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REVIEW ARTICLE

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Skin microbiome alterations in seborrheic dermatitis and dandruff: A systematic review

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Abstract

Seborrheic dermatitis (SD) and dandruff (DF) are common chronic inflammatory skin diseases characterized by recurrent greasy scales, sometimes with erythema and itchiness. Although the exact pathophysiology of the disease is still unclear, current theories highlight the role of microbes on the skin surface in the pathogenesis of SD. Here, we conducted a systematic review to investigate the skin microbiome alterations in patients with SD/DF. We searched Medline/PubMed, Embase and Web of Science for research studies published in English between 1 January 2000 and 31 December 2020. A total of 12 studies with 706 SD/DF samples and 379 healthy samples were included in this study. The scalp and face were predominated by the fungi of Ascomycota and Basidiomycota and the bacteria of Actinobacteria and Firmicutes. In general, the included studies demonstrated an increased *Malassezia restricta/Malassezia globosa* ratio and a reduction in the *Cutibaterium/Staphylococcus* ratio in the setting of SD/DF. *Staphylococcus* was associated with epidermal barrier damage, including elevated levels of trans-epidermal water loss and pH, while *Cutibacterium* had a positive correlation with water content. *Malassezia* was also found to be related to an increased itching score and disease severity. Further studies focusing on the interactions between various microbes and the host and microbes can help us to better understand the pathogenesis of SD/DF.

KEYWORDS
dandruff, microbiome, seborrheic dermatitis

1 | INTRODUCTION

Human skin accommodates diverse commensal microorganisms and dysbiosis of the skin microbiome play a role in several skin inflammatory diseases. Seborrheic dermatitis (SD) is a common chronic, relapsing inflammatory skin disease that affects approximately 5% of the worldwide population. An increased prevalence of this condition has been reported in AIDS and Parkinson's disease groups. Clinically, SD manifests as thin patches with greasy scales that usually involve sebaceous-gland-rich areas, such as the scalp, face, chest, back and body folds.[1,2] Dandruff (DF) is a light disease state of SD that has a higher prevalence of 17%–50% in human individuals.[1] It is characterized by mild inflammatory reactions that present as abnormal flaking of the scalp and sometimes with mild erythema. Since SD/DF causes physical damage to the skin accompanied by itch or prickling sensations, some patients may have psychological problems.

The pathogenesis of SD/DF is still unclear. They are considered to be a result of rapid replacement of the stratum corneum, which exhibits disrupted cohesion between keratinocytes.[3] Previous studies have suggested that several factors are related to the occurrence of this disorder, such as genetic tendency, barrier function damage, increased sebaceous secretion, immune response and microecological disorder. The

presence of *Malassezia* spp. has been shown to play an important role in the development of SD, and an increased *M. restricta*-to-*M. globosa* ratio was found to be associated with the SD/DF scalp.[4] *Malassezia* interact with the skin surface through direct activation of the aryl hydrocarbon receptor or their metabolites, further disrupt the skin barrier and activate inflammatory response.[5] In recent years, studies investigating the skin microbial composition in disease states demonstrated that many other microbes were overrepresented in SD/DF individuals, including *Staphylococcus*, *Candida*, *Aspergillus* and *Filobasidium*.[6]

In this review, we aim to summarize current research on the skin bacterial and fungal microbiome in SD/DF. Further studies interpreting the role of the microbes in these disorders can further explain the pathogenesis of SD/DF.

2 | MATERIALS AND METHODS

2.1 | Search strategy and eligibility criteria

A systematic review was conducted to identify studies investigating the microbiome of SD/DF patients. The Medline/PubMed, Embase and Web of Science databases were searched using the following terms: ("seborrheic dermatitis" OR "dandruff") AND ("microbiome" OR "microbiota" OR "microflora"). References of included papers were checked and screened. Primary research studies were included if they applied culture-independent methods to characterize the skin microbiome of patients with SD/DF and published in English between 1 January 2000 and 31 December 2020. Review papers, case reports, meeting abstracts, studies irrelevant to skin microbiome alterations in SD, and studies using culture-dependent techniques were excluded from the analysis.

