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Review Article

Topical Probiotics: A Review on Current Status and Challenges

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ABSTRACT

This review article exclusively explores the growing interest and potential of topical probiotics. It briefly presents the history, estimated market value, and merits of topical probiotics. The composition of skin microbiota, interaction between skin and beneficial microbiota and their role in maintaining skin health has been described. The factors responsible for causing skin disorders are discussed. The natural sources of topical probiotics, the involvement of microorganisms and their therapeutic uses are explained. The steps involved in the formulation of topical probiotics have been outlined. A comparison of existing marketed topical probiotics to outline the formulation aspects and techniques to be followed during their development has been emphasized. The applications of topical probiotics in treating various skin disorders have been elaborated. The challenges to be addressed regarding formulation, stability, efficacy, and regulatory guidelines have been substantiated. The impact of orally administered probiotics on skin health is beyond the scope of this article.

INTRODUCTION

The World Health Organisation defines "probiotics" as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host"[1]. The term "probiotics" was used by Lilly and Stillwell, for the first time, in 1965[2]. Topical probiotics are the emerging set of formulations in the field of pharmaceutical sciences. It can be defined as the preparations which consist of beneficial microorganisms that can improve and supplement the skin health when administered topically. In 1912, the first known attempt of topical bacteriotherapy was made, using *Lactobacillus bulgaricus*, to treat acne[3]. The topical probiotics is in nascent stage, in terms of research and development, in comparison to oral probiotics. Oral probiotics have gained immense popularity due to the establishment of gut-brain axis relationship along with research-based evidences. It has demonstrated effectiveness in treating various digestive disorders, systemic diseases and enhancing the immune system. The

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global market value of cosmetic probiotics was estimated to be USD 311 million in 2023 and expected to reach USD 706 million in 2032 at an annual growth rate of 8.5%[4]. The oral probiotics has the largest global market for any probiotics and is valued at USD 2.5 billion in 2022 and can breach the USD 4 billion mark in the year 2032 with a projected annual growth rate of 6.5%[5].

Topical probiotics is gaining popularity due to rise in awareness among people about maintenance of skin health. The need for the topical probiotics can be attributed to following reasons:

1. Growing demand for safe and natural alternatives to conventional, synthetic topical interventions.
2. Increased customer awareness for products which can be used to treat various skin disorders such as acne, dermatitis, dry skin etc.
3. Need for novel approaches to treat skin infections is becoming critical as the causative pathogens have developed resistance to existing antibiotics[6].

Merits Of Topical Route Of Probiotic Delivery

Topical probiotics are significantly different in comparison to oral probiotics. These preparations are designed to deliver beneficial microbes directly into the skin, alongside active medicaments, to enhance the therapeutic effects specifically at the skin surface. The topical preparations can confer better activity in strengthening the property of skin as a physical barrier. The topical route provides an opportunity for painless, non-invasive administration of drug; which is comparatively easy and convenient. It also provides target- specific action, of medicament on skin, with immediate effects. It can be viewed as a tool to carry useful microorganisms to address several dermatological concerns for various skin types. Unlike oral probiotics, topical probiotics do not involve the gut-skin axis interaction.

Role Of Skin Microbiota

Composition of Skin Microbiota

The skin is the largest organ which encompasses an average area of about 1.8 m^2 in an adult human[7]. The skin microbiota houses distinct types of microorganisms that serve as a physical barrier against the external environment. The skin microbiota comprises two main groups of microbes, resident and transient microbiota. The resident microbiota refers to the group of microbes present superficially in the epidermis (*stratum corneum*). These non-pathogenic microorganisms form an integral part of skin physiology. They regulate the number of colonizing microbes and inhibit the growth of pathogenic transient microbes[8]. The transient microbiota refers to the group of microbes that temporarily resides on the skin for varied period of time. The presence of these microbes can be due to exposure of skin to different surfaces in environment. The four most prevalent bacterial phyla in skin microbiota are *Actinobacteria*, *Firmicutes*, *Proteobacteria* and *Bacteroides*. The three most common genera, constituting about 60% of residential microbiota, are *Corynebacterium*, *Cutibacterium* and *Staphyl ococci*[9,10]. The most common bacteria found among transient microbiota include Escherichia coli, Klebsiella, Pneumococci, Clostridia and Acetinobacter[11].

