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Chapter

Skin and Gut Microbiota in Psoriasis: A Systematic Review

Atiya Rungjang, Jitlada Meephansan and Hok Bing Thio

Abstract

Paying attention to a microbial approach may lead to improvements in diagnosis, treatment, prevention, and prognosis of psoriasis. A systematic review was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines searching strategy to identify the pattern of the microbiome and the association of skin and gut microbiota with psoriasis, including the factors that may affect the results of the microbial study. In total, 16 studies were included in this systematic review. Ten studies investigated the skin microbiome, of which six studies were cross-sectional and four studies were prospective studies. Six studies investigated the gut microbiome, including five cross-sectional studies and one prospective study. The understanding of the relationship between microbiota and psoriasis may lead to diagnostics and treatment improvements. Currently, there is a slight consensus on some specific features that define psoriasis. However, no specific taxa have been identified as biomarkers of the disease, even from large-scale cohort studies. Thus, future cohort studies with standardized methodologies and proof-of-concept investigations in animal models may uncover the role of microbiota and the microbial pathways in psoriasis.

Keywords: psoriasis, microbiome, alpha diversity, beta diversity, dysbiosis

1. Introduction

Psoriasis is one of the most common immune-mediated inflammatory skin diseases. The prevalence of the disease has been reported, with ranges from 0.09 to 11.43% by the WHO Global Report 2016 [1]. Psoriatic skin lesions are characterized by hyperproliferation of keratinocytes, infiltration of immune cells, including neutrophils, T cells, dendritic cells, and macrophages. To date the etiology of this disease is not fully understood; genetic and environmental interaction plays a crucial role in the disease development [2, 3]. Recently, the immunological approach has helped to significantly clarify the pathophysiology of the disease. Dysregulation of both the bacteria, including *Staphylococcus aureus* [4], *Streptococcus pyogenes* [5], and fungi such as Malassezia [6] through innate and adaptive immune systems in genetically susceptible individuals, such as immune cells in the skin, Tumor necrosis factor α, dendritic cells—particularly pathogenic T cells that produce high levels of IL-17 in response to IL-23, all contribute substantially to the pathogenic process [7].

Previous studies have indicated an association between psoriasis and numerous comorbidities that share the chronic inflammatory state. Moreover, increasing evidence indicates that the gut microbe contributes to the onset of the low-grade inflammation, which is a pathological phenotype of these metabolic disorders [8].

Additionally, it has been known that several microorganisms contribute to psoriasis exacerbation alterations in the innate and adaptive immune processes [9]. The increasing evidence here suggests that the microbiota may play a critical role in psoriasis pathogenesis. This systematic review aims to elucidate the correlation between the microbiome and psoriasis pathogenesis, and the microbiota modulation that may lead to possible therapeutic interventions.

2. Psoriasis and microbiota

The initial search revealed a total of 629 studies of which 501 studies were excluded based on their title and abstract. The full texts were reviewed, and a further 116 studies were excluded. An additional four studies from the reference lists of already included studies were included in the systematic review. In total, 16 studies were included in this systematic review; 10 studies investigated the skin microbiome, of which 6 studies were cross-sectional and 4 studies were prospective study. Six studies investigated the gut microbiome, including five cross-sectional studies and one prospective study. The most commonly used method was 16S r RNA (skin swab, biopsies, curette); Langan et al. [10] used traditional culture combined with mass spectrometry (MALDI-TOF) (**Table 1**).

