Review Article

Therapeutic Potential of Probiotics & Prebiotics in Dermatological Formulations

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ABSTRACT

The human skin microbiome is complex and diversified. Microbiota may contribute to healthy skin together with immune modulation and skin barrier function. The therapeutic efficacy of probiotics, prebiotics, and symbiotics—providing balanced skin microbiota to manage dermatological diseases—has been established by recent advances in dermatological science. Prebiotics, defined as non-digestible substrates that stimulate the growth of beneficial microbes, and probiotics, or live microorganisms, have been shown to assist with a range of skin ailments, including psoriasis, acne vulgaris, atopic dermatitis, and wound healing. Specific strains of *Lactobacillus, Bifidobacterium*, and *Bacillus* species have been found in clinical and experimental studies to improve hydration, elasticity, and barrier function and decrease inflammation and pathogenic colonization. Also, postbiotics are gaining popularity along with probiotics and prebiotics. Non-viable metabolites of probiotics, also referred to as postbiotics, can possess anti-inflammatory, antioxidant, and cosmetic effects. Technological advances in microbiome profiling can enable the development of dermatological products customized to each patient's microbiome for a tailored regimen. The need for standardization is also argued by the point that regulation of probiotic and prebiotic products used in cosmetics varies internationally, even though the encouraging statistics. The use of probiotics and prebiotics as effective, safe, and natural therapeutic treatment options for dermatological uses will continue to be enhanced by studies on strain specificity, dosage and stability, and general long-term safety.

Keywords: Probiotics, Prebiotics, Skin microbiome, Microbes, cosmetics.

INTRODUCTION

Prebiotics are defined as non-digestible food ingredients that positively alter the host by selectively stimulating the growth/power of one or a limited number of gut bacteria.[1] A prebiotic is currently defined as a substrate that is selectively utilised by host microorganisms conferring a health benefit.[2]

Probiotics are microorganisms that affect the health of their host in a positive way. The major purpose of probiotics is to change the strength of the immune system.[3]

Typically, the term skin of colour, also referred to as ethnic skin, characterizes the skin of people from African, Asian, Native American, Middle Eastern, and Hispanic backgrounds. Skin of colour type is usually considered Fitzpatrick types III to VI.[4] A characteristic biological feature for skin of colour individuals is the amount of cutaneous pigment, melanin, and the distribution of the pigment in the epidermis. The biosynthesis of melanin is conducted in the metabolic unit melanocyte, called the melanosome.[5,6]The melanocyte is an exocrine cell located in the basal layer of the epidermis and the matrix of the hair bulb. Neural crest melanoblasts migrate to the epidermis during embryonic development, at approximately week 18, and differentiate into the melanocyte.[7-9]

The human skin is stratified epithelium; the different tissue layers each extend specialized cell types that do different functions. It is generally divided into three layers the overlying epidermis, dermis and hypodermis (subcutis). In terms of divisions, the epidermis can also be further divided from outside-in, into the strata, the stratum corneum (horny layer), stratum granulosum (granular layer), stratum spinosum (prickle cell layer) and stratum basale (basal layer or stratum germinativum). The strata of stratum basale and stratum spinosum can also be called the Malpighian Layer. Additionally, in the areas of the body with thickened skin, like the palm and bottom of the foot, there will be a (generally) included layer called the stratum lucidum (clear layer). However, the stratum lucidum is often not considered an independent, individual epidermal layer, but rather the lower strata of stratum corneum. Along with these tissue layers, there is appendageal features including hair follicles and sweat ducts that go through one or more of the tissue layers.[10]

The main functions of skin, the epidermis, the outermost layer of skin, provides a waterproof barrier and contributes to skin tone. The dermis, found beneath the epidermis, contains connective tissue, hair follicles, blood vessels, lymphatic vessels, and sweat glands. The deeper subcutaneous tissue (hypodermis) is made of fat and connective tissue.[11]

The skin is the largest organ of the human body and is the interface with the environment. The skin is an extremely diverse community of microbes. Specifically, there are at least 1,000 species of bacteria, fungi, viruses, and other microbes on human skin. The overwhelming majority are either mostly harmless or beneficial to humans. Colonization of the skin can vary widely, based on endogenous host factors, topographic location, and exogenous environmental factors. These symbiotic microorganisms can occupy a wide variety of skin niches and provide protection against potential invasion from