A Note on Skin Types

The skin state can be defined as the condition of the skin at a given time. It can be classified as normal, dry, oily or combination type of skin[12]. Oily skin is characterized by excess secretion of sebum by sebaceous glands, thus providing an anaerobic environment in the skin[13]. It provides an ideal environment for thriving of *Cutibacterium acnes* which causes acne[11, 12]. It can facilitate the growth of aggregates of *Cutibacterium* species around the hair follicles, inhibit the action of macrophages and utilize the lipid molecules for their growth[14]. Dry skin occurs due to inability to

retain sufficient amount of moisture by the skin. It can be caused due to excess contact with water, exposure to dry climate, synthetic medicaments or altered genetic makeup. It is characterized by scaling, itching, flaking of the skin as well as formation of powdery mass from the skin surface[15]. The decreased lipid content in the skin makes it prone to microorganisms like *Staphylococcus*, *Malassezia* and *Corynebacterium*[16]. These organisms tend to grow better in moist and humid conditions as well[13]. The normal skin is characterized by the optimal levels of moisture and oily secretion. The combination skin state refers to existence of oily and dry skin at different parts of the body, based upon their location and exposure to environment.

Factors affecting Skin Conditions

Various factors affect the general status of skin microbiota. Host factors such as age, sex, hormonal changes, diet, stress, exercise and environmental stresses such as sun exposure, pollution, climatic factors and geographical location may cause a shift of the non-pathogenic microbes into pathogenic microbes. This shift might result in inflammation, itching, scaling and other clinical signs, suggesting an imbalance between the skin and its microbiota[13, 17]. Any imbalance in these microorganisms results in skin disorders[18].

Natural Sources of Topical Probiotics

Natural topical probiotics include yoghurt, *kefir*, *kimchi*, *sauerkraut*, *miso* and *kombucha*.

Yoghurt (curd) is one of the most commonly used sources of topical probiotics. It is a natural remedy which is rich in *Lactobacillus* and *Streptococcus*. It contains lactose, lactic acid and enzymes such as lipase, protease and amylase[19].

Kefir is a fermented dairy product produced by inoculation of milk with *kefir* grains. *Kefir* grains are white, gelatinous clumps of inoculum which is useful in milk fermentation and can be recovered after the process[20]. It is a complex structure which houses homofermentative and heteroferementative bacterial species (*Lactobacillus*, *Acetobacter)* and yeast species (*Saccharomyces*, *Candida and Kazachstania*). These microbes are embedded in a matrix made up of polysaccharides and proteins. Kefiran, an exopolysaccharide obtained from *Lactobacillus kefiranofaciens*, is an excipent of pharmaceutical importance due to its rheological properties[20-22]. *Kimchi* is a Korean vegetable dish prepared by fermentation in the presence of *Lactobacillus* species[23]. *Sauerkret* is prepared by fermentation of raw cabbage in the presence of lactic acid bacteria[24]. *Miso*, a traditional Japanese seasoning, involves the fermentation in presence of several microbial species. It involves the fermentation of steamed rice, barley or soyabean by *Aspergillus oryza (Koji)* for a particular period of time. Addition of salt as a preservative prevents the spoilage of *miso* by unnecessary microbes[25]. *Kombucha* is a tea drink prepared by fermentation process in the presence of symbiotic culture of bacteria and yeast (SCOBY). SCOBY comprises yeast species such as *Zygosaccharomyces*, *Brettanomyces* and bacterial species of *Lactobacillus* and *Acetobacter*[26]. Table 1 lists out the beneficial microorganisms which are involved in preparation of topical probiotics.

Table 1: Beneficial Microorganisms Involved in Topical Probiotics

S. No.	Genera	Species
1.	Lactobacillus	L. bulgaricus, L. acidophilus, L. casei, L. rhamnosus, L. johnsonii, L.acidophilus, L.delrueckii, L.salivarius, L.paracasei, L.fermentum, L.reuteri, L. plantarum, L.hilgardii, L.iners, L.paraplantarum, L.sakei, L. buchneri

2.	Bifidobacterium	B.breve, B. lactis, B. longum, B. animalis, B.biftdum
3.	Streptococcus	S. thermophilus, S.pyogenes
4.	Staphylococcus	S. epididermis, S.hominis, S.aureus
5.	Saccharomyces	S.cerevisiae

Preparation Of Topical Probiotics

Formulation of topical dosage forms using microbes is quite different from one that includes an active drug. Efforts have been made to develop topical pharmaceuticals as well as cosmetics with the inclusion of microorganisms. Fermentation and lyophilization are the two most common methods that are employed for incorporating probiotics into the topical formulations.