2.1 Skin microbiota in psoriasis

Several studies reported the characteristic features of microbiota in psoriatic skin (**Table 2**). Significant differences were observed between psoriatic lesion and control skin, but the changes were different in each study. Gao et al. [19] and Chang et al. [14] reported an increase in lesional skin diversity compared to non-lesional and control. In contrast, subsequent studies by Fahlen et al. [18] found wider range of Shannon index values in the control suggesting that the trend of decrease in lesional psoriasis microbiome diversity is consistent with the findings by Alexseyenko et al. [17] who observed a decrease in the diversity and significantly lower Shannon index in lesional skin. Consistent with previous studies, Tett et al. [16] found that psoriatic plaques at the ear are characterized by a significant decrease in microbial diversity. When beta diversity was analyzed to describe heterogeneity of microbial community, Fahlen et al. [18] reported a lower beta diversity in psoriasis compared to control, while Alexseyenko et al. [17] found that beta diversity was the highest in lesional skin, followed by unaffected skin, and the lowest in healthy skin. In line with the study by Tett et al. [16], which reported that ear lesions revealed higher beta diversity, Loeshe et al. [12] and Chang et al. [14] also reported a higher beta diversity at dry skin sites in psoriasis. At the phylum level, most skin bacterial composition fall into four major phyla: *Actinobacteria*, *Firmicutes*, *Bacteroidetes*, and *Proteobacteria*. Within these phyla, the three most abundant genera are: *Propionibacterium*, *Corynebacterium*, and *Staphylococcus*. From the studies of Gao et al. [19], Fahlen et al. [18], and Langan et al. [10], it has been revealed that at the phylum level, compared to healthy skin, psoriatic skin was associated with an increase in the relative abundance of *Firmicutes* but a decrease for *Actinobacteria*, which is partially consistent with Alexseyenko et al. [17] who identified psoriatic lesion as cutaneo type 2, which was dominated by *Firmicutes* and *Actinobacteria*. In contrast, *Firmicutes* were lower in the studies by Loeshe et al. [12], Assarsson et al. [13], and Drago et al. [15]. *Proteobacteria* showed inconsistent abundance, lower in lesional skin as observed by Gao et al. [19] whereas Fahlen et al. [18] observed an increase, and Drago et al. [15] reported that *Proteobacteria* and *Bacteroidetes* were the dominant microbiota in psoriasis lesion. At the genus

Study	Study design/ ratings of the quality	Population	Result
Langan et al. [10] (2019)	Cross-sectional/4	23 Pso, 20 C	Pso L At the phylum level: ↑ *Firmicutes*, ↓*Actinobacteria* At the genus level: ↑*Prevotella*, *Staphylococcus*, ↓*Anaerococcus* and *Propionibacterium* *Prevotella* and *Staphylococcus* significantly associated with Pso L Pso NL ↑*Anaerococcus*, *Propionibacterium*
	Prospective systemic treatment/2		*Actinobacteria*-to-*Firmicutes* ratio, partially reversible during treatment Biological therapies demonstrated the largest impact on the ratio of *Actinobacteria* to *Firmicutes* *Corynebacterium*, *Staphylococcus*, significantly correlated with PASI scores
Stehlikova et al. [11] (2019)	Cross-sectional/4	34 Pso, 25 C	Beta diversity: no significant differences between Pso L and Pso NL Pso L ↑ *Streptococcus* regardless of the sampling site ↑ *Brevibacterium* richness and evenness in in the elbow lesions, compared to back lesions ↓*Propionibacterium* PsoL, PsoNL compared C in elbow lesions Remark Alpha diversity and bacterial taxa from skin swab, scraping, and biopsy are comparable
Loesche et al. [12] (2018) Remark: study did not include healthy control	Cross-sectional/4	114 Pso	Beta diversity: Pso L > Pso NL Pso L At the phylum level: ↑*Actinobacteria* in leg, scalp, and trunk lesions ↓*Firmicutes* in scalp and trunk lesions At the genus level: ↓*Caulobacteraceae*, *Corynebacterium* leg lesions At the species level: ↑*Bacilli*↓*Propionibacterium acnes* in scalp lesions *Streptococcus* colonization of skin does not correlate with severity in lesional and non-lesional skin
	Longitudinal RCT/1	89 Pso	Pso L and Pso NL respond similarly to ustekinumab Significant change in abundance from baseline in all body sites No difference diversity in Pso L vs. Pso NL except ↑ in trunk Pso L microbiota was not converging with Pso NL as treatment progressed Microbiota diverged further between Pso L and Pso NL across body sites
Assarsson et al. [13] (2018) Remark: study did not include healthy controls	Cross-sectional/4	26 Pso	Pso L ↓*Firmicutes Staphylococcus*
	Longitudinal Narrowband UVB/2		Pso L ↓*Firmicutes*, *Staphylococcus*, *Finegoldia*, *Anaerococcus*, *Peptoniphilus*, *Gardnerella*, *Prevotella*, *Clostridium* Pso NL ↓*Firmicutes* ↓*Pseudomonas* in treatment responders

