Review article

Microbiome manipulation – the future of inflammatory skin disease treatment?

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Abstract

The manipulation of the human microbiome presents a transformative frontier in addressing prevalent dermatological conditions, like acne and atopic dermatitis. Strategies for skin and gut microbiome modification, such as microbiome transplantation and oral or topical application of probiotics, prebiotics, and postbiotics, offer promising solutions for different skin disorders. Bacteriophages, viruses that target bacteria, also provide an alternative microbiome manipulation platform. However, despite the promising initial results, further investigation is essential to unravel the underlying mechanisms, assess efficacy, and ensure safety across diverse populations, as the interplay between microbial communities and skin health is very complex. In the transformative era of microbiome manipulation techniques it is important to ensure that these are applied beyond the realms of scientific exploration and benefit the global advancement of skin health. The aim of this review is to capture the increasing volume of research in this field that reflects a growing interest and dedication to advancing our understanding of microbiome manipulation techniques with the potential applications in dermatology. It represents an overview of the possibilities of treating the skin diseases via microbiome modulation are discussed, focusing on two of the most common inflammatory skin diseases of today: acne and atopic dermatitis.

Keywords

microbiome; skin diseases; biotechnology; dermatology; acne; atopic dermatitis

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Manipulacija mikrobioma – prihodnost zdravljenja kožnih bolezni?

Izvleček

Manipulacija človeškega mikrobioma predstavlja izjemen potencial za zdravljenje pogostih dermatoloških stanj, kot so akne in atopijski dermatitis. Strategije manipuliranja kožnega in črevesnega mikrobioma vključujejo transplantacijo mikrobioma, peroralno ali topično uporabo probiotikov, prebiotikov in postbiotikov ter manipulacijo kožnega ali prebavnega mikrobioma z uporabo bakteriofagov. Začetne raziskave, v katerih so omenjene strategije uporabili za zdravljenje nekaterih pogostejših kožnih bolezni so pokazale obetavne rezultate. Naraščajoč obseg raziskav na tem področju pa odraža željo po napredku razumevanja in uporabe tehnik manipulacije mikrobioma v dermatologiji. Ker so interakcije med mikrobioto in kožo zelo kompleksne, je za čim uspešnejši prenos novih znanj v prakso nujno dobro poznavanje tako osnovnih mehanizmov v ozadju teh interakcij, kot ocene učinkovitosti zdravljenja ter zagotavljanje varnosti tovrstnih posegov pri različnih populacijah. Ključno je, da najnovejše informacije in odkritja s tega področja preidejo okvirje znanstvenega raziskovanja in s prenosom spoznanj v prakso lahko pripomorejo h globalnemu izboljšanju zdravja kože. V objavi povzemamo najnovejše raziskave na področju povezav med človeškim mikrobiomom in kože, s poudarkom na potencialih novih pristopih zdravljenja atopijskega dermatitisa in aken z manipulacijo mikrobioma kože in prebavil.

Ključne besede

mikrobiom; kožne bolezni; biotehnologija; dermatologija; akne; atopijski dermatitis

Introduction

Skin is the largest organ of the human body. It consists of three main layers – the epidermis, dermis, and subcutaneous tissue, with all three layers being prone to various skin conditions. It serves several important functions, the most important being its defensive role as it acts as a physical barrier between the external environment and the interior of the human body, protecting against the intrusion of microorganisms, ultraviolet (UV) radiation, mechanical, and chemical injuries, among others (Boer et al., 2016; Marks & Miller, 2019).

According to recent estimates, the human body is inhabited by approximately 3.8×10^{13} microorganisms (Sender et al., 2016), which are importantly contributing to the maintenance of our health and homeostasis. The concept of the human microbiome encompasses the entire population of microorganisms residing on or in the human body. They are found in various areas of the body, with the highest concentrations present in the digestive tract, nose, genitals and on the skin. Disruption of the microbial population balance, resulting from genetic or environmental factors, can lead to various health conditions, including skin-related issues (Ellis et al., 2019). This implies that reestablishment of the microbiome homeostasis via modulation strategies could potentially contribute to the treatment of various skin diseases (Yang et al., 2022).

There are more than 3,000 known skin diseases, varying in symptoms and the severity of the condition. They rank fourth on the list of the most common human diseases. At least one-third of the global population is estimated to be affected by at least one skin condition (Karimkhani et al., 2017). Tizek et al. (2019) conducted a study at the Bavarian Central Agricultural Festival to explore the prevalence of skin diseases among individuals outside medical facilities, who usually never seek medical attention for certain conditions. Random passers-by were examined for potential skin disorders. Out of a total of 2,701 individuals, at least one skin condition was detected in 64.5% of people. Two-thirds of the participants were unaware of the identified skin abnormalities. The results indicate that the prevalence of skin diseases may be much higher than commonly perceived. Although a smaller percentage of skin diseases leads to fatal outcomes, they still represent a significant health and economic burden. This includes physical, psychological, and socio-economic

