

Topical probiotics: the unknowns behind their rising popularity

Griffin R Lee¹ BA, Melody Maarouf² MHS, Aleks J Hendricks³ BS, Dylan E Lee⁴ MD, Vivian Y Shi³ MD

Affiliations: ¹John A. Burns School of Medicine, University of Hawaii, Honolulu, Hawaii, USA, ²College of Medicine, University of Arizona, Tucson, Arizona, USA, ³Division of Dermatology, Department of Medicine, University of Arizona, Tucson, Arizona, USA, ⁴Department of Medicine, John A. Burns School of Medicine, University of Hawaii, Honolulu, Hawaii, USA

Corresponding Author: Vivian Y. Shi³ MD, Division of Dermatology, Department of Medicine, University of Arizona, 7165 North Pima Canyon Drive, Tucson, Arizona 85718, Email: versushi@email.arizona.edu

Abstract

Objective: Topical probiotics have been used for skin care and treatment since the early 20th century. Over the past decade, there has been a dramatic surge of commercially-available topical probiotic products. We conducted a systematic search of clinical data relating to the use of topical probiotics and identified relevant clinical and regulatory gaps.

Methods: PubMed and Google Scholar searches were conducted for trials and reviews of probiotics. FDA definitions of cosmetics, drugs, and regulation of topical probiotics were reviewed.

Results: Topical probiotics have shown efficacy in a number of limited trials, particularly those involving the treatment of acne, atopic dermatitis, and rosacea. However, there is a paucity of literature on the safety profiles, mechanistic action, and therapeutic potential of topical probiotic products. Several regulatory gaps exist, including approval and classification of topical probiotic products by the FDA; currently there are no topical probiotic products the FDA has approved as drugs.

Conclusion: With increasing popularity among the general public, but insufficient clinical data to demonstrate large-scale effectiveness and a thorough understanding of side effects, there is a need for further mechanistic and clinical investigation, as well as improved regulation and standardization of topical probiotic products.

Keywords: topical probiotics, probiotics, hygiene hypothesis, skin, microbiome

Introduction

The cutaneous microbiome is a diverse microbial community that plays a critical role in the innate and adaptive immune responses and maintenance of skin barrier function [1, 2]. The hygiene hypothesis proposes that a lack of early childhood pathogen exposure related to over-cleansing and antimicrobial use limits natural immune development, including that of the skin barrier, and predisposes one to develop allergic conditions [3-5]. Additionally, cutaneous dysbiosis alters the immune milieu and has been implicated in a number of skin diseases, including atopic dermatitis (AD), psoriasis, acne vulgaris, and seborrheic dermatitis [1, 6]. In the past decade, commercially available topical probiotics have gained tremendous popularity — a Google search of “topical probiotics” yields over 3 million results. Despite their rising popularity amongst the general public, how much information is the medical community equipped with regarding the safety and efficacy of topical probiotics?

Discussion

In contrast to topical bacteriotherapy, the transplant of skin microbiota from one person to another, topical probiotics involve the transfer of laboratory-cultured bacteria. Use of topical bacteriotherapy was first proposed as a treatment for cutaneous diseases in 1912, when topical application of *Lactobacillus bulgaricus* was reported to improve acne and seborrhea [7]. Following the boom of oral probiotics,

numerous topical probiotic formulations have been proposed to correct skin dysbiosis and establish immune homeostasis by equilibrating the skin microbiota [3]. Topical probiotics have demonstrated notable efficacy in limited clinical trials in acne, atopic dermatitis, and rosacea [8-13].

