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SYSTEMATIC REVIEW

Probiotics, Prebiotics, and Synbiotics for the Treatment and Prevention of Adult Dermatological Diseases

Manisha Notay[1] · Negar Foolad[1] · Alexandra R. Vaughn[1,2] · Raja K. Sivamani[1,3]

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Abstract

Background Probiotic, prebiotic, and synbiotic supplementation is becoming more prevalent nowadays. Clinical studies have demonstrated some of the medical benefits of probiotics, prebiotics, and synbiotics within dermatology but an evidence-based review of their effects in adults is needed.

Objective The aim of this study was to identify evidence for the use of supplementation with probiotics, prebiotics, or synbiotics for the prevention and treatment of dermatological diseases in adults.

Data sources We conducted a search of the Ovid MEDLINE, Cochrane Central Register of Controlled trials and EMBASE electronic databases from 1 January 1946 to 11 January 2017.

Study selection Trials examining supplementation in the treatment of dermatological diseases using oral or topical probiotics, synbiotics, and prebiotics in adults over the age of 18 years were selected.

Data extraction Of 315 articles, 12 met the inclusion criteria.

Data synthesis Nutritional supplementation with probiotics and prebiotics was shown to improve atopic dermatitis (AD) symptomatology, quality of life, or clinical severity in six of nine studies. One study in psoriasis was shown to improve inflammatory markers, and one study suggested that probiotics could be used as adjunctive therapy in the treatment of acne.

Conclusion Preliminary studies are optimistic for the use of some strains of probiotics for symptomatic and clinical improvement in AD, and as adjunctive treatment with antibiotics for acne. Further research is necessary to better assess how probiotics and prebiotics may be used within dermatology.

Key Points

Probiotics may be useful in the treatment of adults with atopic dermatitis and acne.

The mechanism of action remains unclear but is thought to be due to the alteration of the gut microbiome and modulation of the immune system.

More studies of probiotics and prebiotics for the skin are warranted.

1 Introduction

Probiotics are live microorganisms that can confer health benefits when administered in adequate doses [1]. The most commonly used microorganisms are *Lactobacillus, Bifidobacterium, Enterococcus, Pronionibacterium,* and some yeasts such as *Saccharomyces boulardii*. Their health benefits include the prevention of antibiotic-associated diarrhea, treatment of irritable bowel syndrome, and inflammatory bowel disease [2].

✉ Raja K. Sivamani
raja.sivamani.md@gmail.com

[1] Department of Dermatology, UC Davis, 3301 C Street, Suite 1400, Sacramento, CA 95816, USA

[2] Drexel University College of Medicine, Philadelphia PA, USA

[3] Department of Biological Sciences, California State University – Sacramento, Sacramento, CA, USA

Prebiotics are ingredients and substances that can promote the growth of certain bacteria in the gut. It is believed that an ingredient must possess three key features to be considered a prebiotic. First, it should resist breakdown by mammalian enzymes and gastrointestinal absorption; second, it must be fermented by the microbiotia of the intestine; and, last, it must be able to selectively stimulate the growth and/or activity of the intestinal bacteria, which have been associated with improving human health [3]. Prebiotics usually target the activity of *Lactobacillus* and *Bifidobacterium* [4].

Synbiotics are composed of a combination of prebiotics and probiotics. The prebiotic component is thought to assist with the implantation and survival of live microbial dietary supplements. Specifically, the prebiotic component must selectively favor the probiotic organisms in the formulation [5].

There is a growing body of research involving the use of prebiotics, probiotics, and synbiotics in pediatric atopic dermatitis (AD). Research suggests pre- or probiotics may be beneficial in the prevention and amelioration of AD [6], which is thought to be due to the alteration of the intestinal microbiome and modulation of the immune system. Fewer studies exist regarding the use of prebiotics and probiotics in adults with dermatological diseases, and we sought to investigate and review the current clinical evidence [7].