3

Study	Study design/ ratings of the quality	Population	Result
Chang et al. [14] (2018)	Cross-sectional/4	28 Pso, 26 C	Alpha diversity: Pso L > Pso NL > C ↑ Beta diversity in all dry skin sites Psol L ↑ Alpha diversity at dry skin sites, with a trend at the sebaceous (scalp) site, and no increase at moist sites ↑*S. aureus* and *S. pettenkoferi* Pso NL ↑*S. sciuri* C ↑*P. acnes*, *P. granulosum*
Drago et al. [15] (2016)	Cross-sectional/4	3 adult first cousins— 1 AD, 1 Pso, 1 C (same lifestyle and environmental factors)	Pso L At the phylum level ↓ *Firmicutes*, ↑ *Proteobacteria* in Pso L compare to AD and C At the family level ↑ *Streptococcaceae*, *Rhodobacteraceae*, *Campylobacteraceae*, *Moraxellaceae* in Pso L compare to AD and C ↓*Staphylococcaceae*, *Propionibacteriaceae* in Pso L compare to AD, C. At the species level: ↓ *Propionibacterium* acnes in Pso compare to AD and C. ↓ *S. aureus* in Pso L < C < AD, no difference in Psp NL
Tett et al. [16] (2017) Remark: study did not include healthy control	Cross-sectional/4	28 Pso	Alpha diversity: Pso L < Pso NL in ear lesions (richness did not correlate with PASI score) Beta diversity: Pso L > Pso NL in ear lesions Pso L At the phylum level: *Actinobacteria* and *Firmicutes*. At the genus level: *Staphylococcus* At the species level: *S. epidermidis*, *P. acnes*, *S. caprae/capitis*, and *M. luteus*
Alekseyenko et al. [17] (2013)	Cross-sectional/4	75 Pso, 124 C	Alpha diversity: Pso L < Pso NL and C Beta diversity: Pso L > Pso NL > C. Pso L At the phylum level: Cutaneotype 2 (dominated by *Actinobacteria*, *Firmicutes*) At the genus level: ↑ combined relative abundance of *Corynebacterium*, *Propionibacterium*, *Staphylococcus*, *Streptococcus* ↓*Cupriavidus, Flavisolibacter, Methylobacterium, Schlegelella*. At the species level: *Acidobacteria, Schlegelella* *Acidobacteria* positively correlated with PASI C: Cutaneotype 1 (dominated by *Proteobacteria*) ↓ *Cupriavidus, Flavisolibacter*
	Longitudinal 12 weeks, 36 weeks after systemic treatment/1	17 Pso, 15 c	No statistically significant difference was observed between the lesion and unaffected groups, or longitudinally within groups Pso L ↑Relative abundance of *Corynebacterium*, *Propionibacterium*, *Staphylococcus* and *Streptococcus*

Study	Study design/ ratings of the quality	Population	Result
Fahlen et al. [18] (2012)	Cross- sectional/4	10 Pso, 12 C	Alpha diversity: no difference observed when using the Shannon index Beta diversity: Pso L < C Pso L At the phylum level: ↓ *Actinobacteria*, ↑ *Proteobacteria* in trunk lesions At the phylum level: ↓ *Propionibacterium* in all sites, ↓*Staphylococcus* ↑*Streptococcus/Propionibacterium* ratio
Gao et al. [19] (2008)	Cross- sectional/4	6 Pso, 6 C	Alpha diversity: Pso L > Pso NL, C Beta diversity: Pso L > C At the phylum level: ↑ *Firmicutes*, ↓ *Actinobacteria, Proteobacteria* At genus level: ↓ *Propionibacterium*, ↑ *Streptococcus* At the species level: ↓ *P. acne*, ↓ Anaerobic species

Pso—Psoriasis, C—Control, Pso L—Psoriasis lesional skin, Pso NL—Psoriasis non-lesional skin.