consequences that affect both the patient and their family, ultimately impacting the healthcare system as well (Ahmed et al., 2016; Karimkhani et al., 2017; Seth et al., 2017). Most illnesses cause physical discomfort and deteriorate the quality of life for patients, subsequently affecting the psychological and social aspects of their lives. Patients often develop negative emotions such as shame and embarrassment, impacting both personal and professional relationships. The combination of these factors can lead to depression and even suicide (Ahmed et al., 2016; Karimkhani et al., 2017; Seth et al., 2017). In a study including 1510 participants, Yew et al. (2020) concluded that individuals with skin diseases more frequently experienced symptoms of depression, social isolation, loneliness – all accumulating to a lower quality of life. The socio-economic consequences include lost opportunities in professional life (indirect costs) and costs to the healthcare system (direct costs). For the year 2013 alone, in the United States, direct costs associated with skin diseases were estimated at $75 billion (including office visits and procedures, medications, vaccines, and other specific treatment-related procedures), and indirect costs at $11 billion (Lim et al., 2017). In addition to the widespread occurrence of skin diseases, the high costs of treatment are also attributed to the fact that these conditions often manifest as chronic and prolonged illnesses. Besides the prolonged and sometime unsuccessful treatments of common inflammatory skin conditions that may also result in unfavourable reactions to the traditional medications, the emergence of bacterial resistance to antibiotic therapies also represents a significant future challenge justifying the urge to search for novel treatment approaches.

Human microbiome-skin connection

The skin represents a habitat of millions of bacteria, fungi, and viruses that make up its microbiota. Cutaneous microorganisms play a crucial role in protecting the body against the invasion of pathogens and shaping our immune system. As the largest organ in the human body, healthy skin is colonized by trillions of microorganisms and serves as a physical barrier to prevent the entry of pathogens. When skin barrier is compromised or when the balance between commensals (harmless microorganisms) and pathogens is disrupted, the development of skin (or even systemic) diseases may occur (Grice & Segre, 2011; Zeeuwen et al., 2013; Oh et al., 2016). The skin microbiome is influenced by individual factors such as genotype, gender, age, lifestyle, as well as potential use of antibiotics and various cosmetic products. Furthermore, the diversity and location of microorganisms on the skin are influenced by environmental factors such as pH, moisture, sebum content, and the salinity of specific skin areas. Each of the skin areas with the specific microenvironment is populated by its own microbial community. *Propionibacterium*, *Corynebacterium* and *Staphylococcus* represent the three most dominant microbe genera in the skin microbiome, each importantly contributing to human health (Yang et al., 2022).

In sebum-rich areas of the skin, such as the face, back, etc., typically lipolytic species like *Cutibacterium acnes* (formerly *Propionibacterium acnes*) prevail (Zeeuwen et al., 2013; Lee et al., 2019). These species thrive in such environments due to their ability to degrade sebum produced by the sebaceous glands, which is facilitated by the extracellular lipolytic enzymes. The released fatty acids as a substrate for fermentation not only to the producing species but also for some other surrounding bacteria (Mayslich et al., 2021). In the areas rich with sebaceous glands, lipophilic commensal representatives of fungi are also found, such as *Malassezia restricta*, *M. globosa*, and *M. sympodialis*. These fungal species are present in the areas of the skin with different moisture contents, covering the entire surface. The greatest diversity of fungal species has been described on the feet surface (Zeeuwen et al., 2013; Jo et al., 2016; Byrd et al., 2018). Besides *Malassezia* species, also *Cryptococcus*, *Rhodotorula* and *Candida* species have been identified as skin commensals (Boxberger et al., 2021).

In addition to bacteria, *Archaea* belonging to *Thaumarchaeota* and *Euryarchaeota* were also shown to be a part of human skin microbiome. Analysis of *Thaumarchaeota* detected on human skin, placed them close to ammonia-oxidizing archaea from the soil. Although it remains to be proven, the role of these archaea could be explained by chemolithotroph ammonia turnover, which may influence the pH regulation of the human skin, natural protective barrier of the body (Moissl-Eichinger et al. 2017; Boxberger et al., 2021)

In addition to bacterial, archaeal and fungal communities; viruses, predominantly bacteriophages, also inhabit

skin surfaces. The latter are believed to regulate bacterial populations through their lytic activity, contributing to the maintenance of skin homeostasis (Boxberger et al., 2021). Metagenomic analysis has shown that the prevalent skin phages inhabit genera *Cutibacterium* and *Staphylococcus* (Liu et al., 2015). Other viruses were also identified (*Densovirus*, *Alphapapillomavirus*, *Human papillomavirus*, *Merkel cell polyomavirus*, *Molluscum contagiosum virus* etc.) and some of them were already linked to certain skin conditions (Boxberger et al., 2021).

Furthermore, increasing number of studies reveal strong connection between the skin conditions and gut microbiome. Significant differences in the composition of stool microbiota between individuals with acne and healthy controls were identified (Deng et al., 2018). In contrast to the healthy control group, acne patients exhibit reduced diversity in gut microbiota and an elevated ratio of *Bacteroidetes* to *Firmicutes*, which is associated with the western diet and other inflammatory diseases. This also implies the influence of the western diet on the onset of acne vulgaris, highlighting the potential for dietary adjustments and probiotic-based interventions in both preventing and managing this skin condition (Deng et al., 2018).