more pathogenic or harmful microorganisms. For instance, *Bacillus subtilis* is one bacteria that offers protection to the skin. *Bacillus subtilis* produces bacitracin on the skin, which is a toxin it uses to compete and protect itself from other microbes. Since bacitracin has bactericidal properties, it has been harnessed and manufactured as an antibiotic for use in human medicine. Due to the interactions and effects that microorganisms have on colonization, skin microflora may play an important role in educating the billions of T cells (upregulating) of the potential for T cell responses to pathogens they have marked as identical. To sum up, skin microbiota, skin cells, connections, and both the innate and adaptive immune systems are important for the interfaces, establishment, and maintenance of skin as a barrier. The immune system is critical to recognize the resident skin microbiota from the pathogenic microorganisms while avoiding an inflammatory response which is key to commensal tolerance. The skin serves to protect from infection and pathogens by blocking invading organisms from entering through skin. The skin accomplishes this through it's three specialized layers; hypodermis, dermis, and epidermis. The epidermis is the outermost waterproof layer that consists of the stratum corneum (SC), stratum granulosum (SG), stratum spinosum (SS), and stratum basale (SB).[12-15]

PROBIOTICS AND PREBIOTICS:

Prebiotics: Certain types of dietary carbohydrates that are not digestible, but are fermentable, may promote the growth of specific bacterial species residing in the colon, such as bifidobacteria, lactobacilli and eubacteria, which are thought to be beneficial to the human host, and collectively these foodstuffs are referred to as prebiotics. Clinical short-chain carbohydrates (SCC) are also commonly called nondigestible oligosaccharides, or low-digestible carbohydrates (LDCs). These SCC or LDCs present interesting opportunities for incorporation into conventional food products because of their presumed "bifidogenic" properties and several such preparations are currently in development for food applications. Inulin and fructo-oligosaccharides are perhaps the most common used prebiotics.[16]

Probiotics: Vergio (1954) was probably the first to use the term "probiotic" in a scientific text when in his manuscript "Anti- und Probiotika" he contemplated detrimental effects of antimicrobials on the gut microbial population, contrasting as it was a comparison of "Probiotik" favourable to gut microflora. Lilly and Stillwell (1965), referred to probiotics as a "microorganisms which promote growth of other microorganisms". Current generally agreed definition of a "probiotic" is any viable microbes, which promote or support a favourable balance of the resident autochthonous microbial population of the GIT. Probiotics are live microorganisms that can confer health benefits when administered in adequate doses[16]. The most commonly used microorganisms are Lactobacillus, Bifidobacterium, Enterococcus, Propionibacterium, and some yeasts such as Saccharomyces boulardii. Their health benefits include the prevention of antibiotic-associated diarrhoea, treatment of irritable bowel syndrome, and inflammatory bowel disease.[17] Prebiotics are ingredients and substances that can promote the growth of certain bacteria in the gut. It is believed that an ingredient must possess three key features to be considered a prebiotic. [18]First, it should resist breakdown by mammalian enzymes and gastrointestinal absorption; second, it must be fermented by the microbiota of the intestine; and, last, it must be able to selectively stimulate the growth and/or activity of the intestinal bacteria, which have been associated with improving human health [19]

PROBIOTICS AND PREBIOTICS ON SKIN HEALTH

There are very few studies conducted with healthy subjects to evaluate the positive effects of probiotics on skin health.[20-24] One of the studies, using the H61 strain of L. lactis (in women aged middle-aged women (40 - 59), oral supplementation of *Lactococcus lactis H*, once a day, resulted in improvement in their skin elasticity and bodily characteristics (ie skin appeared to be more hydrated and hair follicles showed improvement) after eight weeks of continuous supplementation.[24] In another study, oral intake of *L. plantarum*; (HY7714) in subjects aged 41 - 59, also demonstrated the effects of supplementation with probiotics as there were significant increases in skin moisture levels as well as reduced depth of existing wrinkles and improvement overall glossiness and elasticity of their skin following supplementation with probiotics.[21] Additionally, other studies have suggested commercially available formulations containing probiotic and para-probiotic *L. reuteri*, taken orally and irrespective of topical concession, for at least 12 weeks demonstrated increased melanin and decreased levels of trans epidermal water loss (TEWL).[23] These effects are consistent with studies using other probiotics (e.g., L. rhamnoses, B. breve Strain Yakult, L. lactis, S. thermophilus) and prebiotics (e.g., galacto-oligosaccharides; GOS), which suggested (i) improved skin hydration levels and cathepsin-L-like activity levels (a marker of keratinocyte differentiation, as well as skin barrier function), and (ii) reduced urine and serum phenol levels (e.g., toxic byproducts of gut bacteria.)