Table 1.
Skin microbiota in patients with psoriasis.

level, *Streptococcus* were higher in lesional skin by Gao et al. [19], Fahlen et al. [18], Alexseyenko et al. [17], Stehlikova et al. [11], and Drago et al. [15] while Loeshe et al. [12] found no correlation between psoriasis lesional and unaffected skin. *Staphylococcus* were detected more frequently in the lesion by Gao et al. [19] and Tett et al. [16] opposite to Fahlen et al. [18] who found that *Staphylococcus* were increased in abundance in healthy controls. Lower abundance of *Propionibacterium* in lesional skin was reported by Gao et al. [19], Fahlen et al. [18], Drago et al. [15], Stehlikova et al. [11], and Loeshe et al. [12], which is in contrast to Alexseyenko et al. [17] who reported an increase in the relative abundance of combined Gram positives such as *Corynebacterium*, *Propionibacterium*, *Staphylococcus*, and *Streptococcus*. In the subsequent study by Langan et al. [10], the presence of *Corynebacterium* and *Staphylococcus* was found to be significantly correlated with PASI scores while *Anaerococcus* and *Propionibacterium* were associated with non-lesional skin. These are consistent with the reports by Gao et al. [19] and Chang et al. [14] that at species level lesional skin psoriasis had an increased level of *S. aureus* but a decreased level of *P. acne*. On the other hand, study on the importance of site-specific microbiota without related disease reported that at the species level the most abundant bacteria were *S. epidermidis* and *P. acne* irrespective of disease status and hence suggested that an underlying subject-specific microbial signature better defines the microbiome.

There is a challenge to identify the explicit features of healthy or psoriasis microbiomes. Investigations of such a complex system of bacteria, fungi, and viruses are difficult and there is also high variation between samples. The composition of these communities of microorganisms depends on skin characteristics, such as sebaceous gland concentration, moisture content, topography, and temperature, as well as on host genetics and exogenous environmental factors [20]. Thus, the skin microbiome is biogeographically specific for each body site [21]. Demographic differences, such as gender, age, place of residence, living with animals, hygiene habits, occupation, and ethnicity also influence the composition of the skin microbiome [22]. The underlying disease and/or disease severity may also have an effect on the microbiome diversity or alterations in microbial communities due to disease states.

	Finding	By
Alpha diversity	Increased	Gao et al. [19], Chang et al. [14]
	Decreased	Fahlen et al. [18], Alexseyenko et al. [17], Tett et al. [16]
Beta diversity	Lower	Fahlen et al. [18]
	Highe	Alexseyenko et al. [17], Tett et al. [16], Loeshe et al. [12], Chang et al. [14]
Phylum level		
Firmicutes	Increased *Firmicutes*	Gao et al. [19], Fahlen et al. [18], Langan et al. [10]
	Decreased *Firmicutes*	Loeshe et al. [12], Assarsson et al. [13], Drago et al. [15]
Actinobacteria	Decreased *Actinobacteria*	Gao et al. [19], Fahlen et al. [18], Langan et al. [10]
	Increased *Firmicutes* and *Actinobacteria*	Alexseyenko et al. [17]
Proteobacteria	Decreased *Proteobacteria*	Gao et al. [19]
	Increased *Proteobacteria*	Fahlen et al. [18], Drago et al. [15]
Genus level		
Streptococcus	Increased *Streptococcus*	Gao et al. [19], Fahlen et al. [18], Alexseyenko et al. [17], Stehlikova et al. [11], Drago et al. [15]
	No correlation	Loeshe et al. [12]
Staphylococcus	Increased *Staphylococcus*	Gao et al. [19], Tett et al. [16]
	Decreased *Staphylococcus*	Fahlen et al. [18]
Propionibacterium	Lower *Propionibacterium*	Gao et al. [19], Fahlen et al. [18], Drago et al. [15], Stehlikova et al. [11], Loeshe et al. [12]
Gram positives	Increased relative abundance of combined Gram positives: *Corynebacterium*, *Propionibacterium*, *Staphylococcus*, and *Streptococcus*	Alexseyenko et al. [17]
	Corynebacterium and *Staphylococcus* were significantly correlated with PASI scores	Langan et al. [10]
	Increased *S. aureus,* decreased *P. acne*	Gao et al. [19]
	Site-specific microbiota without related disease	Tett et al. [16]

Table 2.
Summary of skin microbiota findings in psoriasis.

Moreover, microbiome diversities differ between studies; however, the more recent studies demonstrate decreased alpha diversity with increased beta diversity in psoriasis. Also, there are data that demonstrate a trend toward a changing microbial composition in psoriasis-affected skin. *Propionibacterium* is known as a protective commensal bacterium that is related with SCFA and propionate production, which regulates immune function. The decrease in the relative abundance of this microorganism in psoriasis may be related to the course of disease. In most studies, *Staphylococcus* are dominant in psoriatic skin, as species such as *S. aureus* proposed pathogenic Th17 activation while S. *epidermidis* appear to modulate immune and barrier functions. Interestingly, a study by Tett et al. [16] reported

S. epidermidis strains contain known virulence-related genes that are predominate in psoriasis-affected skin. Therefore, a future study at the species and the strain level may provide more information.