Both, the skin as well as gut microbiomes control the colonization of potentially pathogenic microorganisms, regulate the immune response, and are essential for the optimal functioning of the immune system. This suggests that maintaining balance within these communities if crucial for our health (Grice & Segre, 2011; Zeeuwen et al., 2013).

Skin microbiome manipulation by microbiome transplantation, probiotics, prebiotics and postbiotics

Manipulation of the skin microbiome opens new possibilities for the therapy of skin diseases and can be achieved in various ways (Arora et al., 2023). One of the potential approaches is the transplantation of the skin microbiome, which involves the application of skin microbiome from a healthy individual to the affected skin pre-treated by antiseptic agent. Although this method has the advantage of obtaining microorganisms from the natural environment, it has not been proven entirely reliable. Furthermore, only a limited number of bacteria can be obtained from the skin and the method is not suitable for serial use (requires suitable donors, can only be performed in an outpatient setting). Additionally, there is a risk of transferring pathogenic microorganisms to an already weakened microbiome, potentially causing more harm than benefit (Callewaert et al., 2021).

The skin microbiome can also be altered by applying probiotics, prebiotics, or postbiotics to restore the microbial balance on affected skin (Callewaert et al., 2021). Probiotics are live microorganisms that, in appropriate concentrations, provide beneficial effects to the host (e.g., traditionally bacteria belonging to the *Bifidobacterium* and *Lactobacillus* species). On the other hand, postbiotics are formulations of non-viable microorganisms or their structures or metabolic by-products that also contribute to maintaining host homeostasis (e.g., peptides, enzymes, vitamins) (Vallianou et al., 2020; Salminen et al., 2021). Prebiotics are substrates that stimulate the growth of specific health-promoting microorganisms (e.g., inulin and galacto-oligosaccharides). In contrast to skin microbiome transplantation, the production and use of such preparations is easier and more widely applicable (Arora et al., 2023). Another advantage of this approach lies in the possibility of using concentrated preparations, theoretically enhancing the effectiveness of therapy (Callewaert et al., 2021). Topically applied probiotics act through competition for binding sites, thereby preventing the colonization of potential pathogens (Lopes et al., 2017). However, the use of probiotics and postbiotics also has its limitations. The environment rich in sebum may be unfavourable for some probiotic bacteria which may not properly adapt to it. Moreover, the use of high concentrations of bacteria, their components, or products can induce an immune reaction and skin irritation (Callewaert et al., 2021).

The advantage of skin prebiotics is that they do not contain living microorganisms or their components, reducing the likelihood of skin immune reactions. Additionally, they are typically well-defined compounds with well predicted potential side effects. However, as an indirect method of microbiome modifications, this method may result in less obvious effects compared to therapies with probiotics or postbiotics. In addition, prebiotics may also stimulate non-target bacteria, leading to unpredictable effects on the skin microbiome, physiology, and immune response in different individuals (Callewaert et al., 2021).

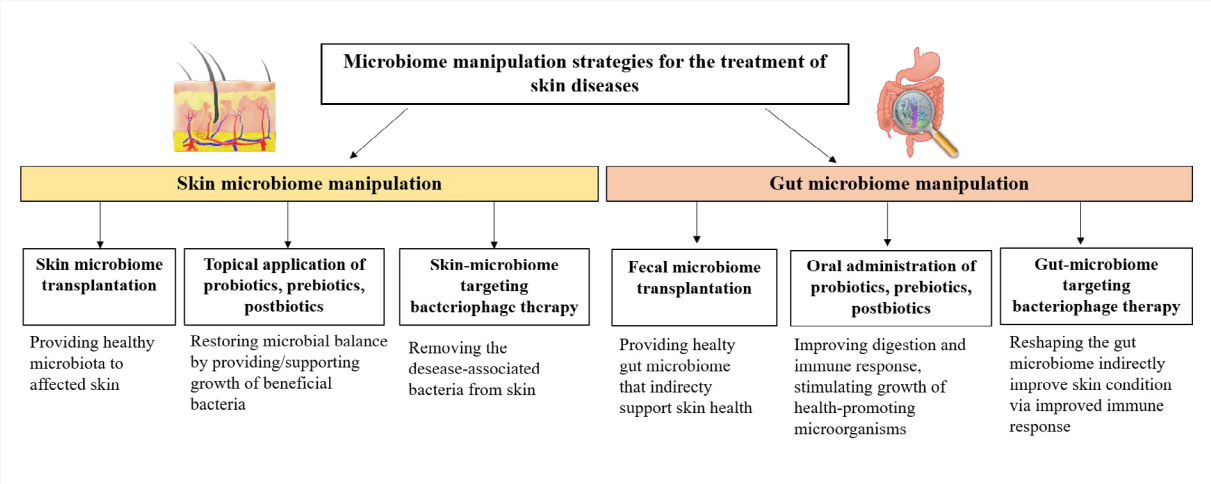

Figure 1. Overview of the microbiome manipulation strategies potentially applicable in inflammatory skin disease treatment.

