotics

Inhibition of pathogens ^[6]
Immune stimulation ^[7]
Cholesterol reduction and cardiovascular disease risk ^[8]
Reduction of cancer risk ^[9]
Mineral absorption ^[10]
Lipid regulation ^[11]

Table 3. Indications of probiotics in dermatology

Atopic dermatitis
Acne vulgaris
Bacterial vaginosis
Vulvovaginal candidiasis
Oral mucositis
Prevention of HIV

Table 4.

STUDY	PARTICIPANTS	PROBIOTICS	STUDY DESIGN	DURATION	OUTCOME
1.Kalliomeki et al ^[50]	132 high risk infants for atopy	<i>Lactobacillus rhamnosus GG</i>	R,DB,PC	From 2-4 weeks prenatally to 24 weeks postnatally	At 2 years AD frequency halved in probiotic group vs placebo(23% vs 46%)
2.Kukkonen et al ^[51]	925 high risk infants for atopy	<i>Lactobacillus rhamnosus GG</i> (5 × 10 ⁹ cfu), <i>L. rhamnosus</i> LC705 (5 × 10 ⁹ cfu), <i>Bifidobacterium breve</i> Bb99 (2 × 10 ⁸ cfu), <i>Propionibacterium freudenreichii</i> ssp. Shermanii JS (2 × 10 ⁹ cfu) twice daily	R, DB, PC	From 2–4 weeks prenatally to 6 months post delivery	Probiotics reduced AD
3.Kuitunen et al ^[52]	891 high-risk infants for atopy	<i>Lactobacillus rhamnosus GG</i> (5 × 10 ⁹ cfu), <i>L. rhamnosus</i> LC705 (5 × 10 ⁹ cfu), <i>Bifidobacterium breve</i> Bb99 (2 × 10 ⁸ cfu), <i>Propionibacterium freudenreichii</i> ssp. shermanii JS (2 × 10 ⁹ cfu) twice daily	R, DB, PC	To mothers from 36 weeks of gestation prenatally and to infants postnatally until 6 months of age	At 5 years of age no significant difference appeared in frequencies of AD and IgE associated (atopic) eczema between probiotics and placebo groups. Only cesarean delivered children had significantly fewer incidence of AD
4.Viljanen et al ^[53]	230 children (mean age 6.4 months) with AD and suspected CMA	LGG (5 × 10 ⁹ cfu) or mixture: LGG (5 × 10 ⁹ cfu), <i>L. rhamnosus</i> LC705 (5 × 10 ⁹ cfu), <i>Bifidobacterium breve</i> (2 × 10 ⁸ cfu), <i>Propionibacterium freudenreichii</i> ssp. Shermanii JS (2 × 10 ⁹ cfu) twice daily	R, DB, PC	4 weeks	Reduction in SCORAD score only in IgE-associated AD in LGG group
5.Gerasimov et al ^[54]	90 children (1–3 years of age) with moderate to severe AD	<i>Lactobacillus acidophilus</i> (5 × 10 ⁹ cfu) and <i>Bifidobacterium lactis</i> (5 × 10 ⁹ cfu) twice daily	R, DB, PC	8 weeks	Probiotics improved significantly clinical severity of AD with a greater decrease in SCORAD score in children supplemented
6. Panduru M et al ^[55]	Meta-analysis of 26 randomized controlled studies	<i>Lactobacillus</i> and <i>Bifidobacterium</i>	Meta-analysis		Probiotics seem to have a protective role in AD prevention if there are administration in pre and postnatal period in both general and allergic risk population.
6.Robert H. Silver ^[56]	300 patients with acne vulgaris	<i>L.acidophilus</i> and <i>L.bulgaricus</i>		8 days followed by 2 weeks wash out and re-introduction for 8 days	80% had clinical improvement and intervention was most valuable in inflammatory acne
7.Marchetti F ^[57]	40 patients with acne vulgaris	Freeze dried <i>L.acidiphilus</i> and <i>B.bifidum</i>		12 weeks	Better clinical outcome and better compliance with antibiotics
8. Wang Y et al ^[58]	Patients with acne vulgaris	<i>Staphylococcus epidermidis</i>			<i>S.epidermidis</i> ferments glycerol and produce succinic acid which inhibits