2 Methods

We conducted a search of the Ovid MEDLINE, Cochrane Central Register of Controlled Trials, and EMBASE electronic databases for articles published from 1 January 1946 to 11 January 2017. For Ovid MEDLINE, we used the search terms 'probiotics', 'prebiotics', 'synbiotics', 'skin diseases', 'humans' and 'clinical trial. The following Medical Subject Heading (MeSH) terms were combined using the 'AND' Boolean operator to find relevant studies in the Cochrane Central Register of Controlled Trials: 'skin diseases', 'probiotics', 'prebiotics', and 'synbiotics'. Additionally, the following search terms were used in EMBASE for relevant studies: 'skin', 'diseases', 'probiotic agent', 'prebiotic agent', 'synbiotic agent', 'clinical trial', and 'humans'. Our searches were limited to articles that tested probiotics, prebiotics, or synbiotics among adults only. Furthermore, we searched through the references of the chosen articles for additional studies.

2.1 Inclusion and Exclusion Criteria

We included clinical trials and cohort studies that examined the effect of probiotics, prebiotics, or synbiotics among adults 18 years of age and older with a dermatological condition. Studies that reported the treatment or prevention of dermatological diseases were selected. Publications were excluded if infants, children, or adolescents were included.

2.2 Study Selection and Data Extraction

On the basis of our selection criteria, all authors (MN, NF, ARV, and RKS) independently reviewed all eligible studies and the final 12 full-text articles, and resolved any differences by consensus. For each study, the following information was abstracted and is documented in Tables 1 and 2: (1) skin disease, (2) number of subjects, (3) study design, (4) probiotic intervention, (5) intervention dosage, (6) primary outcome measures, and (7) major results. A total of 420 patients were included in these 12 studies (Fig. 1).

2.3 Quality of Included Studies

Study quality was assessed independently using the Jadad score for analyzing randomized controlled trials (RCTs) [8]; the Jadad score establishes the methodological quality of studies based on a 5-point scale according to reproducibility and appropriateness of randomization, blinding, and the fate of subjects. Using this system, the quality of a trial is categorized as 'high' (Jadad score 3–5) or 'low' (Jadad score 0–2) [8].

3 Results

3.1 Atopic Dermatitis

Nine studies assessed the impact of probiotics in adults with AD [1], and no studies were identified in adults for the treatment of AD with prebiotics or synbiotics.

3.1.1 Bifidobacterium

One randomized, double-blind, placebo-controlled study using *Bifidobacterium animalis* (subsp. lactis LKM512) found that subjects in the probiotic group experienced a significant improvement in itch after 8 weeks [9]. This group also experienced an improvement in the dermatology-specific quality-of-life (QoL) questionnaires. The researchers followed the severity of AD utilizing a 5-point scale and found that while probiotic supplementation improved clinical severity compared with baseline, there was no significant difference in severity scores between groups. Researchers found an increase in the anti-nociceptive metabolite kynurenic acid (KYNA) in three patients whose itch improved after the administration of

Table 1 Human clinical trials of probiotics, prebiotics, and synbiotics for the treatment of atopic dermatitis in adults