Slika 1. Pregled strategij manipulacij človeškega mikrobioma s potencialom za zdravljenje vnetnih kožnih bolezni.

Skin microbiome manipulation in the treatment of acne

Acne represent the most common inflammatory skin disorder in the Western world, affecting approximately 85 % of the population, primarily adolescents (Yang et al., 2022). It is a multifactorial disease of the pilosebaceous unit (a unit composed of the hair follicle and sebaceous gland), influenced by both genetic and environmental factors (microbiome composition, hormonal and immune status of the individual, sebum production, diet, genetics, etc.) (De Pessemier et al., 2021). The condition is typically presented by open and closed comedones, red pustules, and yellowish papules, as well as inflamed nodules below or above the skin surface. Severe cases may lead to chronic scarring. Post-inflammatory hyperpigmentation can also be observed on the skin (Ayer & Burrows, 2006).

It is presumed that the skin commensal bacterium *Cutibacterium acnes* plays a significant role in the disease, with certain strains mediating the inflammatory response and leading to the formation of acne lesions (Gollnick et al., 2003). *C. acnes* is a Gram-positive, aerotolerant bacterium that is part of the skin microbiome. It thrives in lipid-rich environments, and it is often found in areas of the skin with the highest density of pilosebaceous units (face, neck, back, chest) (Spittaels et al., 2020). Discerning between strains that confer benefits to human health by inhibiting pathogen growth and those that pose a threat presents a substantial challenge, but also opens avenues for novel treatment strategies (O'Neill & Gallo, 2018). Further exploration of the intricate interplay between *C. acnes* strains and their impact on the skin microbiome holds promise for advancing our understanding of acne etiology and developing targeted therapeutic interventions.

The main therapeutic approach for treating acne currently relies on antibiotics, which may have side effects, and their excessive use raises concerns about the alarming spread of bacterial resistance. Moreover, the therapy is often unsuccessful, or the condition recurs after the end of the treatment. There is a need for the development of new therapeutics that are both safer and more effective (Newman et al., 2011).

In the study of Paetzold et al. (2019) microbiome samples from two healthy individuals were transplanted to individuals with acne. After three consecutive days of applications (once daily), the recipient's microbiome became more similar to that of the donor. It was revealed that the result of the transplantation reflected the composition of individuals' microbiomes (both recipients and donors) as well as the quantity and concentration of the bacteria used. This study demonstrated the potential use of live bacteria to regulate the composition of the skin microbiome (Paetzold et al., 2019).

Karoglan et al. (2019) tested the hypothesis that the application of *C. acnes* strains that are not associated with acne could positively impact the skin microbiome and

thereby contribute to a reduction in the extent of acne. They initially treated the skin with benzoyl peroxide for 7 days to significantly reduce the skin microbiota which was followed by application of a bacterial mixture of two (type C3 and K8, 50% each) or four live strains (C3, K8, A5, and F4, each contributing in varying proportions) with a total combined concentration of 10^6 colony-forming units per gram of *C. acnes* twice per day for 5 consecutive weeks. No adverse effects, visible irritation, or inflammation were observed. The number of comedones decreased. However, they did not detect any difference in the use of mixtures containing two or four strains (Karoglan et al., 2019). These findings inspired a Belgian company S-Biomedic to further develop products based on these probiotic mixtures, leading to the launch of their first product, Sencyr—a probiotic cream for acne treatment (S-Biomedic, n.d.).

A study performed by Lebeer et al. (2022) demonstrated the use of topical probiotics for acne treatment with lactobacilli. Selected strains (*Lacticaseibacillus rhamnosus* GG, *L. plantarum* WCFS1 and *Lactiplantibacillus pentosus* KCA1) were applied as a cream twice daily on the skin of volunteers with mild or moderate acne for eight consecutive weeks with a minimal dose of 10^6 colony forming units per application. The therapy successfully reduced inflammatory lesions on the participants' skin. A change in the composition of the skin microbiome with a decrease in the relative abundance of staphylococci was also observed. Even after individuals stopped using the cream, the reduction in acne persisted for several weeks, indicating that lactobacilli partially act by modulating the immune system (Lebeer et al., 2022).

In a recent study, the the efficacy of a fermentation lysate of *Lactiplantibacillus plantarum* VHProbi® V22 in ameliorating acne was tested by aplying the anti-acne skincare cream containing fermentation culture lysate o subjects with mild-to-moderate acne vulgaris for 4 weeks. Significant improvements in the acne lesion proportion ($P < 0.01$), transepidermal water loss ($P < 0.001$), and sebum secretion ($P < 0.05$) were observed in comparison to the baseline in the subjects, suggesting the treatment as a complementary option to the treatment of the above-mentioned conditions (Cui et al., 2022). Furthermore, a post-biotic containing heat-treated *Pediococcus acidilactici* LM1013 previously isolated from the Korean traditional fermented alcoholic beverage-makgeolli, has recently been demonstrated as effective *C. acnes* inhibitor (Bae et al., 2023).