Fermentation

Fermentation is the process in which the microorganisms break down the natural polysaccharides into simple sugars. The microorganisms can act on natural substances such as plant extracts, milk, and raw fruits and vegetables. The process is characterised by formation of fermentate which is rich in metabolites such as lactic acid, glycerol, short chain fatty acids (SCFA) like propionate, butyrate etc.[31]. The fermentation by *Lactobacillus* facilitates the growth of antimicrobial proteinaceous molecules called as bacteriocins. The fermentation in presence of *Aspergillus* facilitates the release of proanthocyanidins which confers antioxidant property to improve the skin health[32]. The release of fatty acids maintains acidic environment and acts as a self preservative[31].

Lyophilization

Lyophilisation, commonly called as freeze drying, is the process in which the moisture is frozen and sublimated, thus resulting in removal of moisture and formation of a dry product. The concentrated cell culture is frozen. The crystallised water is removed during primary drying by application of heat and reduced pressure. The remaining moisture is removed by the process of desorption. The effects of the ice crystals on the cell morphology, the selection of suitable lyophilising solvent and the relationship between the physiological functions of the microbial genera on the process has to be determined and taken care during preformulation studies[28,33]. The most commonly used cryoprotectants are sugars such as sucrose, glucose, lactose, trehalose; polyhydroxyl alcohols such as adonitol, glycerol, polyethylene glycol etc.[30]. The generalised formulation scheme in preparation of topical probiotics is outlined in **Figure 1.** The steps involved in the preparation of topical probiotics can be summarised as follows[46,47]:

1. Procurement of source of the microorganism
2. Identification of the microbial strains using molecular techniques.
3. Isolation and characterisation of the identified microbial strain.
4. Culture of the identified microbial strain on suitable culture media.
5. Processing of the cell culture
6. Product recovery and purification.
7. Preparation of the purified probiotics to optimal concentration.
8. Incorporation of the probiotic preparation into pharmaceutical formulation.
9. Evaluation of the probiotic formulation by necessary quality control tests.
10. Stability studies for assessing the properties of the formulation on storage.
11. Optimization of the formulations.
12. Proper packaging and labelling instructions.
13. Regulatory guidelines regarding quality, safety and efficacy to be complied.

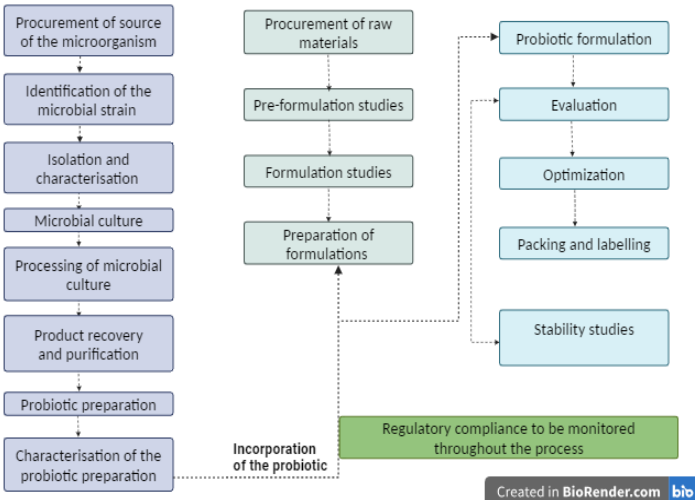

Fig 2: Generalised formulation scheme for topical probiotics (Created with BioRender.com)

Comparative Analysis Of Marketed Topical Probiotics

Considerable efforts are being made in development of effective topical probiotics formulations. The comparative review of various marketed products has helped in identifying the common ingredients and techniques that can be employed in development of topical probiotics. The different marketed brands of topical probiotics along with their key ingredients have been described in **Table 2**.