2.2 | Study selection and data extraction

Two authors (TR and WRJ) independently searched and screened the eligible papers. Inconsistencies were resolved by group discussion with a third reviewer (LRY). All types of study designs were eligible for inclusion. Out of the 283 papers identified from searching the databases, 12 papers were considered the most relevant to the association between the skin microbiome and SD/DF (Figure 1). Data extraction was performed independently by two authors, and the following information was extracted from eligible studies: author(s), publication year, country where the research was performed, characteristics of participants (number, mean age ± standard deviation, sex, lesional site), study methodology (sample collection and storage, DNA extraction, sequencing or identification method, platform and target, data analysis platform and reference sequences database), results of the alpha and beta diversity analysis, skin microbiome composition and physiological parameters.

3 | RESULTS

3.1 | Study characteristics

A total of 12 observational studies investigating the skin microbiome in patients with SD/DF were included. No interventional design was used in any of the included studies. Ten papers investigated the skin microbiome of the scalp in 366 patients (556 samples) in comparison with 246 healthy controls (317 samples); and the facial microbiome was assessed in 4 papers in a total of 77 patients (150 samples) and 46 healthy subjects (62 samples). Nine of the studies focused on the skin bacterial microbiome, and 11 studies reported the fungal

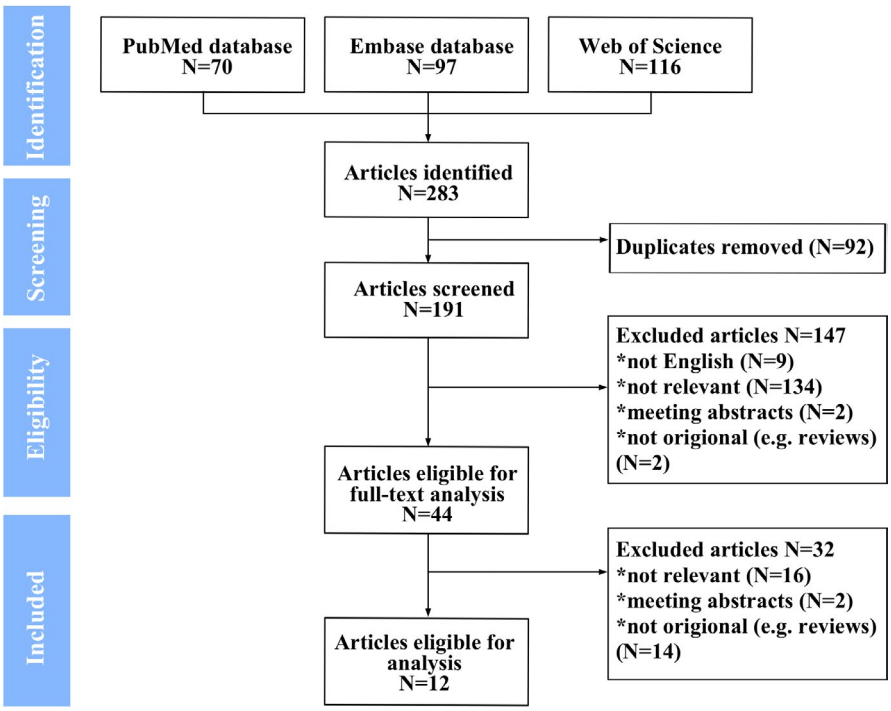

FIGURE 1 PRISMA flowchart of the literature search and selection

microbiome alterations in patients with SD/DF. A study by Saxena et al. was based on the shotgun metagenome sequencing method, and functional analysis of the KEGG pathways was performed.[4] Data on participants' demographics and study methodologies are summarized in Table S1 and Table S2 (in supplementary materials), respectively.