Skin microbiome manipulation in atopic dermatitis

Atopic dermatitis (AD) is increasingly common inflammatory skin disease affecting around 34% of the world population. It occurs in all age groups, with the highest prevalence among younger children (Hadi et al., 2021). The disease is characterized by dysfunction of the skin barrier, chronic inflammation, and microbial imbalance on the skin. The development of the condition is significantly influenced by an individual's genetics and the environment (Leung & Guttman-Yassky, 2014). It is often associated with food allergies and asthma as the compromised skin barrier in AD patients allows the absorption of allergens from the environment through the skin, promoting systemic hypersensitivity to allergens, predisposing individuals to the development of food allergies and asthma (Brough et al., 2015).

The damaged skin of AD patients is typically associated with low bacterial diversity. An increased proportion of *Staphylococcus aureus* and *Staphylococcus epidermidis* has been found, while the proportion of other common skin commensals (such as *Cutibacterium*, *Corynebacterium*, *Streptococcus*, *Acinetobacter*, *Prevotella* and *Malassezia*) was found to be reduced (Kong et al., 2012). In healthy individuals, *S. aureus* is rarely detected on the skin (Guzik et al., 2005), while in AD patients, the density of skin colonization with *S. aureus* is strongly associated with the severity of the condition. The distribution over the body surface has also been shown to be linked to the distribution of dermatitis (e.g., on the face and limbs) (Tauber et al., 2016; Kennedy et al., 2017; Iwamoto et al., 2019).

Currently, the treatment of atopic dermatitis (AD) is based on the use of immune response inhibitors—corticosteroids and systemic immunosuppressants, which can cause severe side effects (Newsom et al., 2020). Prolonged use may lead to skin atrophy and disruption of the skin barrier function, resulting in increased water loss, reduced hydration levels, and increased skin transparency. The severity of these side effects depends on the strength, duration, and dosage of the treatment, as well as the morphological characteristics of the skin in different anatomical areas (Atherton, 2003).

Myles et al. (2016) investigated the impact of exposing the skin to various strains of Gram-negative bacteria belonging to *Roseomonas mucosa* and P*seudomonas aeruginosa* species, to improve the condition of atopic dermatitis (AD).

Strains of both species, isolated from the skin of healthy individuals demonstrated the ability to inhibit the growth of *S. aureus* in *in vitro* cell cultures. The effectiveness was also tested *in vivo* using mouse models of AD. They induced dermatitis similar to AD on the ears by applying a vitamin D analogue MC903, and then applied selected isolates of *R. mucosa* and *P. aeruginosa* to the skin once per day for three consecutive days. In mice treated with *R. mucosa* isolates, visible reduction in redness occurred and no observed side effects. On the other hand, applying *P. aeruginosa* isolates did not lead to improvement in the skin condition (Myles et al. 2016).

These findings led to a smaller clinical study testing the therapeutic capabilities of *R. mucosa* isolates. The study involved 10 adults with atopic dermatitis (AD) who applied the formulation twice a week for six consecutive weeks to any area of the body. No adverse effects or complications were recorded during the treatment, while visibly reduced redness was observed. Participants also reported reduced itching and a decreased need for corticosteroid use. Because the therapy proved to be safe, the study included five younger patients, aged nine to fourteen, who applied the formulation twice a week for 16 consecutive weeks. Similar results were reported, including visibly reduced redness, decreased itching, and a reduced need for corticosteroids. The results suggest that *R. mucosa* alleviates AD symptoms and could potentially represent a form of therapy in the future (Myles et al., 2018).

Keratinocytes contribute to defence against pathogens by secreting antimicrobial peptides. It is presumed that their deficiency is associated with a loss of protection against the spread of *S. aureus* on the skin (Howell et al., 2006). Nakatsuji et al. (2017) demonstrated that commensal bacteria of the skin microbiome, *Staphylococcus hominis*, provide selective protection against S. aureus by secreting lantibiotics, a type of antimicrobial peptides. Isolated strains were multiplied and applied to patients' skin. While they did not measure clinical improvement in symptoms, they detected a reduced level of *S. aureus* colonization, demonstrating the role of these commensal bacteria in providing protection against pathogens and preventing the dysbiosis of the skin microbiome than can lead to the development of a diseased condition (Nakatsuji et al, 2017). These findings led to the establishment of MatriSys Bioscience, with the goal of obtaining a single strain to be sold as a probiotic formulation for alleviating dermatitis symptoms (MatriSys Bioscience, n.d.).

Bacteriophage-assisted skin microbiome manipulation

Bacteriophages are viruses that infect bacteria, taking over their host and using it for reproduction. A bacteriophage can recognize, infect, and kill a specific type or even a particular strain of bacteria. Consequently, they play a crucial role in regulating bacterial populations (Palaniappan & Dayanithi, 2021). They can only multiply within host cells, making them active only at the site of infection where pathogenic bacteria are present (Abedon et al., 2011).