2.2 Gut microbiota in psoriasis

The fecal sample study by Scher et al. [23] revealed that gut microbiome in skin psoriasis and psoriatic arthritis had a decrease in alpha diversity compared to control, and *Actinobacteria* had a decrease in relative abundance at the phylum level. This is in line with Masallat et al. [24] who found that the relative abundance of *Actinobacteria* was reduced in psoriasis versus healthy controls with a negative correlation of PASI score whereas the ratio of *Firmicutes* to *Bacteroidetes* was positively correlated with PASI score. This is consistent with Codoner et al. [25] who found a lower abundance of *Bacteroides* at the genus level and characterized core microbiome of psoriasis by an increase in *Feacalibacterium* but a decrease in *Bacteroides* spp. The abundance of *Akkermansia*, *Ruminococcus*, and *Pseudobutyrivibrio* was found to be lower in psoriatic arthritis compared to controls by Scher et al. [23]. Eppinga et al. [26] found that the abundance of *Faecalibacterium prausnitzii* was reduced in psoriasis with a significant increase in the relative abundance of *Escherichia coli* (**Table 3**).

The gut is considered as a major immune organ, with gut-associated lymphoid tissue (GALT) being the most complex immune compartment [30]. It is well known that change in the microbe composition may promote both health and disease [31]. Intestinal dysbiosis has been implicated in the etiology of various diseases [32], such as Crohn's disease and obesity [33, 34]. Moreover, there is strong evidence that indicates intestinal dysbiosis is clinically relevant to psoriasis [35, 36]. The importance of the gut-skin axis in the pathogenesis of psoriasis has recently been documented in humans, as well as in animal models of psoriasis [9, 37]. A study by Tan et al. identified that the signature of gut microbiota and its function are significantly altered in the gut of patients with psoriasis [28]. Intestinal and skin microbiota directly regulate imiquimod-induced skin inflammation (IISI), and emphasizes the importance of microbiota in the pathogenesis of psoriasis [38]. A study by Zákostelská et al. has shown that exposure of mice to antibiotics inhibited the induction of psoriasis [37].

To identify bacterial pathways, which may be involved in the pathogenesis of psoriasis, it should be highlighted that SCFAs potentially regulate the generation and function of Th17 cells [39]. Moreover, in psoriasis the loss or depletion of *Faecalibacterium prausnitzii*, a major source of the protective SCFAs in the gut, may be associated with disease development [26]. In psoriatic arthritis, decreased *Akkermansia* and *Ruminococcus*, which are protective bacteria that regulate the intestinal barrier that produces SCFA, may be related with disease severity. Gut dysbiosis markedly reduced butyrate production, which inhibits NF-κβ, an inflammation pathway that impacts gut epithelial integrity and consequential cross-talk between gut proteins, bacteria, and the innate and humoral immune systems [27]. Alterations in the pathways involved in LPS function were also observed in psoriasis patients. Additionally, LPS is also thought to be involved in gut inflammation and has been linked to the pathogenesis of insulin resistance and diabetes mellitus [40], which has been epidemiologically associated with psoriasis. A decrease in *Bacteroides*, which are known to play an immunomodulatory role in the gut through the production of polysaccharide A that induces regulatory T cells, may result in an altered immune response [41]. Whereas a decrease in *Actinobacteria*, a phylum that includes the Bifidobacterium species that have been shown to reduce intestinal inflammation, suppresses autoimmunity, and induces regulatory T cell expression. There are also several studies that have shown how bacterial translocation from the