3.2 | Fungal microbiome alterations in SD/DF

The α-diversity, which measures the evenness and richness of fungal composition, was assessed in five studies using next-generation sequencing (NGS) methods. Two studies from East Asian countries showed decreased α-diversity, including lower richness and evenness, in DF scalps compared to healthy scalps.[7,8] However, two studies which were based on an Indian cohort and a Brazilian cohort showed an opposite trend with significantly higher Shannon diversity in the scalp and forehead of patients with SD/DF.[4,6] Geographic regions and the warm climate in Brazil and India might have an impact on the skin fungal microbiota. The β-diversity was investigated to evaluate the between-sample diversity of a microbiome. Three studies revealed distinct fungal communities among SD and healthy groups using principal coordinates analysis (PCoA), analysis of similarities (ANOSIM), metric multidimensional scaling (MDS) and non-metric multidimensional scaling (NMDS).[6–8] Most studies showed no clustering of samples in the fungal composition according to disease status or disease severity in SD/DF subjects.[7,9,10] The changes in α- and β-diversity in patients with SD/DF are presented in Table 1.

Significant shifts in the skin fungal community composition were shown in patients with SD/DF compared to healthy individuals. At the phylum level, the scalp and facial skin were dominated by Ascomycota and Basidiomycota, and the latter was increased in the patients with SD/DF.[7,11] In NGS-based studies, the predominant fungal genus of the skin microbiome was *Malassezia*, in which *M. restricta* and *M. globosa* were the major species. Increased relative abundances of the genera *Malassezia*, *Mycosphaerella*, *Candida* and *Filobasidium* were observed in SD patients compared to healthy individuals, and *Ganoderma*, *Exidia*, *Pilatoporus* and *Engyodontium* were enriched in healthy individuals.[7] However, controversial results were shown involving the trend of the change in *Aspergillus* between studies that were conducted in different geographic regions.[6,7] At the species level, studies using amplicon sequencing reported an increasing trend in the relative abundance of *M. restricta* and a decreasing trend in the relative abundance of *M. globosa* in lesional areas compared to non-lesional areas and healthy controls.[4,8,9,12,13] The same changing trend of the absolute abundance of *M. restricta* was observed in SD scalp in quantitative PCR-based studies, though facial SD was found to be associated with an slightly decreased abundance of *M. restricta*.[9,14,15] In addition, a significantly higher abundance of uncharacterized or unclassified *Malassezia* spp. was observed in DF scalps compared to healthy scalps.[4,9] A study using RFLP and Sanger sequencing showed a decreased abundance of *M. sympodialis*, *M. dermatis* and *M. pachydermatis* in DF which was, however, not observed in amplicon sequencing-based studies.[10] Alterations of the skin microbial composition in SD/DF are summarized in Table 2.

3.3 | Bacterial microbiome alterations in SD/DF

A total of nine studies investigated the composition and alterations of the bacterial microbiome in SD/DF patients (Table 1 and Table 2). Discrepancies exist between studies that were based on different populations or methodologies. The bacterial α-diversity was higher in the scalp of SD/DF patients compared to healthy individuals, though no difference was found between the lesional and non-lesional sites.[6–8] However, a study that focused on the facial SD microbiome demonstrated no difference in Shannon diversity between SD patients and controls.[16] Analysis of β-diversity revealed distinct bacterial community clustering between SD/DF scalps and healthy controls.[4,6–9,16] Higher between-sample distances were shown within the healthy scalps than within the DF scalps.[4]