Table 2: Different marketed brands of topical probiotics

S.No.	Brand Name	Dosage Form	Comments	References
1.	SebaMed Pro!	Serum	It contains *Lactococcus* ferment lysate and leaf cell extract of *Psilanthus bengalensis*. It helps in treating wrinkles.	48
2.	Glowbiotics	Lotion, Cream	It involves incorporation of probiotic derived bioactives (PDBs) through fermentation process. It produces varied therapeutic uses to treat skin disorders and addresses the needs of different types of skin.	49
3.	Mother Dirt	Cosmetics in the form of body wash, body oil, deodorant and serum	It involves combination of herbal extracts, active phytoconstituents along with beneficial microbial strains across the entire skin.	50
4.	TULA	Cream	It is a non toxic, anti-aging cream which contains prebiotics, probiotics and extracts of apple and watermelon.	51
5.	Probiotic Action	Spray, lotion and cream	It contains various dosage forms with probiotic concentrates that could be used to maintain the skin health as well as treat skin disorders.	52

6.	Pacifica	Cream	It contains probiotics as well as coconut water. It promotes skin hydration.	53
7.	LiviaOne	Spray	It is proprietary probiotic blend which contains 12 symbiotic microbial strains. It is a vegan and organic preparation.	54
8.	Hyalogic	Powder	It is used as an adjuvant which can be used along with application of serum or moisturiser. It contains Triclyst® (combination of bacterial species) and sodium hyaluronate.	55
9.	Clinique	Gel	It is an oil-free dosage form which provides necessary hydration to skin.	56
10.	BioGaia	Ointment	It is used for skin care of babies.	57
11.	FCL	Lotion	It contains probiotics, fensobiome and aquaxyl. It is useful in detoxifying the skin and improving the skin microbiome.	58

Applications Of Topical Probiotics

Skin disorders can arise due to various reasons such as genetic factors, age and hormonal changes. Environmental factors such as exposure to allergens (pollen, dust, animal dander) can trigger skin concerns. Sedentary lifestyle, poor diet and stress negatively impact the skin health[48]. Underlying medical conditions can severely affect the skin health. These factors can alter the cutaneous microbiota and make the skin susceptible to microbial infections[49]. Topical probiotics have shown promise in treating various skin diseases such as acne, atopic dermatitis and rosacea. It has shown promise to treat wrinkles and can be explored as anti-ageing agent[50,51]. Although, the exact mechanism of action and potential side effects are not completely understood, the probable activity and safety of the probiotics have been outlined using the available literature[52]. *Acne vulgaris*, commonly called as acne, is one of the most common skin diseases. It is caused by factors such as altered follicular keratinization and increased sebum resulting in the colonization of *C. acnes*. The bacterial action helps in the release of pro-inflammatory mediators and makes the skin more oily and sticky[50,53]. Studies have shown that certain *Lactobacillus* strains have suppressed the lipid degradation activity of *C. acnes.* Lactic acid was found to have antimicrobial and anti-inflammatory activity on the oily skin[54]. *Lactobacillus paraplantarum*, isolated from *kimchi*, was found to have anti-acne effect[55]. Atopic dermatitis (AD), also called as eczema, is a chronic inflammatory skin condition characterized by severe itching and scaly sores due to intense allergic reaction[50]. It is characterized by increased count of *Staphylococcus aureus*[56]. Scientists have found out that *Roseomonas mucosa* can be used as symptomatic prophylaxis against eczema as these bacteria can restore the lipid component into the skin[57]. 5% extract of *Vitreoscilla filiformis* was able to relieve AD symptoms when incorporated into an emollient[58]. Topical probiotics can accelerate wound healing by regulation of release of inflammatory mediators[51]. Application of *Lactobacillus* promotes re-epithelisation of damaged skin and improves the wound healing. This bacterium was

found to be effective against the infection caused by *Pseudomonas aureginosa*[59]. A gel was formulated by incorporating the stabilised extract of *Lactobacillus casei* as an anti-dermatophytic agent to treat fungal infections[60]. A cosmetic ointment containing *Lactiplantibacillus plantarum* was investigated for anti-aging property[61]. Fermented plant extract of *Lactobacillus buchneri* improved the production of elastin, collagen and could be used as an anti-wrinkling agent[29]. *Lactiplantibacillus plantarum*, identified in fermented cabbages, was found to inhibit the growth of microbes such as *Porphyromonas*, *Fusobacterium* and *Aggregatibacter*. This bacterium showed ability to treat periodontal diseases[62]. Psoriasis is a chronic autoimmune skin disorder. The pathogenesis of psoriasis is yet to be completely understood[18]. It is cause due to the mutation of CARD14 and could be worsened in the presence of allergens[63]. Efficacy of topical probiotics against psoriasis is yet to be proved.