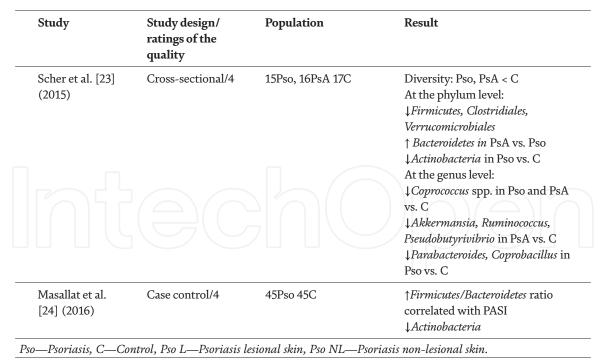| Study	Study design/ ratings of the quality	Population	Result
Shapiro et al. [27] (2019)	Cross-sectional/4	24 Pso 22 C	Alpha diversity, beta diversity: no significant differences At the phylum level: ↑*Firmicutes, Actinobacteria* ↓*Bacteroidetes, Proteobacteria* At the species level: ↑*Ruminococcus gnavus, Doreaformici generans* and *Collinsella aerofaciens, Prevotella copri* and *Parabacteroides distasonis*
Tan et al. [28] (2018)	Cross-sectional/4	14 Pso 14C	Pso L At the phylum level: ↓*Verrucomicrobia, Tenericutes* At the class level: ↓*Mollicutes, Verrucomicrobiae* At the order level: ↓*Verrucomicrobiales*, RF39 At the family level: ↓*Verrucomicrobiaceae*, S24–7 At the genus level: ↑*Bacteroidaceae, Enterococcaceae*, ↓*Akkermansia* At the species level: ↓*Akkermansia muciniphila*, ↑*Clostridium citroniae*
Codoner et al. [25] (2018) Remark: study did not include healthy control	Cross-sectional/4	52Pso compared with a cohort of over 300 healthy individuals extracted from the human microbiome project	Pso: ↑Beta diversity Enterotype 2 (predominance of *Prevotella*) tended to experience more frequent bacterial translocation and higher inflammatory status ↓*Bacteroides*, ↑*Akkermansia, Faecalibacterium*
Chen et al. [29] (2018)	Cross-sectional/4	32Pso 64 C	Diversity: no significant difference between Pso and C At the phylum level: ↑*Firmicutes*, ↓*Bacteroidetes* At the genus level: ↑ *Ruminococcus, Megasphaera* At the family level: ↓*Bacteroidaceae, Prevotellaceae* ↑ *Ruminococcaceae, Lachnospiraceae* Other covariates: sex, disease activity assessed by PASI score, phototherapy, arthritis, as well as diet, alcohol, smoking, coffee, tea, and habit of exercise, did not significantly affect the abundance profile of intestinal microbiota among Pso and C
	Patients receiving systemic treatment (DMARDs or biologics drugs BioSysDrug) subgroup analyses /2	20 Pso	↓the species *Prevotella stercorea*, belonging to *Prevotellaceae*, of the phylum *Bacteroidetes*, in patients receiving BioSysDrug

Study	Study design/ ratings of the quality	Population	Result
Scher et al. [23] (2015)	Cross-sectional/4	15Pso, 16PsA 17C	Diversity: Pso, PsA < C At the phylum level: ↓*Firmicutes, Clostridiales, Verrucomicrobiales* ↑ *Bacteroidetes* in PsA vs. Pso ↓*Actinobacteria* in Pso vs. C At the genus level: ↓*Coprococcus* spp. in Pso and PsA vs. C ↓*Akkermansia, Ruminococcus, Pseudobutyrivibrio* in PsA vs. C ↓*Parabacteroides, Coprobacillus* in Pso vs. C
Masallat et al. [24] (2016)	Case control/4	45Pso 45C	↑*Firmicutes/Bacteroidetes* ratio correlated with PASI ↓*Actinobacteria*

Pso—Psoriasis, C—Control, Pso L—Psoriasis lesional skin, Pso NL—Psoriasis non-lesional skin.

Table 3.
Gut microbiota in patients with psoriasis.

gut and skin into the bloodstream may take place in psoriasis, and be responsible for driving the chronic, systemic inflammatory nature of the disease [42].