Skin condition	Study	No. of subjects	Study design and duration	Intervention	Dosage	Control or placebo	Primary outcome measures	Results	Study limitations	Jadad score (RCT)
AD	Matsumoto et al. [9]	44 Male and female Japanese adults with moderate or severe AD, mean age 33–34 years (age cut-off not specified)	8-week, rand, db, pc, parallel-group comparative study	Capsules containing *B. animalis* (subsp. *lactis* LKM512)	6×10^9 CFU *B. animalis* subsp. *lactis* LKM512 per capsule (capsule also contained skim milk, glucose, inulin, dextrin, and silicon dioxide)	Placebo capsule containing skim milk, glucose, inulin, dextrin, and silicon dioxide	Severity grading of AD (5-point scale based on clinical assessment) Itch grading during the day and at night (VAS score) QoL questionnaire Fecal microbiome analysis using RT-PCR and T-RFLP Fecal KYNA concentrations	NS difference in severity of AD or VAS scores between groups. Severity scores of AD group did improve compared with baseline in the probiotic group Improvement in itch and QoL scores in probiotic group only SS higher fecal populations of *Atopobium* and LKM512 in the probiotic group compared with placebo KYNA concentration significantly increased in feces of the probiotic group compared with the placebo group		5
AD	Matsumoto et al. [10]	10 Adult males and females diagnosed with moderate AD (average age 22.1 years, age cut-off not specified)	12 weeks (4 weeks treatment yogurt, 4 weeks washout, 4 weeks placebo yogurt) db, rand, pc crossover study	LKM512 yogurt: *B. animalis* (subsp. *lactis* LKM512), *Lactobacillus delbrucckii* (subsp *bulgarius* KLM1759), and *Streptococcus thermophiles* LKM1742	5.2×10^7 CFU/g *B. animalis* (subsp. *lactis* LKM512) 4.7×10^8 CFU/g the lactic acid bacteria Dose: 100 g/day of yogurt per individual	Yogurt fermented with *L. delbrucckii* (subsp. *bulgaricus* LKM1759) and *S. thermophiles* LKM1742	Subjective symptoms ('itch' and 'burning') Fecal short chain fatty acids Serum cytokines (IL-4, IL-5, IL-10, IL-12, IFNγ)	Improvement in itch and burning in 4/10 and 3/8 with LKM512 yogurt consumption. Improvement in itch and burning in 1/10 and 2/8 subjects in placebo groups NS increase in acetate, propionate, butyrate, and isobutyrate after LKM512 yogurt SS increase in IFNγ in the LKM512 group	Small sample size All subjects enrolled had been previously undergoing long-term Kampo treatment, therefore all changes cannot be solely attributable to LKM512 yogurt consumption	
AD	Yoshida et al. [12]	24 Adult patients (aged 20–65 years) diagnosed with AD	8-week, rand, db, pc study	Test capsules filled with lyophilized powder of live *Bifidobacterium breve* (strain YY)	2.0×10^{10} CFU per capsule, subjects took two capsules per day	Placebo capsules (contents unspecified)	AD severity using SCORAD Serum IgE, eosinophils, and plasma TARC QoL questionnaire	SS decrease in the objective SCORAD of the probiotic group. NS change in SCORAD in the placebo group NS change in serum IgE, plasma TARC, or serum eosinophils in either group SS decrease in QoL score in the probiotic group, but NS change in the placebo group	The overall symptoms of disease severity were lower in the placebo group than the treatment group at baseline Small subject number	2

Table 1 continued

Skin condition	Study	No. of subjects	Study design and duration	Intervention	Dosage	Control or placebo	Primary outcome measures	Results	Study limitations	Jadad score (RCT)
AD	Drago et al. [14]	38 Males and females, aged 18–46 years, with moderate/severe AD	16-week, rand, db, pc study	Sachets containing freeze-dried *L. salivarius* LS01	1×10^9 CFU/g in maltodextrin, twice daily	Maltodextrin alone, twice daily	AD severity using SCORAD DLQI questionnaire Serum IgE Quantification of fecal bacteria	SS decrease in SCORAD score only in the probiotic group DLQI score progressively decreased, with maximum decrease at week 8 in the probiotic group only NS change in serum IgE in either group SS decrease in fecal staphylococci in the probiotic group, persisting even 1 month after treatment ended		5
AD	Kaur et al. [15]	16 Healthy male and female volunteers with mild-to-moderate AD aged 20–42 years	12-week, rand, open comparative study	Goat milk fermented with *L. fermentum* (ME-3)	200 mg/day containing 3×10^9 CFU/ml	Control group did not receive probiotic drink	AD severity using SCORAD Skin iron level Total glutathione and GSSG of skin and blood Oxidized LDL Serum TAC and TAA	NS decrease in SCORAD index in treatment and control groups SS decrease in skin iron from 300 to 100 umol/g in the probiotic group SS decrease in GSSG in the probiotic group Oxidized LDL SS decreased in the probiotic group compared with the control group SS increase in TAC and TAA in the probiotic group compared with the control group	Limited subject number No blinding, thus increasing the risk for bias	2
AD	Moroi et al. [16]	34 Male and female Japanese adults, aged 20–65 years with mild to moderate AD	12-week, prospective, rand, db, pc, parallel-group comparative	Heat-killed *L. paracasei* K71	100 mg ($\sim 2 \times 10^{11}$) heat-killed *L. paracasei* and 400 mg dextrin NSD300 (dissolved in water, coffee, or tea)	500 mg dextrin and 0.45 mg carotene (dissolved in water, coffee, or tea)	5-point skin severity score (0 = no symptom, 1 = mild, 2 = moderate, 3 = severe, 4 = extremely severe) Itch scores VAS at daytime and night QoL questionnaire AE	SS decrease in skin severity scores in the *L. paracasei* group compared with placebo ($p < 0.01$) No change in itch or QoL scores in either group No AE reported	Use of topical medications during the study could confound the results	5