Challenges And Limitations

Despite having several benefits, there is a need to throw light upon the existing drawbacks of the topical probiotics. The current section discusses the challenges and limitations to be addressed regarding topical probiotics. The topical probiotics involves incorporation of microorganisms as a part of the formulation. Further research on the skin microbiota is essential to identify the types of microbes that could be introduced into the skin. There is a need to understand and establish the endogenous and exogenous factors affecting the skin microbiota. Further scientific backing is required to highlight the efficacy of the product in treating dermatological diseases. Efforts have to be made in developing topical probiotics as prophylactic interventions. Also, there is a need to simplify the dosage form such that the user can conveniently include it as a part of their skin care routine. During pre-formulation studies, the drug-excipients interaction and excipient- microbial strains interaction should be analysed and kind of incompatibility should be addressed. Excipients such as preservatives, antioxidants, buffers, surfactants or emulsifiers should not alter the viability and activity of the microbial strains.

It is necessary that the properties of the formulation align with normal skin conditions and probiotic strains incorporated in it. Physicochemical properties like pH, viscosity, particle size, rheological properties, optimum level of moisture content etc. are of utmost importance to be taken care during formulation. It is crucial to determine the appropriate concentration of these microorganisms to ensure the stability of the formulation[64]. Factors such as viability of the microbial cells, number of colony forming units (CFUs), stability, shelf life and storage conditions are critical and should be carefully optimised. Novel drug delivery systems such as nanoparticles, nanogels, nanoemulsions, hydrogels, and microencapsulation can be developed to incorporate lipophilic drugs along with the probiotics. It is essential to develop methods that preserve the viability of live microbes and maintain the activity of the formulation. Table 2 has also helped in identification of herbal ingredients and nutraceuticals that could be incorporated to improve the formulation activity. Biopolymers such as collagen peptide, hyaluronic acid, chitosan, carragenan, pectin and starch can be explored to provide unique properties to topical formulations[45]. The packaging material should not degrade the efficacy of the probiotics and the ingredients. The packaging material should be resistant to heat and light. It should be impervious to moisture or air. Processes like leaching, phase separation or loss of solvent can deteriorate the product. The storage conditions, preferably low or sub-zero, should be taken care by proper cold chain supply. The dosage form should be cost effective. Strategies have to be planned and

executed to enable cost optimisation of the product.

Unknown mechanisms of action of probiotics and their potential adverse effects have limited the prospect of clinical research regarding topical probiotics. This uncertainty complicates the identification of biomarkers needed for personalized therapeutic interventions. Large-scale clinical trials are essential to establish the quality, safety, and efficacy of probiotics.

Several regulatory gaps such as approval and classification of topical probiotic products by the United States Food and Drug Administration (USFDA) exist. Currently, there are no topical probiotic products approved by USFDA. There is a need for an agency and guidelines for regulating topical probiotics. Although topical probiotics are showing significant positive results, there is a need to establish data regarding long term safety profile for intended use[3, 65]. Increased microbial load makes it difficult for the classification and testing of topical probiotics[18]. Efforts should be made to establish definite product safety and efficacy guidelines for topical skin probiotics[50,52].

CONCLUSION

Topical probiotics holds promising potential for advancing skincare and dermatological treatments. Further research is essential to fully understand the complexities of the skin microbiota and identification of specific strains of beneficial microbes that can effectively address various skin conditions. Innovations in formulation and delivery systems will be crucial in overcoming current limitations. Additionally, exploring personalized skincare approaches based on individual microbiota profiles could lead to more effective and customized treatments. While several promising topical probiotic products are already in the market, they face limitations that require adherence to defined regulatory aspects. By addressing these challenges, we can harness the full benefits of topical probiotics for effective and targeted treatments for various skin conditions.

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