The dominant bacteria of the face and scalp were Actinobacteria, which accounted for 64.9%, and Firmicutes, which accounted for 32.5% of the bacterial population.[6,13] At the genus level, *Cutibacterium*, *Staphylococcus* and *Corynebacterium* were the major bacteria. The included studies showed, overall, that the relative abundances of *Staphylococcus* and *Streptococcus* were increased in SD patients compared to healthy subjects, and that *Cutibacterium* was depleted in lesional sites of SD but overrepresented in the non-lesional sites.[6–9] The changing trend of the bacteria community composition in studies using quantitative PCR was mainly in accordance with those using NGS methods.[9,13,16] The ratio of *Staphylococcus/Cutibacterium* was significantly higher in individuals with DF than in healthy controls.[12,14] Due to the limited taxonomic resolution of the amplicon sequencing method, species-level analyses were mainly obtained from studies using metagenome sequencing or quantitative PCR with targeted primers. The abundances of *S. epidermidis* and *Pseudomonas nitroreducens* were found to be significantly elevated in patients with DF.[4,14]

3.4 | Enriched functional pathways in SD/DF

Out of the 12 included studies, only a study by Saxena et al.[4] performed shotgun metagenome sequencing to investigate the enriched functional pathways in SD/DF and their association with the skin microbiome.

The bacterial microbiome presented a number of decreased KEGG metabolic pathways, including those related to the metabolism and biosynthesis of vitamins, cofactors and amino acids and antibiotic resistance. These pathways were found to be negatively correlated with the DF score and itching. In addition, the commensal microorganisms such as *Cutibacterium* spp. carry genes for the synthesis of biotin and other vitamins, which is important to maintain a healthy scalp state.[4] For the fungal metabolic pathways, a higher metabolic diversity was observed in DF scalps, which was associated with an

TABLE 1 Skin α-diversity and β-diversity in seborrheic dermatitis and dandruff

Study	α-Diversity in SD/DF	β-Diversity in SD/DF
Fungal microbiome		
Lin et al. (2020)[7]	• Decreased Shannon diversity in SD scalps compared to healthy scalps • No significant changes in lesional sites compared to non-lesional sites of SD scalps	• PCoA could distinguish SD scalps and healthy scalps • No significant changes in lesional sites of SD scalps as compared to non-lesional sites
Grimshaw et al. (2019)[9]	N/A	• NMDS plots showed no distinct community clustering between SD scalps and heathy scalps
Saxena et al. (2018)[4]	• Significantly higher Shannon diversity in DF scalps compared to healthy scalps.	N/A
Park et al. (2017)[8]	• Significantly lower richness (Chao1) and lower evenness (Simpson's index) in SD/DF group	• PCoA and MDS plots showed distinct community clustering between SD/DF scalps and healthy scalps
Soares et al. (2016)[6] Soares et al. (2015)[10]	• Significantly increased Shannon diversity in DF scalps and foreheadN/A	• ANOSIM and NMDS plots showed distinct community clustering according to body sites, and between lesional and non-lesional sites in DF • NMDS plots showed no grouping of samples by disease severity
Clavaud et al. (2013)[14]	• No significant changes in Shannon-Weaver index in different body sites	N/A
Bacterial microbiome		
Lin et al. (2020)[7]	• No significant changes between SD group and healthy controls • No significant changes in lesional sites compared to non-lesional sites of SD scalps	• PCoA could distinguish SD scalps and healthy scalps • No significant changes in lesions as compared to non-lesional sites of SD scalps
Grimshaw et al. (2019)[9]	N/A	• NMDS plots showed bacterial communities of HC and non-lesional sites clustered away from lesional sites of SD/DF scalps
Saxena et al. (2018)[4]	• No significant changes between DF scalps compared to healthy scalps	• UniFrac distances showed significant difference between SD/DF scalps and healthy scalps
Park et al. (2017)[8]	• Significantly higher richness (Chao1) and lower evenness (Simpson's index) in SD/DF group	• PCoA and MDS plots showed distinct community clustering between SD/DF scalps and healthy scalps
Tanaka et al. (2016)[16]	• No significant changes between non-lesional and lesional sites	• PCoA showed clear separation between lesional and non-lesional sites
Soares et al. (2016)[6]	• Significantly increased Shannon diversity in DF scalps and forehead compared to healthy controls	• ANOSIM and NMDS plots showed distinct community clustering according to body sites and between lesional and non-lesional sites in DF