2.3 Skin mycobiota

An investigation by Findley et al. suggests that fungal diversity is increased in psoriatic lesions, compared to healthy skin sites. Furthermore the skin of psoriatic patients, at the genus level, is dominant with Malassezia [43]. Whereas the study by Takemoto et al. found that psoriatic skin revealed higher diversity and decreased relative abundance of Malassezia, which is still the most abundant phylum compared to controls. Moreover, the ratio of *M. globosa* to *M. restricta* is lower in psoriatic lesions [44]. Stehlikova et al. [11] found no significant difference in alpha and beta diversity and a significant increase in abundance of *M. restricta* in back lesions and *M. sympodialis* in the elbow lesions. Conversely, however, Paulino et al. showed that psoriatic lesions on the back, in decreasing order of abundance, are predominated by *M. restricta*, followed by *M. globosa* and *M. sympodialis*, respectively. Paulino et al. concluded that there was no significant difference between the fungal compositions of psoriatic and healthy skin [45]. Furthermore, Paulino et al. also showed there was no consistent variation between psoriasis and healthy controls [46] as *M. furfur* was found only in the skin of psoriasis participants in the study by Jagielski et al. [47] compared to healthy controls and atopic dermatitis.

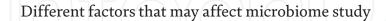## 2.4 Factors affecting microbiota study

So far, no specific patterns of microbiota in psoriatic patients have been identified (**Tables 1** and **3**).

The difficulty to establish such precise features, although a plethora of published studies have attempted to do so, is due to the lack of standardized protocols. Differences in sample collection and processing, sequencing methods, and analysis procedures between studies may impact the study results [48], and can confound comparisons and results in incompatible outcomes (**Table 4**).

	Findings	**By**
Alpha diversity	Decreased	Scher et al. [23]
Actinobacteria	Decreased	Scher et al. [23], Masallat et al. [24]
Bacteroides	Lower	Codoner et al. [25], Masallat et al. [24]
Feacalibacterium	Increased	Codoner et al. [25]

Table 4.
Summary of gut microbiota findings in psoriasis.

Different factors that may affect microbiome study

- Host factors: Not many studies accounted the interpersonal and intrapersonal factors that affect the microbial community.

- Samples collected from different body sites cannot be compared due to site-specific niches, as described previously [21].

- Sampling method: Several studies showed that different skin layers contain different bacterial communities [48]. Most of the published research on cutaneous microbiota has been based on skin swabs, which represent the surface of the skin. Prast-Nielsen et al. [49] found differences in both diversity and taxonomic composition of the microbiome obtained from swabs and biopsies of the same individual, while an investigation by Stehlikova et al. showed that various sampling approaches (swab, scraping, and biopsy) in affected and unaffected skin of psoriatic patients and in healthy control skin results in similar bacterial diversity despite the different genera abundance that is observed [11]. Grice et al. used three different sampling strategies in the antecubital fossa of five patients: swabs, skin scrapes, and punch biopsies, and concluded that similar microbial populations were captured by each technique and that the dominant species was present in the noninvasive swabs [50]. Recent studies have also reported that the tape stripping method may capture more viable bacteria than the swabbing method [51].

Sequencing methods, analysis procedures, and techniques for studying the microbiome:

- Langan et al. demonstrated that the changes in the microbiome during treatment that were detected by 16S rRNA were not detected by culture data. This suggested that changes in bacterial populations may have been too subtle to be detected by culture, or that changes are predominantly in nonculturable species [10].

- Studies using the most often used 16S rRNA have shown that the accuracy of molecular signatures depends on DNA sequencing and downstream analysis protocols. Therefore numerous combinations of primer pairs have been previously tested to select the most appropriate one for skin microbiome surveys; however, standardized methodology is still lacking [52].

  ○ Several studies suggested that primers for V1V3 and V3V4 hypervariable regions were described to sufficiently cover the skin bacterial diversity [20].

○ Statnikov et al. concluded that using 16S rRNA data from the V3–V5 locus leads to accurate and statistically significant molecular signatures, whereas data from the V1–V3 locus carry a limited diagnostic signal [53].

○ The latter study by Stehlikova et al. observed that variable regions of the V3V4 region capture a wider microbial diversity than the V1V2 region, where observed and estimated richness was significantly higher when using the V3V4 region compared to the V1V2 region [11].

- Whole-genome shotgun metagenomics offers the most comprehensive and robust data; however, as a result of its high cost, only a few shotgun metagenomic studies have been conducted on the microbiota associated with the skin, such as the Human Microbiome Project [54]. We found very few studies on psoriasis microbiome.