Table 1 continued

Skin condition	Study	No. of subjects	Study design and duration	Intervention	Dosage	Control or placebo	Primary outcome measures	Results	Study limitations	Jadad score (RCT)
AD	Iemoli et al. [18]	48 Males and females with AD, aged 30–35 years	12-week, db, rand, pc study	Freeze-dried mixture of *L. salivarius* LS01 DSM 2275 and *B. breve* BR03 DSM 16604	1×10^9 CFU/g each bacterial stain in maltrodextrin, twice daily	Placebo: maltrodextrin, twice daily (freeze-dried powder)	AD severity using SCORAD DLQI questionnaire Gut permeability barrier (plasma LPS) Immunologic parameters (peripheral blood mononuclear cells, activated CD8+ T cells, Th1, Th2, Th17 and Treg cells)	SS decrease in SCORAD index in the probiotic group only after 12 weeks SS decrease in DLQI in the probiotic group only after 12 weeks Plasma LPS was SS higher in the control group than the treatment group at the end of treatment Activated $CD8^+$ T cells decreased throughout treatment in the probiotic group SS increase in unstimulated Tregs in the probiotic group Probiotic-induced SS increase in Th1 cells and decrease in Th2 and Th17 cells SS decrease in staphylococci in the probiotic group compared with placebo	Low patient number Higher number of patients with respiratory allergy in the probiotic group (could explain elevated LPS)	5
AD	Roessler et al. [19]	30 15 healthy patients (mean age 24 ± 3 years) and 15 people with AD (mean age 23 ± 3 years) [age cutoff not specified]	8-week × 2 db, pc, rand crossover study	Probiotic yoghurt drink containing *S. thermophilus, L. paracasei* LPC-37, *L. acidophilus* 74-2, and *B. animalis subsp. lactis DGCC*420	100 mL twice daily	Placebo drink: identical composition as treatment drink, but without the probiotic strains	AD severity using SCORAD Major leukocyte subset phenotypes of blood Phagocytic and oxidative burst activity of granulocytes and monocytes	The SCORAD in AD group decreased by 15.5%, but NS SS increase in $CD57^+$ in healthy subjects after probiotic supplementation, but not in the AD group. SS decrease in $CD4^+CD54^+$ in AD patients, only No difference in $CD4^+CD25^+$ T cells between groups SS increase in phagocytic activity of granulocytes and monocytes in healthy subjects after probiotic treatment		5

Table 1 continued

Skin condition	Study	No. of subjects	Study design and duration	Intervention	Dosage	Control or placebo	Primary outcome measures	Results	Study limitations	Jadad score (RCT)
AD	Drago et al. [20]	25 Males and females, aged 25–63 years with AD	30-day, prospective, controlled pilot trial	Sachets containing freeze-dried mixture of *L. salivarius* LS01DSM 22775 and *S. thermophiles* ST10 DSM 25246	5×10^9 CFU/sachet of *L. salivarius* 2×10^9 CFU/sachet of *S. thermophilus*	Gluten-free maltodextrin	AD severity using SCORAD Fecal counts of *S. aureus* and clostridium using DNA sequencing	SS decrease in SCORAD index in the probiotic group and no change in the placebo group No change in fecal counts of clostridia between probiotic and placebo groups 10 of 13 patients in probiotic group had NS decrease in fecal *S. aureus*	Use of topical corticosteroids and other medications was not recorded, therefore results could be confounded Duration of study (only 30 days) was much shorter compared with other published clinical studies No follow-up data after probiotic discontinuation	3