PHARMACEUTICAL FORMULATIONS CONTAINING PROBIOTICS AND PREBIOTICS WITH ITS THERAPEUTIC APPLICATIONS

Atopic Dermatitis

Atopic dermatitis (AD) is a common condition. Recently, it has been demonstrated that the modified gut microbiome is implicated in AD. Probiotics and/or prebiotics have been employed in the management and prevention of AD to restore the altered gut microbiome. To date, meta-analyses reported some evidence to support probiotics for AD prevention, but effects are only observed when given both prenatally and postnatally. There is less supporting evidence for prebiotics and symbiotics for AD prevention or management due to conflicting findings. Explanations for the discrepancies in findings can relate to environmental

factors, probiotic/prebiotic factors, and host factors that can impact the efficacy of probiotic/prebiotic combinations. There is a need for additional studies to elucidate the mechanisms of action for probiotics/prebiotics while determining their true efficacy for preventing and treating AD.[25]

Acne

Acne vulgaris is a common skin disorder that affects a substantial portion of the world population, most often adolescents and younger adults. Standard therapies often limit the clinician due to side effects or antibiotic resistance. Probiotics may be able to inhibit the growth of acne-related bacteria while also modulating the immune response. Prebiotics can promote the growth of beneficial bacteria and balance the overall health of the microbiome. Postbiotics provide similar outcomes without the risk associated with live bacteria. Combining biotic strategies is a promising option for delivered therapies to standard care, and they may improve acne outcomes both qualitatively and quantitatively by addressing symptoms, as well as mechanisms related to the gut-skin axis.[26]

Psoriasis

Psoriasis is a long-term inflammatory skin disease with an autoimmune basis. Recent research has revealed associations between psoriasis, inflammation, and changes in gut microbiota, as well as benefits from probiotics and prebiotics in populations with psoriasis. This 12-week, open-label, single-centre clinical trial, evaluates the efficacy of probiotics (*Bacillus indicus* (HU36), *Bacillus subtilis* (HU58), *Bacillus coagulans* (SC208), *Bacillus licheniformis* (SL307), and *Bacillus clausii* (SC109)) and precision prebiotics (fructooligosaccharides, Xylooligosaccharides, and galactooligosaccharides), in patients with psoriasis that was also being treated with topical therapy. Potential metabolic, immune, and gut microbiota changes were evaluated for each of the study participants ($n=63). The first 42 patients that entered the study were assigned to the intervention and the next 21 were assigned to the control group (non-randomized, 2 to 1) ratio. There were between-group differences in some of the baseline patient characteristics including age; disease severity of psoriasis (greater in the intervention vs the control), nail psoriasis, and psoriatic arthritis, though it is unclear how or if any of the differences may impact the results of clinical trials. Patients with psoriasis receiving anti-psoriatic local therapy and probiotic and prebiotic supplementation performed better in measures of disease activity, including Psoriasis Area and Severity Index, Dermatology Life Quality Index, inflammatory markers, and skin thickness compared with those not receiving supplementation.[27]

Wound healing

Lactiplantibacillus plantarum cells were encapsulated in a mixture of cationic and anionic polymers, with the final composition stabilized through freeze-drying. A D-optimal design was used to examine the effects of different polymer concentrations as well as adding prebiotics on the probiotic viability and swelling behaviour of the formulations. Scanning electron micrographs revealed stacked particles capable of rapidly absorbing significant amounts of water. These images corresponded to initial swelling percentages of around 2000% for the optimal formulation. The optimized formula had a viability percentage of more than 82%, with the stability studies suggesting that the powders should be stored at refrigerated temperatures. The physical characteristics of the optimized formula were examined to ensure compatibility with its application. According to antimicrobial evaluations, the difference in pathogen inhibition between formulated and fresh probiotics was less than a logarithm. The final formula was tested *in vivo* and showed improved wound healing indicators. The optimized formula resulted in a higher rate of wound closure and infection clearance. Furthermore, the molecular studies for oxidative stress indicated that the formula could modify wound inflammatory responses.[28]

RECENT ADVANCEMENTS AND FUTURE TRENDS IN THERAPEUTIC POTENTIAL OF PROBIOTICS & PREBIOTICS IN DERMATOLOGICAL FORMULATIONS

Research indicates that both oral and topical probiotics (certain strains of Lactobacillus and Bifidobacterium) reduce the frequency and severity of atopic dermatitis (AD) in children. Topical formulations with Lactobacillus plantarum have even shown to improve skin barrier function, reduce the quantity of pathogenic bacteria (such as Staphylococcus aureus) and reduce inflammation.[29]