Abbreviations: ANOSIM, analysis of similarities; DF, dandruff; MDS, metric multidimensional scaling; N/A, not available; NMDS, non-metric multidimensional scaling; PCoA, principal coordinates analysis; SD, seborrheic dermatitis.

increased diversity of the fungal microbiome. The enrichment of the fungal species *M. restricta* in DF was suggested to be correlated with several enriched KEGG metabolic pathways, such as amino acid metabolism and those related to general functions and genetic information. The N-glycan biosynthesis pathway, which is essential for glycoprotein biosynthesis and adherence to the host surface, has a significant positive correlation with *M. restricta*. The decreased eukaryotic pathways were mainly those for genetic information processing, such as base excision repair and oxidative phosphorylation pathways, which have close ties with *Malassezia obtusa* and *Malassezia furfur*. The study also suggested that clinical parameters, such as disease score, itch and trans-epidermal water loss (TEWL), have a positive correlation with essential cellular pathways, including N-glycan biosynthesis, cell cycle and RNA transport, and a negative correlation with amino acid and lipoic acid metabolism.[4]

3.5 | Correlation between skin microbiome and host factors

Physiological parameters, including pH, hydration, sebum and TEWL, and symptomatic factors, including itching and DF scores,

TABLE 2 Skin microbiome and mycobiome alterations in seborrheic dermatitis and dandruff

Sample collection	Fungal abundances differing from controls	Bacterial abundances differing from controls
Lin et al. (2020)[7]	*Malassezia*↑, *Mycosphaerella*↑, *Aspergillus*↓, *Ganoderma*↓, *Exidia*↓, *Pilatoporus*↓, *Engyodontium*↓	*Staphylococcus*↑ (**), *Brevibacterium*↑, *Pseudomonas*↓ (**)
Grimshaw et al. (2019)[9]	Unclassified *Malassezia* sp.↑ (*) LS: *M. restricta*↑ (***) NLS: *M. globosa*↑ (***)	*Staphylococcus*↑ (***), *S. capitis*↑ (***), *S. epidermidis*↓ (**) LS vs. NLS: *Staphylococcus*↑ (***), *Cutibacterium*↓ (***)
Saxena et al. (2018)[4]	*M. restricta* /*M. globosa* ratio↑ (*), uncultured *Malassezia* sp.↑ (***), *M. globosa* ↓ (***)	*S. epidermidis*↑ (***), *Pseudomonas nitroreducens*↓ (***), *C. acnes*/*S. epidermidis*↓ ratio (*)
Park et al. (2017)[8]	*M. restricta*↑, *M. globosa*↓	*Chryseobacterium*↑, *Cutibacterium*↑, *Staphylococcus*↑ (*), *Streptococcus*↑ (*), *Rhizobium*↓, *Gordonia*↓, *Sphingomonas*↓
Tanaka et al. (2016)[16]	N/A	LS: Acinetobacter↑, *Staphylococcus*↑, *Streptococcus*↑
Xu et al. (2016)[13]	LS: *M. globosa*↓ (*)	LS: *Staphylococcus*↑ (***), *Cutibacterium*↓ (***)
Soares et al. (2016)[6]	*Candida*↑, *Aspergillus*↑, *Filobasidium*↑	*Pseudomonas*↑, *Leptotrichia*↑, *Micrococcus*↑, *Selenomonas*↑, *Erwinia*↑, *Enhydrobacter*↑, *Bartonellaceae*↑, *Cutibacterium*↓
Wang et al. (2015)[12]	*M. restricta*/*Cutibacterium* ratio↑ (**)	*S. caprae*↑, *S. capitis*↑, *Staphylococcus*/*Cutibacterium* ratio↑ (*), *C. granulosum*↓ (absent)
Soares et al. (2015)[10]	*M. restricta*↑, *M. globosa*↑, *M. sympodialis*↓, *M. dermatis*↓, *M. pachydermatis*↓	N/A
Clavaud et al. (2013)[14]	*M. restricta*↑ (*), *M. restricta*/*C. acnes* ratio↑ (**)	*S. epidermidis*↑ (*), *C. acnes*↓ (**), *S. epidermidis*/*C. acnes* ratio↑
Park et al. (2012)[11]	Basidiomycota↑ (***), *Filobasidium floriforme*↑ (***), *Malassezia* spp. ↑ (***), *Penicillium* spp.↑ (***), Ascomycota↓ (***), *Acremonium*↓ (***), *Cryptococcus*↓(***), *Didymella*↓ (***), *Rhodotorula*↓ (***)	N/A
Tajima et al. (2008)[15]	LS vs. HC: *M. globosa*↑, *M. restricta*↓ LS vs. NLS: *M. globosa*↑, *M. restricta*↑	N/A