AD Atopic dermatitis, *AE* adverse event, *CFU* colony forming unit, *db* double-blind, *DLQI* Dermatology Life Quality Index, *GSSG* oxidized glutathione, *Ig* immunoglobulin, *IL* interleukin, *IFN* interferon, *KYNA* kynurenic acid, *LDL* low-density lipoprotein, *LPS* lipopolysaccharide, *NS* not statistically significant, *pc* placebo-controlled, *QoL* quality of life, *Rand* randomized, *RCT* randomized controlled trial, *RT-PCR* real-time polymerase chain reaction, *SCORAD* SCORing Atopic Dermatitis, *SS* statistically significant, *Th* T helper, *Treg* T regulatory, *TAC/TAA* total antioxidant capacity/total antioxidant ability, *TARC* thymus and activation-regulated chemokine, *T-RFLP* terminal restriction fragment length polymorphism, *VAS* visual analog scale

LKM512 [9]. It was postulated that this improvement was due to KYNA production in the intestines; therefore, this could be a potential treatment for AD-associated pruritus [9].

Additionally, a prior 8-week crossover trial found that patients taking *B. animalis* (subsp. lactis LKM512) experienced moderate improvement in the symptoms of itch and burning when compared with placebo [10]. All patients enrolled had been previously treated with long-term Kampo medicine (the practice of Chinese herbal medicine in Japan), which could make it difficult to differentiate between the effects of Kampo medication and the effects of *B. animalis*. A statistically significant increase in interferon (IFN)-γ was observed in both groups, however the increase was greater in the probiotic group [10]. The authors of the study did not suggest an explanation for this; however, studies in children have shown an increase in IFNγ after the administration of probiotics. It has been postulated that this is a reflection of an increased T helper (Th)1 response [11], although the significance of this is not clear.

In a study by Yoshida et al. [12], *Bifidobacterium breve* (strain YY) was administered to adults with AD over an 8-week period. Compared with controls, the probiotic group ($n = 16$) demonstrated a decline in the SCORAD (SCORing Atopic Dermatitis) index after 8 weeks [12]; however, the only parameter of the SCORAD index that showed a statistically significant decline was the intensity criteria (8.0 ± 2.9–6.8 ± 3.0; $p = 0.018$). There was a statistically significant reduction in the objective SCORAD (33.7 ± 13.6–23.8 ± 4.0; $p = 0.034$), which consisted of the extent and intensity parameters but excluded subjective symptoms. Furthermore, there was a statistically significant decline in the QoL 'Skindex-29-J' scores (a questionnaire that assesses symptoms, functioning, and emotions in AD patients over the previous 4 weeks [13]) in the probiotic group ($p = 0.019$) compared with baseline. In the study, subjects were not randomized according to disease severity, and subjects with higher disease severity were found in the probiotic arm of the study. The average total baseline SCORAD scores for the probiotic and placebo groups were 41.0 and 25.7, respectively ($p = 0.027$). This may have unevenly affected the ability of each treatment group to improve. In the study, stool samples demonstrated the probiotic was able to colonize the gastrointestinal (GI) tract as there was an increase in the colonization rate of the gut microbiome with Bifidobacteria [12].

3.1.2 *Lactobacillus*

Researchers studied the effects of *Lactobacillus salivarius* LS01 for 16 weeks in adults with AD [14] and noted a significant reduction in the SCORAD and Dermatology Life Quality Index (DLQI) ratings in the probiotic-treated

group (week 0: 27.6 ± 3.4 vs. week 16: 13.1 ± 0.3; $p < 0.001$). Moreover, there was a statistically significant decline in Th1 and Th2 cytokines compared with baseline in the placebo group only (T0: 28.2 ± 2.5 pg/ml vs. T16: 33.0 ± 3.3). The staphylococcal load in the fecal microbiome in the probiotic-treated group was reduced [14].

One study used *Lactobacillus fermentum* (ME-3) over a 3-month period in 10 patients with AD compared to another group that did not receive a probiotic [15]. Patients in both groups experienced a non-significant improvement in their SCORAD index. Among the probiotic-treated group, a significant reduction was seen in skin iron levels, diene conjugate (DC) levels, and glutathione redox ratios, which are all markers of oxidative stress. In addition, there was a statistically significant decline in blood markers of oxidative stress, such as oxidatively modified low-density lipoprotein (oxLDL). This demonstrated that AD patients could be at higher oxidative burden, which may be reduced by the administration of a probiotic [15]. The significance of the reduction in oxidative stress is not clear since there was no difference in the improvement of the SCORAD index.