The excessive use of antibiotics in treating various diseases and in intensive livestock farming has led to the emergence of antibiotic resistance. The problem is further exacerbated by the lack of newly discovered antibiotic agents (Ventola, 2015). This is particularly significant in the treatment of skin diseases where antibiotics are frequently prescribed. The use of bacteriophages and phage cocktails in treating various diseases appears as a promising alternative to antibiotic treatment or, at the very least, a supportive therapy to existing treatment methods (Palaniappan & Dayanithi, 2021).

Bacteriophages exhibit the following advantageous characteristics: 1) they attack both Gram-positive as well Gram-negative bacteria, 2) they are highly specific to individual species and even strains of bacteria; 3) due to different mechanisms of action compared to antibiotics, they also act on antibiotic-resistant bacteria, 4) after infection, they replicate only locally and do not affect the rest of the microbial population, 5) their properties can be enhanced via genetic engineering; 6) identification, isolation, and production of bacteriophages for therapeutic purposes is cheaper than developing new antibiotic agents, 7) they have the ability to mutate (adapt) to the altered host characteristics, 8) resistance of bacteria to individual bacteriophages can be avoided by using bacteriophage cocktails, and 9) they are considered safe and do not induce unwanted side effects (Palaniappan & Dayanithi, 2021). Currently, bacteriophage therapy is only applied when all other forms of treatment have been exhausted (Palaniappan & Dayanithi, 2021). The limitations of bacteriophage treatment include an incomplete understanding of the phage life cycle and the potential for transduction of pathogenic genes. Optimal dosages, methods, and frequency of applications, as well as the duration of treatment and short-/ long-term effects for each therapy, need to be determined. There is currently

a lack of standardized guidelines for bacteriophage preparations manufacturing (Castillo et al., 2018).

The prolonged and excessive use of both topical and oral antibiotics in the treatment of acne has led to a significant resistance of *C. acnes* strains to antibiotics (Walsh et al., 2016). As a result, treatment is becoming less effective, and resistance to available antibiotics is one of the main reasons for treatment failure. Alternative approaches that reduce the presence of pathogens while not harming commensals are therefore necessary (Golembo et al., 2022). Bacteriophage therapy could potentially replace or complement current approaches to acne treatment. Golembo et al. (2022) identified and characterized 21 *C. acnes* bacteriophages. Three of them were used to prepare a phage cocktail. The cocktail was first tested on an *ex vivo* skin model of the epidermis to assess its infectivity upon topical application and the safety of the preparation. The product proved to be safe at all concentrations (100x, 10x and 1x fold concentrations of the maximal intended dose for human exposure and compared to tissues exposed to negative control; specific information on concentrations was not revealed) as no inflammation was detected. The results from the skin model experiment were sufficient for the next step, a clinical study, and animal model studies were deemed unnecessary.

Furthermore, the clinical study involved 75 participants with mild to moderate acne, divided into three groups. Each group applied the preparation once a day for four weeks. The first group applied the higher concentration, the second the lower concentration (a 2 log10 lower dose than the high concentration), and the third applied the same formulation but without bacteriophages (negative control). Cheek skin swabs underwent processing for bacterial DNA extraction and were subject to analysis through specific quantitative PCR (qPCR) targeting *Cutibacterium* spp. This aimed to assess the absolute quantity of this bacterium and its alteration from the baseline, relative to the vehicle, following the application of BX001. Only the first group, compared to the third, showed a significant reduction in the presence of the *C. acnes* bacterium one week after the last application (up to 24 %), indicating that a higher concentration is needed to achieve the results. Despite a month of daily application of the preparation, no development of bacterial resistance was observed. Additionally, there were no severe side effects, and any reported effects were similar to those in the control group, confirming the safety of the preparation (Golembo et al., 2022).

Shimamori et al. (2021) proposed and investigated the possibility of bacteriophage therapy as a potential strategy for treatment of atopic dermatitis without affecting the rest of the skin microbiome. An atopic mouse model was used to examine whether the *S. aureus* SaGU1 bacteriophage could be used as a tool to prevent disease exacerbation. Application of SaGU1 to the mouse's back skin reduced the concentration of *S. aureus* and improved the disease condition. The results suggest that treatment using the bacteriophage SaGU1 could be a promising clinical approach for atopic dermatitis (Shimamori et al., 2021).

Gut microbiome manipulation and inflammatory skin conditions

The gastrointestinal tract microbiome is a dynamic ecosystem influenced by various factors (including diet, genetics, and medical interventions), originating from the host or the host's environment. A healthy microbiome contributes to host health and colonization resistance by training the host immune system, nutrient sequestration, antimicrobial compound production and competition for binding sites with pathogens. Not only microorganisms but also different microbial compounds (vitamins) and metabolic products play an important role in the interaction of the microbiome with the immune system. Any sort of changes in the gut microbiome composition can potentially lead to some sort of inflammation, which manifest on the skin as well (McCuaig & Goto, 2023). Several therapeutic strategies therefore strive to improve the well-being of the gut microbiome and fortify its ability to remain in balance, indirectly contributing to skin health as well.