2.5 Therapeutic implements

Several studies reveal that psoriasis treatment changes the gut and skin microbiome, such as the correlation between psoriasis systemic treatment and the *Actinobacteria*-to-*Firmicutes* ratio. Biological therapies demonstrated the largest impact [10] during ustekinumab treatment; the composition of microbiota diverged further between lesional and non-lesional skin, across body sites, which could be due to the regression of lesions that returns the skin to more normal environments and increases the body site-specific niches [12]. Secukinumab (anti-IL17) therapy is associated with distinct and more profound gut microbiome shifts than ustekinumab therapy (anti-IL 12/23), in patients with psoriasis by increasing the relative abundance of *Proteobacteria* and decreases in *Bacteroidetes* and *Firmicutes* [55]. Burns et al. demonstrates that UVR has profound qualitative and quantitative influences on the composition of the skin microbiome by an increase in the phylum Cyanobacteria and a decrease in the family Lactobacillaceae and Pseudomonadaceae [56]. This suggests that skin microbiome alterations after UVB treatment could be related to treatment and treatment responses [13]. Thus, it may be implied that the modulation of the gut and skin microbiota can improve disease condition.

Therapeutic modalities that target the shifting microbiota:

The use of orally administered antibiotics, prebiotics, probiotics, and most recently, fecal transplantation [57] also appears to improve the disease condition and may be a practical prospect as a therapeutic avenue.

- Antibiotic treatment of psoriasis can alter the bowel flora toward normality, and therapy might include the use of appropriate antibiotics to reduce susceptible microbes while permitting others to flourish [58]. Saxena and Dogra reported that administration of benzathine penicillin in psoriasis vulgaris patients showed a significant improvement [59] and administration of azithromycin revealed a significant improvement at 12 weeks in the patient with psoriasis [60].

- Pro- and prebiotics are commonly used to modulate the microbiome by promoting the growth of specific species. Three studies using three distinct probiotic species affecting distinct pathways of the pathomechanism of psoriasis [61, 62] have all shown improvement in the course of the disease. The probiotics resulted in the improvement of epithelial barrier function, increased production of TNF-alpha by epithelial cells, and regulated activation of the NF-κβ pathway [63]. An issue with probiotic supplementation is

that the colonization of probiotic bacteria in the gut is mostly transient as they are only detectable for less than 2 weeks after cessation of intake [64]. However, a study by Maldonado-Gómez et al. demonstrated that a certain *Bifidobacterium longum* (*B. longum*) strain was able to persist for over 6 months in a subset of subjects where it was originally absent [65]. A recent, randomized, double-blind, placebo-controlled trial evaluated the effect of a probiotic mixture as co-adjutant treatment together with topical steroids in 90 patients with plaque psoriasis. The results showed a large reduction in the score of severity indexes in the probiotic group, compared with the placebo group. Gut microbiota analysis demonstrated the efficacy of the probiotic in modulation of the composition of the microbiota. After the end of the probiotic or placebo intake, patients were followed up for 6 months. The results showed a lower risk of relapse in patients in the probiotic group [66].

- Topical probiotics show that after sequential applications of a donor microbiome, the recipient microbiome becomes more similar to the donor [67]. The use of topical probiotics may have special subclinical significance, for example, to improve skin defense with probiotic-containing cosmeceuticals. It has been reported that *B. longum* strains exert pro-differentiating, as well as and pro-regenerating, effects on primary human epidermal keratinocytes [68]. Thus, using the most suitable oral probiotic strain in combination with topical probiotics and/or prebiotics might help in the personalized treatment of skin disorders.

- Fecal microbiota transplantation (FMT) is currently being used to restore the balance of the intestinal microbiota [69, 70]. Particularly, this procedure has demonstrated >90% clinical resolution of recurrent, or refractory, *Clostridium difficile* infections [71]. Also, multiple FMTs seem to be able to induce remission in patients with IBD [72]. Due to these results, FMT is now being tested as a potential novel treatment for other gastrointestinal and extraintestinal diseases [73] as it greatly improves outcomes compared with those before treatment.

3. Conclusion

The function of microbiota may be more important in psoriasis. The metabolic activity of microbiota may become an upcoming research area in near future for identifying crucial biomarkers and new therapeutic approaches for psoriasis. Future cohort studies with standardized methodologies and proof-of-concept investigations in animal models may uncover the role of microbiota and the microbial pathway in psoriasis. This, then, may lead to the development of diagnostics and therapeutic opportunities.

Conflict of interest

The authors have no conflict of interest to declare.

Notes/Thanks/Other declarations

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