Although the exact mechanism of probiotics remains unknown, they are hypothesized to exert anti-inflammatory effects by stimulating regulatory T-cells and release of anti-inflammatory cytokines such as IL-10, competing with pathogens for nutrients and aggregating and displacing pathogens [14]. Probiotic strains containing commensal skin microbes such as *Lactobacillus*, *Bifidobacterium*, or *Streptococcus* have demonstrated cutaneous immuno-regulatory effects through inhibition of biofilm formation, reduction of systemic inflammatory cytokines, and direct, competitive inhibition of binding sites [6, 7]. Lactobacilli specifically exhibit antimicrobial activity against skin pathogens including *Escherichia coli*, *Pseudomonas aeruginosa*, and pathobionts (resident microbes with pathogenic potential), such as *Cutibacterium* (formerly *Propionibacterium*) *acnes* [6]. Recently, a small open label study of 10 adults and 5 pediatric AD patients treated with topical microbiome transplantation (*Roseomonas mucosa* lysate cultured from healthy volunteers) led to a >50% improvement in SCORing Atopic Dermatitis (SCORAD) index in 10 patients (P=0.016). *R. mucosa* is believed to improve AD symptoms by restoring epithelial barrier function and innate/adaptive immune balance as well as via inhibition of *S. aureus* growth [15].

Despite promising findings in preliminary bacteriotherapy studies, the mechanism and side effects of topical probiotics remain largely unknown. Transfer of antibiotic resistance among pathogens, bacteremia, and allergic reactions to inactive ingredients have been proposed as potential adverse effects. However, a recent review by the Agency for Healthcare Research and Quality (AHRQ) concluded that the available literature is not sufficiently equipped to determine the safety of probiotic use with confidence [16]. Furthermore, the clinical effects of topical probiotics also vary

depending on bacterial speciation. A 2017 study of 14 topical probiotic species found that each species had a unique spectrum of characteristics, including keratin adhesion, inhibitory action, organic acid production, and inhibition of biofilm formation [6]. The isolation of probiotics from their natural environments inhibits quorum sensing and may produce behavior distinct from that exhibited in their native microbial communities.

Currently, the FDA categorizes probiotics into different product categories such as foods, food additives, cosmetics, dietary supplements, medical devices, or drugs on a case-by-case basis, but does not have a regulatory definition or agency that specifically addresses topical probiotics [17]. At this time, there are no probiotics approved as drugs by the FDA [17]. Although topical probiotic products are used to mitigate skin pathologies, their utilization applies more towards the product category of "cosmetics," which the FDA defines as products used to cleanse or beautify the body [17]. The FDA does not require cosmetic products and ingredients to have FDA approval prior to marketing [18]. Therefore, probiotic labeling by manufacturers may include unsubstantiated therapeutic claims, and consumer use in pursuit of these unproven benefits is a growing concern.

Future investigations should evaluate the efficacy and safety of topical probiotics, as the need for improved regulations and labeling will be an ongoing dialogue. Should probiotics and bacteriotherapy become approved as biotherapeutics, these investigations will pave the way for more appropriate regulation and standardization of effective clinical use. Additionally, further investigations in dermatologic conditions for which probiotics have demonstrated efficacy (AD, acne, rosacea) will help to elucidate the mechanisms by which probiotics are able to ameliorate disease symptoms.

Conclusion

Although emerging evidence holds promise, the current view of topical probiotics among dermatologists is one of excitement and cautious optimism. Further investigations are needed to more

thoroughly evaluate their benefits and safety. Additional efforts by the FDA to better define topical bacteriotherapy will help to establish guidelines for product safety and intended use. Patients seeking information about the use of over-the-counter topical probiotics should be advised about their potential clinical benefits but should also be informed of the remaining unknowns regarding their mechanism of action and potential adverse effects. Larger scale clinical trials evaluating efficacy and further research into the mechanisms of topical

probiotic formulations should be undertaken to broaden our understanding of their potential therapeutic applications. Topical probiotics are a promising therapeutic option for inflammatory cutaneous pathologies and future clinical trials and reports regarding their efficacy will be eagerly awaited.

Potential conflicts of interest

The authors declare no conflicts of interests.