Gut microbiome may be manipulated via oral administration of probiotics, which are essentially microorganism formulations proven as efficient and harmless to humans (Rusu et al., 2019). In the context of both atopic dermatitis and acne, several studies have been conducted, mostly demonstrating positive effects of adjunctive therapy with probiotics in improving digestion, immune response, and other beneficial effects on the gastrointestinal tract and skin (Roessler et al., 2008; Yoshida et al., 2010; Drago et al., 2011; Thompson et al., 2020). Adjunctive probiotic therapy has proved even more important in the treatment of acne by antibiotics. Although the antimicrobial properties of anti-

biotics provide significant health benefits, their non-specificity strongly influences the composition and functioning of the microbiome, especially the gut (Mahmud et al, 2022). Disturbances in the balance and reduced diversity of the gut microbiota composition can subsequently lead to various health conditions, including skin-related issues (Forssten et al., 2014).

Results of an open-label study, aimed to investigate the efficacy of probiotics in mitigating the side effects associated with systemic antibiotics and their synergistic impact in treating inflammatory acne, showed some promising results. Forty-five females aged between 18 and 35 years were randomly assigned to three groups. Group A received probiotic supplementation, group B received the antibiotic alone (minocycline), and group C received both probiotics and the antibiotic. The probiotic product used in this study contained a combination of *Lactobacillus acidophilus* (5 billion CFU/capsule), *Lactobacillus delbrueckii* subspecies *bulgaricus* (5 billion CFU/capsule), and *Bifidobacterium bifidum* (20 billion CFU/capsule), encapsulated within an oil matrix in a two-piece hard gel capsule. Those in the probiotic group took capsules in the morning and evening, while the minocycline group took the antibiotic once after dinner. All three groups also used standard topical acne medication and a facial cleanser, following the same regimen throughout the 12-week study, with additional acne treatments prohibited. Over the 12-week study period, all groups showed a significant improvement in total lesion count, with group C exhibiting a notably greater reduction at the 8- and 12-week follow-up visits compared to groups A and B. The findings suggest that probiotics, when used in conjunction with systemic antibiotics, may offer a promising therapeutic approach for acne vulgaris by providing a synergistic anti-inflammatory effect while potentially minimizing adverse events associated with prolonged antibiotic use (Jung et al., 2013).

The effect of oral probiotic supplementation was also tested on children aged 4–17 with atopic dermatitis. Patients were given a daily pill containing a probiotic formulation (consisting of 10^9 colony-forming units of *Bifidobacterium animalis* subsp. lactis, *Bifidobacterium longum*, and *Lacticaseibacillus casei* in a 1:1:1 ratio, with maltodextrin as a carrier) or a placebo (containing only maltodextrin) for a duration of 12 weeks. The probiotic group showed improved AD severity scores and reduced use of topical steroids. While no significant increase in specific probiotics was observed, microbiome analysis revealed decreased *Faecalibacterium* and increased *Bacteroides* levels, suggesting a potential modulation of the gut microbiome. Results indicate the need for further research with larger cohorts and exploration of microbiome changes in different age groups. Safety and efficacy considerations for probiotic consumption were also noted (Climent et al., 2021).

Recently, B. Lee et al. (2023) showed potential for anti-aging effects of the probiotic strain *Limosilactobacillus fermentum* USM 4189 (LF 4189), using a D-gal-induced rat model. They examined various factors associated with skin aging, such as antioxidant capacity, skin elasticity, histological alterations, telomere length, and gene expression linked to apoptosis, senescence and oxidative stress. The experimental groups included 6 young rats receiving daily subcutaneous injections of 0.9% saline (Young group), 6 old rats receiving subcutaneous injections of 600 mg/kg D-gal to induce aging (Old group), a group consisting of aged rats treated with *L. fermentum* 4189 (1×1010 CFU/d) via oral administration (Old+4189), and a group with aged rats treated with metformin (300 mg/kg/d) via oral administration (Old+metformin). Results revealed that administering *L. fermentum* 4189 to aging rats significantly enhanced antioxidant capabilities, diminished lipid peroxidation, and improved skin elasticity compared to untreated aging rats. Histological analysis indicated that the administration of *L. fermentum* 4189 prevented the deterioration of skin structure, increased collagen fibers, and overall improved skin health. Additionally, LF 4189 mitigated telomere shortening, a marker of cellular aging, and influenced gene expression related to apoptosis, senescence, and oxidative stress. These findings suggest that oral administration of *L. fermentum* 4189 may provide antioxidative and anti-aging effects, positioning probiotics as a promising avenue for interventions to support skin health during the aging process (Lee et al., 2023).