Note: Abbreviations: HC, healthy control; LS, lesional sites; N/A, not available; NLS, non-lesional sites.
*$p < 0.05$, **$p < 0.05$, ***$p < 0.05$.

were evaluated to determine skin barrier function and disease severity, respectively, in SD/DF.

Correlation analysis of bacteria and physiological parameters demonstrated a positive correlation between *Staphylococcus* and pH; *Devosia* and *Sediminibacterium* and hydration; *Rhodoplanes* and TEWL, and a negative correlation between *Aspergillus penicilloides* and sebum.[4,7] The study by Xu et al.[13] confirmed a positive trend between *Staphylococcus* and TEWL and water content, and they also found that *Cutibacterium* was positively correlated with sebum and water content. In addition, *S. epidermidis* and *Staphylococcus* spp. were positively correlated with dandruff scores, TEWL and itch, but negatively correlated with hydration, indicating their potential role in causing damage to the skin barrier and exacerbating SD/DF.[4] A negative correlation between *Pseudomonas* spp. and hydration, sebum levels and TEWL was also observed. Further analysis of the association between physiological parameters and disease severity revealed that TEWL was positively associated with itching and DF scores.[4] For the analysis of the correlation between fungi and skin barrier function, the relative abundances of *M. restricta* and *Aspergillus penicilloides* were positively correlated with sebum level.[7] Disease severity parameters such as itch and DF scores were positively correlated with *Malassezia* spp. and uncultured *Malassezia* and negatively correlated with *M. globosa*.[4]

4 | DISCUSSION

The skin, which is colonized by a large variety of microbial communities, maintains a delicate balance in healthy status. Alterations in skin microbial communities have been recognized to be associated with the pathogenesis of SD/DF. This paper provides a comprehensive review of the characteristic shifts in the skin bacterial and fungal microbiome in SD/DF. In general, the included studies demonstrated an increase in the *M. restricta*/*M. globosa* ratio and a reduction in the *Cutibaterium*/*Staphylococcus* ratio in the setting of SD/DF.

Nonculture-based studies can identify microorganisms that do not readily grow in culture medium and more accurately reflect microbial composition. Quantitative PCR has been used in many studies to quantify gene numbers present within samples. However, a major disadvantage of this method is that it is limited to the analysis

of sequences related to those that have already been characterized.[17] In recent years, amplicon sequencing has become the most widely used technique to reflect the composition and characteristics of the microbiome. Amplicon sequencing can display the relative abundance of all of the bacteria and fungi in the sample. However, methods that use relative abundance is limited by the fact that they cannot determine the magnitude of the change of an individual taxon between groups. Another limitation of amplicon sequencing is that the short read lengths of the 16S rRNA regions may cause the reads unable to provide taxonomic resolution at species and strain levels.[18] Also, the 16S rRNA genes may present in multiple copies in some bacteria, which may lead to an artificial over-representation in data.[19] In contrast, metagenome shotgun sequencing is able to detect organisms at the species level.