In another study, 34 subjects with AD were administered placebo or probiotic *Lactobacillus paracasei* K71 fora period of 12 weeks [16]. Skin severity scores (based on eruption intensity and area of involvement developed by the Japanese Dermatological Association [17]) in the probiotic group were decreased from baseline, at week 8 ($p < 0.05$), and at week 12 ($p < 0.01$). There was no influence of probiotic use on the QoL or itch scoring. Subsequently, the placebo group had a 1.9-fold greater use in topical therapeutics in the placebo group; however, this difference was not statistically significant [16].

3.1.3 Probiotic Mixtures

Researchers conducted an RCT using a combination of probiotics containing *Lactobacillus salivarius* LS01 DSM 2275 and *Bifidobacterium breve* BR03 DSM 16604 [18]. Subjects using probiotics had a significant improvement in clinical scores (SCORAD and DLQI). The researchers also observed a reduction in plasma lipopolysaccharide (LPS) in the probiotic group. Plasma LPS is a marker of inflammation and permeability of the intestinal endothelium. It is thought that altered gut permeability leads to toll-like receptor (TLR)-dependent immune activation. They demonstrated a reduction in CD8/CD38/CD45RO T cell activation in the probiotic group, which is thought to be a marker of immune activation. After treatment with a probiotic, it was found that there was a significant decrease in the staphylococcal load of the feces [18].

In the double-blinded, placebo-controlled, randomized crossover study by Roessler et al. [19], a probiotic drink composed of *Streptococcus thermophiles, Lactobacillus paracesi* LPC-37, *Lactobacillus acidophilus* 74-2, and *Bifidobaterium animalis* subsp. lactis DGCC 420 was administered to adults with and without AD [19]. After 8 weeks of probiotics among patients with AD, a non-significant decrease in the SCORAD was observed (from −15.5 to −20.3%; $p = 0.081$). Researchers did not observe a statistically significant decline in immunoglobulin (Ig) E levels in AD patients after administration of probiotics [19].

Drago et al. [20] investigated the effect of adding tara gum and *Streptococcus thermophilus* ST10 DSM 25246 to *L. salivarus* LS01 DSM 22775 [20]. Tara gum is thought to act as a gelling complex, which would adhere to the intestinal mucus and improve barrier function, thereby improving the activity of *L salivarus*. Twenty-five AD patients were included and were randomized to receive either a placebo or probiotic. A statistically significant improvement in the SCORAD index was observed after administration of the probiotic ($p < 0.0001$). *Staphylococcus aureus* is reportedly found more frequently in the gut microbiome of subjects with AD [21]. Although there was a trend toward a decrease in the *S. aureus* load in the fecal microflora of the probiotic group, this decrease was not statistically significant ($p = 0.08$) [20]. Without a follow-up study after the supplementation ceased, it cannot be ascertained whether *L. salivarus* persisted in the gut after treatment ended.

3.2 Acne

Acne vulgaris is one of the most common chronic dermatological conditions affecting both adolescents and adults [22]. Only one study was found regarding the role of probiotics in the treatment of acne. In a prospective, randomized, open-label study, 45 female patients aged 18–35 years with mild to moderate acne vulgaris were enrolled into three groups: probiotic supplementation, minocycline, and treatment with both probiotics and minocycline. The probiotic was a mixture of *Lactobacillus acidophilus* (NAS super-strain), *Lactobacillus delbrueckii* subspecies *bulgaricus* (LB-51 super-strain), and *Bifidobacterium bifidum* (Malyoth super-strain). The treatment period lasted a total of 12 weeks and lesion counts were assessed throughout this time. A total of 43 subjects completed the study.