References

- Schommer NN, Gallo RL. Structure and function of the human skin microbiome. *Trends Microbiol.* 2013;21(12):660-8. [PMID: 24238601].
- Grice EA, Segre JA. The skin microbiome. *Nat. Rev. Microbiol.* 2011;9:244. [PMID: 21407241]
- Romagnani S. Coming back to a missing immune deviation as the main explanatory mechanism for the hygiene hypothesis. *J Allergy Clin Immunol.* 2007;119(6):1511-3. [PMID: 17556059].
- Okada H, Kuhn C, Feillet H, Bach JF. The 'hygiene hypothesis' for autoimmune and allergic diseases: an update. *Clin Exp Immunol.* 2010;160(1):1-9. [PMID: 20415844].
- Flohr C, Pascoe D, Williams HC. Atopic dermatitis and the 'hygiene hypothesis': too clean to be true? *Br J Dermatol.* 2005;152(2):202-16. [PMID: 15727630].
- Lopes EG, Moreira DA, Gullon P, et al. Topical application of probiotics in skin: adhesion, antimicrobial and antibiofilm in vitro assays. *J Appl Microbiol.* 2017;122(2):450-61. [PMID: 27862685].
- Bowe WP, Logan AC. Acne vulgaris, probiotics and the gut-brain-skin axis - back to the future? *Gut Pathog.* 2011;3(1):1. [PMID: 21281494].
- Dreno B, Araviiskaia E, Berardesca E, et al. Microbiome in healthy skin, update for dermatologists. *J Eur Acad Dermatol Venereol.* 2016;30(12):2038-47. [PMID: 27735094].
- Fortuna MC, Garelli V, Pranteda G, et al. A case of Scalp Rosacea treated with low dose doxycycline and probiotic therapy and literature review on therapeutic options. *Dermatol Ther.* 2016;29(4):249-51. [PMID: 27087407].
- Matsumoto M, Ebata T, Hirooka J, et al. Antipruritic effects of the probiotic strain LKM512 in adults with atopic dermatitis. *Ann Allergy Asthma Immunol.* 2014;113(2):209-16 e7. [PMID: 24893766].
- Blanchet-Réthoré S, Bourdès V, Mercenier A, et al. Effect of a lotion containing the heat-treated probiotic strain. *Clin Cosmet Investig Dermatol.* 2017;10:249-57. [PMID: 28721083].
- Wang Y, Kuo S, Shu M, et al. Staphylococcus epidermidis in the human skin microbiome mediates fermentation to inhibit the growth of Propionibacterium acnes: implications of probiotics in acne vulgaris. *Appl Microbiol Biotechnol.* 2014;98(1):411-24. [PMID: 24265031].
- Al-Ghazzewi FH, Tester RF. Effect of konjac glucomannan hydrolysates and probiotics on the growth of the skin bacterium Propionibacterium acnes in vitro. *Int J Cosmet Sci.* 2010;32(2):139-42. [PMID: 19818083].
- Huang M-CJ, Tang J. Probiotics in personal care products. *Microbiology Discovery.* 2015;3(1):5. [DOI: 10.7243/2052-6180-3-5].
- Myles IA, Earland NJ, Anderson ED, et al. First-in-human topical microbiome transplantation with Roseomonas mucosa for atopic dermatitis. *JCI Insight.* 2018;3(9). [PMID: 29720571].
- Hempel S, Newberry S, Ruelaz A, et al. Safety of probiotics used to reduce risk and prevent or treat disease. *Evid Rep Technol Assess (Full Rep).* 2011(200):1-645. [PMID: 23126627].
- Hoffmann DE, Fraser C, Palumbo F, et al. Final report. Federal regulation of probiotics: an analysis of the existing regulatory framework and recommendations for alternative frameworks 2013.
- Human Drugs U.S Food & Drug Administration: 2017 [updated 10/25/2017; cited 2018]. Available from: <https://www.fda.gov/ForIndustry/ImportProgram/ImportBasics/RegulatedProducts/ucm511482.htm>. Accessed on 8/02/2018.