Although most of the studies showed consistent changing trend in the skin microbiome of patients with SD/DF, some studies were conflicting. The discrepancies between study results could be explained by the heterogeneity between individuals, and differences in study population, sampling method and sequencing techniques. Skin fungal microbiota has been found to be varied with geography and ethnicity, with lower proportion of fungal members and different abundancy of specific bacterial species in the Chinese facial samples compared to North American samples.[20] In our review, two studies from Asian countries revealed decreased Shannon diversity in dandruff scalps, which was opposite to studies from India and Brazil revealing an increased trend of fungal diversity.[4,6,7,11] In addition, the changing trend of *S. epidermidis*, *Cutibacterium* and some species of *Malassezia* in SD lesions showed controversial results between studies, which may result from different sequencing methods. The abundance of *M. globosa* was decreased in studies based on amplicon sequencing or quantitative PCR, but an opposite trend in its abundance was found in the study using RFLP and Sanger sequencing.[4,6,7,10] The sequencing regions of the targeted gene may also significantly affect recapitulation of the microbial community composition, and a different changing trend of *Cutibacterium* was found between the study using V4–V5 tag sequencing and those using other tags.[8]

In most of the included studies, an imbalance in the proportion of specific *Malassezia* species has been observed in SD/DF. *Malassezia* is a lipophilic resident yeast that lives in the stratum corneum and follicular infundibulum of sebaceous-gland-enriched skin areas.[21] So far, eighteen lipophilic species of *Malassezia* spp. have been isolated from mammals' skin.[22] Conventional culture-based studies showed that *M. globosa* and *M. restricta* were the predominant species in SD patients.[23] Disequilibrium in the ratio of *M. restricta*/*M. globosa* has been demonstrated in association with the occurrence of SD. *M. restricta* has been shown to cause skin barrier disruption and tissue toxicity; however, more studies are needed to better illustrate the exact pathogenic mechanism of this species in SD.[24] Previous studies show that *Malassezia* spp. play a pathogenic role in SD/DF by extracellular secretions and direct interactions with the host through pattern recognition receptors (PRRs). The lipases and phospholipases secreted by *Malassezia* can break down sebum on the skin's surface into fatty acids and the large amount of unsaturated fatty acids on the skin surface, such as oleic acid and arachidonic acid, can trigger inflammatory response, epidermal proliferation and epithelial barrier disruption.[25–29] It has also been found that the indole-3-carbaldehyde produced by *Malassezia* lesions has a strong binding force with the AhR, to trigger immunological processes in SD.[30] In addition to excretions, *Malassezia* can be directly recognized by the PRRs to activated the downstream inflammatory pathways.[31,32]

Dysbiosis in the bacterial microbiome composition has also been demonstrated in SD lesions. An increased level of *Staphylococcus* has been shown in the lesional sites of SD, and its relative abundance is positively correlated with epidermal barrier damage and the itching and scaly scores of SD/DF.[7,13] The predominance of *Staphylococcus* on the lesional skin of SD patients is consistent with a previous culture-based study which reported a high isolation rate of *S. aureus* in patients with SD compared to healthy individuals.[33] The overgrowth and metabolisms of *Malassezia* may probably have effects on the proliferation of *Staphylococcus*. The unsaturated fatty acids produced by *Malassezia* create a high pH environment, which is favourable for the growth of *S. aureus* and promotes its adhesion to keratinocytes, while the commensal *M. globosa* can secrete aspartyl protease to hinder the biofilm formation and damaging effects of *S. aureus*.[24,34,35]In addition, a significantly decreased level of *Cutibacterium* in SD lesional sites has been demonstrated in most of the included studies, indicating a role of this commensal in maintaining normal skin microbial communities. Similar to *Malassezia* spp., *Cutibacterium* lives in seborrheic areas and produces proteases to acquire nutrients from lipid-rich sebum.[36] Previous studies showed that *Cutibacterium* could suppress the overgrowth of *Staphylococcus* through the secretion of bacteriocin, while *Staphylococcus* possessed an arsenal of different mechanisms to inhibit *Cutibacterium acnes*, such as by the fermentation of glycerol.[13,37,38] A study by Meloni et al. revealed that the co-colonization of *C. acnes*-*M. restricta* can decrease damage to the skin barrier compared to single colonization with *M. restricta*.[24] The beneficial role of *Cutibacterium* in the maintenance of a healthy skin barrier was also demonstrated by a positive correlation between *Cutibacterium* and water content.[13] Thus, the restoration of skin microbial composition by increasing the amounts of protective microbes and reducing the amounts of potential pathogens can help to rebuild the skin barrier.