By week 4, all groups had a significant improvement in total lesion count, with no significant differences between groups. Similarly, at the 8-week mark, all groups continued to have a significant improvement in total lesion count ($p = 0.001$, probiotic only; $p < 0.001$, remaining groups). The trend continued at week 12 for all three groups. By weeks 8 and 12, the group receiving both probiotics and minocycline had a significantly lower total lesion count

compared with those taking probiotics only or minocycline only. All three groups had a significant improvement in non-inflamed lesion count at weeks 4, 8, and 12. At weeks 4, 8, and 12, subjects who were in the probiotic-only group had a greater decrease in non-inflamed lesion count compared with those in the minocycline-only group. Future studies should assess how probiotics affect sebaceous gland function and sebum composition. With regard to the inflamed lesion count, subjects who took either probiotics or minocycline achieved an improvement by week 8, and continued to improve significantly by week 12 compared with baseline. The group that received both probiotics and minocycline experienced a significant reduction as early as week 4, and continued to improve significantly more compared with the other groups.

Thirteen percent of patients in the minocycline-only group experienced vaginal candidiasis. No cases were reported in the group that received both probiotics and minocycline, which suggests that probiotics may help suppress the growth of unwanted microorganisms in the vaginal tract [22]. More studies are needed to evaluate the effects of probiotics on acne treatment, specifically whether it is efficacious as a stand-alone treatment or an adjunctive therapy.

3.3 Wound Healing

Acute wounds and non-healing chronic wounds are a common occurrence in dermatology. Peral et al. evaluated the role of probiotics in wound healing of burn injuries [23]. Eighty patients with second- or third-degree burns were randomized to receive topical wound treatment with either *Lactobacillus plantarum* (strain not reported) or standard silver sulphadiazine (SD-Ag). Treatment with *L. plantarum* was found to have similar effects as SD-Ag to promote complete healing of second-degree and early third-degree burn wounds. In late third-degree burn wounds (3–7 days post-burn), *L. plantarum* application lead to a statistically significant 17% increase in complete healing compared with wounds that had SD-Ag applied. Due to the low number of subjects in each group, researchers were not able to find whether the results were significant. Additional studies with a larger sample size are needed before establishing whether treatment with *Lactobacillus plantarum* is a beneficial alternative for wound treatment.

3.4 Psoriasis

One study compared the effect of the probiotic *Bifidobacterium infantis 35624* on inflammatory markers in three disease states: psoriasis, chronic fatigue syndrome, and ulcerative colitis [24]. Twenty-six patients with psoriasis were recruited and assigned to receive either placebo or probiotic for 8 weeks. Baseline plasma C-reactive protein (CRP), tumor necrosis factor (TNF)-α and interleukin (IL)-6 levels were elevated in psoriasis subjects comparison with healthy controls. CRP declined significantly after 8 weeks of therapy compared with placebo ($p = 0.0425$) and compared with baseline ($p = 0.0161$), and TNFα declined significantly after 8 weeks of therapy compared with baseline ($p = 0.0269$) and placebo ($p = 0.0405$). Researchers did not observe any changes in IL-6 levels in subjects with psoriasis treated with probiotics for 8 weeks compared with control subjects. When performing a combined analysis of all three inflammatory markers (IL-6, TNFα, and CRP), there was a decrease in the combined analysis in 75% of those receiving probiotics compared with 7% in the group receiving placebo. It is unclear how the combined analysis offers more insight over the individual analyses of IL-6, TNFα, and CRP. Interestingly, these three parameters remained unaffected in the healthy control group after treatment with *B. infantis 35624*. In this study, it is unclear if the biochemical improvements were accompanied by clinical improvements as no grading of disease severity was performed after baseline. These results suggest that *B. infantis 35624* is able to reduce proinflammatory biomarkers in a systemic inflammatory disorder [24]; however, future studies should incorporate clinical grading and assessments.

4 Quality Assessment and Risk of Bias

4.1 Study Qualities from the 12 Studies Analyzed (Tables 1 and 2)

The majority of studies randomized and blinded subjects to treatment; however, not all studies were blinded, leading to a risk of bias. For certain disease states such as acne, psoriasis, and wound healing, only one study was identified (Table 2), therefore, no conclusions can be drawn.