Apart from probiotic supplementation, prebiotic oral supplements also offer an alternative option to modulate immune status via gut microbiota. The most common prebiotics are considered indigestible fibers, which remain undigested by the host and can only be fermented by commensal bacteria in the lower gastrointestinal tract. The benefits of these prebiotics are typically associated with the stimulation of short chain fatty acids (SCFAs) producing bacteria (Costa et al., 2021), but they may also improve immune response through the production of immunomodulating compounds and secondary bile acids and training the immune system by providing microbe-associated molecular

patterns (MAMPs) (McCuaig & Goto, 2023). The pectins, for example, have been found to promote SCFA production, particularly acetate. The conversion of acetate to propionate and butyrate varied depending on the resident microbiome community (Pascale et al., 2022). Costa et al. (2021) discuss the effects of another type of prebiotics, namely fructooligosaccharides, on inflammation and gut immune response. A study testing the potential benefits of fructo-oligosaccharides (FOS) and galacto-oligosaccharides (GOS) on adult women with acne revealed these probiotics may indirectly improve the condition. Twelve women with mild to moderate acne that participated in the study, receiving a daily food supplement containing FOS (100 mg) and GOS (500 mg) for three months. The results revealed significant reductions in fasting blood glucose levels and total cholesterol, suggesting a positive impact on metabolic health. While further investigation is needed, these findings imply a potential avenue for prebiotic supplementation in managing metabolic parameters in individuals with adult acne. In addition, the use of oral nutritional supplementation containing the abovementioned prebiotics has been shown to elevate stool colony counts of *Bifidobacteria* and *Lactobacilli*. This contributes to the maintenance of an efficient intestinal mucosal barrier, which could potentially result in the improvement of skin's health (Dall'Oglio et al., 2018).

Fecal microbiota transplantation (FMT) has also been tested for the restoration of gut microbiota in mice with atopic dermatitis (Kim et al., 2019; Kim et al. 2021; Mashiah et al., 2021; Jiang et al., 2023). Apart from the skin condition, the studies measured other parameters, including cytokine levels, blood parameters, histological parameters, and short-chain fatty acid (SCFA) levels. The results revealed a significant restoration of gut microbiota and associated parameters following FMT treatment and indicated promising therapeutic potential of FMT in atopic dermatitis, suggesting a novel approach for addressing the condition by modulating the immune via gut microbiota (Kim et al., 2019).

Conclusions

Microbiome manipulation strategies emerge as a promising frontier in the therapeutic landscape, offering innovative approaches for addressing skin conditions such as acne and atopic dermatitis. The skin microbiome, a complex ecosystem of microorganisms, can be modulated through various approaches, ranging from the transplantation to topical applications of probiotics, prebiotics, and postbiotics. These interventions aim to restore microbial balance, particularly in the face of dysbiosis associated with inflammatory skin diseases. While microbiome transplantation poses some challenges and potential risks, the scalable nature of probiotics and postbiotics provides more accessible and controlled means of manipulating the skin microbiome. Increasing number of studies showcase the potential of live bacteria and topical formulations in regulating the skin microbiome, offering hope for effective and scalable therapies.

Furthermore, the gut microbiome also presents promising avenue for intervention in skin diseases, as different studies imply the interconnectedness of the gut-skin axis and the role of the microbiome in influencing skin health. Probiotics administered orally have demonstrated positive effects in improving digestion, immune response, and overall gastrointestinal health, with implications for skin conditions like acne. Additionally, the emergence of bacteriophage therapy, targeting specific harmful bacteria offer a promising alternative to traditional antibiotic approaches. The specificity, adaptability, and potential to mitigate resistance make bacteriophages a valuable tool in possible skin disease treatments.

In conclusion, despite their prevalence acne and atopic dermatitis and approaches to their treatment covered in this manuscript represent only a small part of the challenges in dermatology. Several other acute or chronic inflammatory conditions (i.e. psoriasis) are also becoming increasingly prevalent in the modern world and should be addressed in future research. In recent years, increasing attention and resources have been dedicated to the development of biotechnological solutions for alleviating or treating skin diseases, which is expected to lead to several innovations in the upcoming years. However, these represent only the beginning of a long journey, which concludes with the improvement of the patient's condition, ideally leading to complete recovery. Investments in research as well as in preclinical and clinical studies are essential for the development of safe products with appropriate dosage and application methods. Additionally, it is important to establish scalable and cost-effective production of therapeutics with good manufacturing practices. The final cost of therapy is a result of multiple factors that must be considered. If the price is too high, significant progress in dermatology may be hindered, as only a handful of affected individuals would be able to afford the treatment.

In the future, we aspire to have not only effective but also accessible methods of treatment. To achieve this goal, it is crucial to change the perception of skin conditions, to accept them, and to end the stigmatization of those affected. Since chronic skin diseases are often not (directly) life-threatening, attention and resources are frequently redirected to other areas. However, the psychological and socio-economic impact of inflammatory skin diseases is often comparable to, if not greater than, that of other chronic health conditions. It should also be kept in mind that skin diseases are usually not only disorders of the skin but also indicative of larger, systemic illnesses and is therefore essential to approach patients in a systemic manner and to identify and treat the primary cause of the conditions.

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Conflicts of Interest

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