					growth of <i>P.acnes</i>
9. Jung GW et al ^[59]	45 patients with acne vulgaris	Group A- Probiotics Group B- Minocycline Group C-Probiotics + Minocycline	R,PC	12 weeks	Group C had significant decrease in lesion count as compared to group A and B.
10. Al-Ghazzewi FH et al ^[60]	Patients with acne vulgaris	Probiotics + konjac glucomannan hydrolysates(GMH)			Probiotics diminish growth of <i>P.acnes</i> and effect is enhanced by GMH.
11.Friedlander ^[61]	38 patients with Bacterial vaginosis	Unspecified Lactobacillus	P	Vaginal douche twice daily for 1-2 weeks, plus daily oral VitB supplement for 6 months	Increased 'normal' flora from 13% to 76% one week post treatment, and 55% at 3 & 6 months .
12.Neri ^[62]	84 patients with bacterial vaginosis	<i>L.acidophilus</i>	R,OB	Yogurt 109 cfu/dose vaginally for 7 days, repeat after one week OR: Untreated OR: Vaginal acetic acid soaked tampon	BV cure: probiotics 87% placebo 5% [women in 1. Trimester]
13.Anukam ^[63]	40 patients with bacterial vaginosis	<i>L. rhamnosus</i> GR-1 <i>L. reuteri</i> RC-14	R,DB,AC	Vaginally daily at 2 x 10 ⁹ cfu/dose for 5 days OR: Vaginal metronidazole twice daily for 5 days	BV cure (<i>Nugent 0-3</i> , <i>Sialidase neg, no discharge</i>) Day 6: 80 vs 45% Day 15: 85 vs 45% Day 30: 90 vs 55%
14.Petricevic ^[64]	40 patients with bacterial vaginosis	<i>L.rhamnosus</i> <i>L.reuteri</i>	R,DB,PC	Tablets orally daily at 2.5 x10 ⁹ cfu/dose each for 14 days OR: Placebo	<i>Nugent Score</i> decreased by 3 points in probiotic group, no decrease in placebo group [Postmenopausal women]
15.Hilton ^[65]	10 female patients with recurrent VVC (>5/year) and symptoms of VVC (positive cultures for <i>Candida</i> in 5 women)	<i>Lactobacillus GG</i>	Prospective cohort	Vaginal suppositories with <i>Lactobacillus GG</i> twice/day for 7 days	Improvement of symptoms and signs (↓ of erythema and discharge). 4/5 women with cultures positive for <i>Candida albicans</i> before intervention: negative cultures 7 days after the completion of intervention
16.Reid ^[66]	10 patients with recurrent urogenital infections (9 with recurrent VVC)	<i>L. rhamnosus</i> GR-1 + <i>L. fermentum</i> RC-14	R	<i>L. rhamnosus</i> GR-1 + <i>L. fermentum</i> RC-14 orally twice/day for 14 days	No symptoms of VVC 5/5 women with history of recurrent VVC & low or no lactobacilli before intervention had normal number of lactobacilli 1 week after start of intervention
17.Shalev ^[67]	46 patients of recurrent (≥4 in the last year) vaginitis (VVC: <i>n</i> = 18, VVC & bacterial vaginosis: <i>n</i> = 8)	<i>L.acidophilus</i>	R	group 1 (<i>n</i> = 23): 150 mL/day yogurt with <i>L. acidophilus</i> for 2 months then no yogurt for the next 2 months then pasteurized yogurt for the last 2 months group 2 (<i>n</i> = 23):	Positive cultures for <i>L. acidophilus</i> : before intervention: 20% (group 1) versus 31% (group 2) after 1 month: 71% (group 1) versus 27% (group 2), <i>P</i> < 0.05 after 2

				<p>pasteurized yogurt for 2 months then no yogurt for the next 2 months then 150 mL/day yogurt with <i>L. acidophilus</i> for the last 2 months</p>	<p>months: 92% (group 1) versus 30% (group 2), $P < 0.05$ positive cultures for <i>Candida</i>: before intervention: 56% (group 1) versus 62% (group 2) after 1 month: 44% (group 1) versus 37% (group 2), $P > 0.05$ after 2 months: 21% (group 1) versus 28% (group 2), $P > 0.05$</p>
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