An approach to manipulate the skin microbiome in patients with SD is by using topical and systemic antimicrobial agents. Ciclopirox olamine and ketoconazole are both recognized as level A recommendations as they are consistently effective across randomized controlled trials.[39] Topical ketoconazole is commonly used for treatment of SD, and the disease-associated species *M. restricta* was found to be susceptible to this medication.[40] Oral itraconazole has been shown to significantly improve erythema, scaling and itching, accompanied by a decreased quantity of *Malassezia* spores in direct smear.[41] Further human studies are needed to explore how the facial microbiome is manipulated by antifungal agents and the association between resilience of the skin microbiome and disease severity. Although the sequencing-based studies suggest that *Staphylococcus*

has a role in the development of SD, the therapeutic effects of antibiotics have not yet been elucidated and need more investigations. In addition, applying moisturizers containing beneficial microorganisms has been shown to be effective for prevention and treatment of atopic dermatitis.[19] Thus, to utilize the skin microbiome as a therapeutic strategy for SD/DF, researches on the dynamic changes in microbial community compositions in relation to clinical severity and different types of treatment can help to predict responses and search for new therapies.

The studies discussed in this review have several limitations. First, we found a high heterogeneity of sequencing or identification methods, including cloning and Sanger sequencing, quantitative PCR, amplicon sequencing and whole metagenome sequencing, among the studies included in this analysis. Although different methodologies may affect study outcome, most of the studies showed similar findings on alterations in microbial composition, suggesting reliable analytic results using any of the sequencing tools. Defects in the technology itself can also influence the accuracy of the results, and amplicon sequencing of the partial 16S rRNA marker genes have been considered unsuitable for species profiling.[42] Moreover, controversy exists over the accuracy of sequencing targeting different hypervariable regions of the 16S rRNA gene: the V1–V3 region of the 16S rRNA gene has been shown to provide more reliable results than the V4 region, however, another study shows that the V4/V5 regions can provide the highest classification accuracy.[43,44] Second, the majority of the studies were performed in the Asia-Pacific region. Since the skin microbiome can be influenced by ethnic group, diet and environment, the impact of geographic factors should be taken into consideration. In addition, no interventional studies comparing the changes in the microbiome before and after treatment were included in this analysis.

5 | CONCLUSION

In conclusion, the included studies in this reviewed showed significant skin dysbiosis in SD/DF patients with an increased relative abundance of *M. restricta* and *Staphylococcus*. These microbes may play a role in the pathogenesis of SD/DF by disrupting the skin barrier and exacerbating inflammation. Some studies also reported a protective role of *Cutibacterium* in maintaining healthy skin barrier function through elevating the water content of the stratum corneum. Further studies focusing on the interaction between different microbes and the host and microbes can provide better insight into the role of microbial alterations in the pathogenesis of SD/DF.

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CONFLICT OF INTEREST

The authors Rong Tao, Ruoyu Li and Ruojun Wang declare no conflict of interests.

AUTHOR CONTRIBUTIONS

R.T and R.W.: Conceptualization. R.T.: Writing—original draft preparation. R.W.: Writing—review and editing. R.L.: Supervision. All authors have read and agreed to the published version of the manuscript.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

Table S1. Characteristics of the included studies.

Table S2. Sample and methodology characteristics of the included studies.

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