Postbiotics (non-viable microbial cells and/or their metabolites) are drawing attention as they may offer many benefits of probiotics -- anti-inflammatory and anti-oxidative activities, while being even safer and more cosmetic-compatible due to their more stable nature. Prebiotics (e.g. Inulin, oat beta-glucan, alpha-glucan oligosaccharide) are another option to promote healthy bacteria growth on the skin, by serving a food source for these beneficial bacteria. Prebiotics promote a healthy skin barrier while promoting an unfavourable environment for unwanted pathogens.[30]

Advancements in sequencing the skin microbiome genome, will lead to personalization for skin care. It may become the case that dermatologists will assess a patient's particular skin microbiome, and provide them with a formulation of the appropriate probiotics and/or pre/probiotic strains based on that assessment. Further, there will be many more symbiotic products that contain both probiotics and prebiotics for the purpose of delivering a synergistic effect. Furthermore, there is a move towards live biotherapeutic products (LBPs) and next-generation probiotics that are defined as specific live bacteria developed to essentially treat disease and not prescribe simply for general health supplements.[31]

REGULATORY REQUIRMENTS OF PREBIOTICS AND PROBIOTICS IN DERMATOLOGICAL FORMULATIONS

A key challenge is telling the difference between a cosmetic and a drug, and this varies depending on the country. The rules for products with prebiotics and probiotics are still being developed, and there's no official, worldwide list of terms for personal care products yet. That said, some standard definitions and categories have started to be used. The International Cooperation on Cosmetic Regulation (ICCR) sees prebiotics as living or "sleeping" microorganisms added to beauty products. Their job is to make your skin look and feel better, either by working directly on the skin itself or by helping out the friendly bacteria that are already living there. Prebiotics are ingredients that feed the beneficial bacteria on your skin. They help these good microbes thrive, which in turn helps improve the look and feel of your skin. Navigating the rules for skin care with good bacteria can be tricky, especially with different standards around the world.[32,33]

Claims and Promises

The way of talking about a product is super important and heavily regulated. There's a big difference between what a cosmetic can claim and what a medicine can. A cosmetic can only promise things that relate to cleaning, protecting, or improving the look of your skin. Think "supports a healthy skin balance" or "promotes glowing skin. You can't say a product "cures" or "treats" a disease like eczema or acne. That would make it a drug, which has a completely different set of rule. All the promises you make about a product must be backed by solid scientific research and evidence.[34]

Quality Control

Making products with live bacteria requires extra care to ensure they are both effective and safe. Companies must follow strict manufacturing guidelines to ensure product quality. The good bacteria need to be handled and stored in a special way to keep them alive and effective. For products with live bacteria, companies often have to prove that the bacteria are still active and working when you use the product.[35]

Global Differences

The rules change depending on where you are. They have very specific rules about what a cosmetic is and what it can claim. Here, it's all about how you market the product. If your claims sound like medicine, it will be regulated as a drug. Countries like Korea have their own unique regulations, including bans on using live bacteria in cosmetic products.[36]

CONCLUSION

The increased application of probiotics, prebiotics, and symbiotics as preventative or remedial interventions for skin well-being is recognized in the article. Prebiotics are non-digestible carbohydrates that promote the development of beneficial bacteria. Probiotics are live microorganisms with possible health benefits, including immune system modulation, microbiome balance, and maintenance of barrier function. Probiotics and prebiotics act symbiotically to affect the cutaneous microbiota and the gut-skin axis. Dysbiosis is linked with several dermatological conditions. The skin harbors a complex microbial community that interacts with barrier function and immune response. Probiotics and/or prebiotics could assist in treating atopic dermatitis, acne, psoriasis, and wound healing. They also have correlations with enhanced skin hydration, elasticity, barrier function, and inflammation decrease, based on both experimental and clinical evidence. The recent advancements in this field are dermatological products derived from microbiome profiling, symbiotics (a synergistic combination of probiotics and prebiotics), and postbiotics (the bioactive metabolites of a non-viable microbe, which might possess anti-inflammatory and antioxidant functions). There are also advancements in next-generation probiotic development for therapeutic products and live biotherapeutics products (LBPs). In dermatology, prebiotics and probiotics hold vast potential for cosmetics and treatment, helping create safer and more natural forms of conventional or supplementary medications. They constitute a fascinating potential component for future skin care and clinical products because they possess unique capabilities to modify the microbiota, barrier function of the skin, decrease pathogenic colonization, and modify immunological reactions. Even with promising outcomes, more meticulously designed clinical trials with optimum strain, dose, formulation, and safety dose studies are needed. Individualized microbiome-directed therapies and symbiotic or stable postbiotic products are future possibilities that may transform skin disease therapy.

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