Of the nine studies investigating probiotic use in AD (Table 1), seven used SCORAD as one of their primary outcome measures. Two of the three remaining studies did not use SCORAD, but instead used different severity scoring systems [9, 16]. The remaining study based the clinical endpoint on patient symptomatology only [10]. Of the seven studies that used SCORAD, only four studies found a statistically significant decline in either the overall SCORAD index or one parameter of assessment [12, 14, 18, 20]. Furthermore, of the three studies that did not conduct SCORAD analysis, two studies found a statistically significant difference in QoL measurements [9] or skin severity grading [16], while the last study assessed subjective symptoms only [10].

Table 2 Human clinical trials of probiotics, prebiotics, and synbiotics for the treatment of acne, wounds, and psoriasis in adults

Skin condition	Study	No. of subjects	Study design and duration	Intervention	Dosage	Control or placebo	Primary outcome measures	Results	Study limitation	Jadad score (RCT)
Acne vulgaris	Jung et al. [22]	45 Females with mild to moderate acne, age 18–35 years	12-week, prospective, rand, open-label study	Probiotic capsule: *L. acidophilus* (NAS super-strain), *L. delbrueckii* subsp *bulgaricus* (LB-51 super-strain), and *B. bifidum* (Malyoth super-strain) (Group A) Probiotic + Minocycline (Group C)	Per capsule: *L. acidophilus* (NAS super-strain)—5 billion CFU/capsule *L. delbrueckii* subsp *bulgaricus* (LB-51 super-strain)—5 billion CFU/capsule *B. bifidum* (Malyoth super-strain)—20 billion CFU/capsule	Minocycline only (100 mg/day) (Group B)	Average total acne lesion count Facial skin tolerability (10-point scale) QoL questionnaire and AE	All three groups had SS decrease in lesion count by week 4. NS difference between the three groups. By week 12, Group C had a significantly lower total lesion count than Groups A and B. There was no significant difference between Groups A and B All three groups had a significant reduction in *inflamed* lesion counts by Week 12. Group C had the most significant reduction compared with Groups A and B. Group B had SS more improvement than Group A 13% of patients in Group B developed vaginal candidiasis	Study only involved fair-skinned females Quality-of-life questionnaire was not validated	1
Wounds	Peral et al. [23]	80 Males and females with burns aged 18–55 years	10-day, open-label study	*L. plantarum* (strain NR)	10^5 culture of *L. plantarum* was applied to gauze at 1 ml/cm^2—gauze applied once daily for 10 days	3-mm layer of silver sulfadiazine (SD-Ag) cream every 24 h for 10 days	Microbial burden at 10 days using 4-mm^3 wound tissue biopsies Clinical evaluation to assess active granulation tissue and changes in graft skin color	Proportional decrease in bacterial load of 0.71 for the *L. planatrum* group, and 0.73 for the SD-Ag group (RR −2.72%) Relative rate values showed no difference between groups in preventing infection, increasing granulation tissue, or healing in early third- or second-degree burns	Low number of subjects per group (between 12 and 15) did not permit power statistical test	0
Psoriasis	Groeger et al. [24]	26 Males and females aged 18–60 years with moderate chronic plaque psoriasis	8-week, rand, db, pc study	Sachets of *B. infantis* 35624	1×10^{10} CFU per sachet per day	5 g maltodextrin per day	Plasma CRP, IL-6, and TNFα	Plasma CRP was SS reduced (−34%) in the probiotic group after 8 weeks compared with baseline. In comparing pre- and post-feeding levels, CRP was SS reduced in probiotic-fed subjects compared with placebo subjects Plasma TNFα was SS reduced (−15.5%) in the probiotic group compared with placebo (0%) at 8 weeks, and pre- and post-feeding levels of TNFα were also SS reduced compared with placebo group. Plasma IL-6 decreased in both groups after 8 weeks, but the results were NS	Subject number is relatively low Only one daily dose of probiotic was administered, therefore no dose-dependent anti-inflammatory effect was observed No clinical assessment of psoriasis was conducted after the probiotic intervention	3

AE Adverse event, *CFU* colony forming unit, *CRP* C-reactive protein, *db* double-blind, *IL* interleukin, *NR* not reported, *NS* not statistically significant, *pc* placebo-controlled, *QoL* quality of life, *Rand* randomized, *RCT* randomized controlled trial, *RR* relative rate, *SS* statistically significant, *TNF* tumor necrosis factor

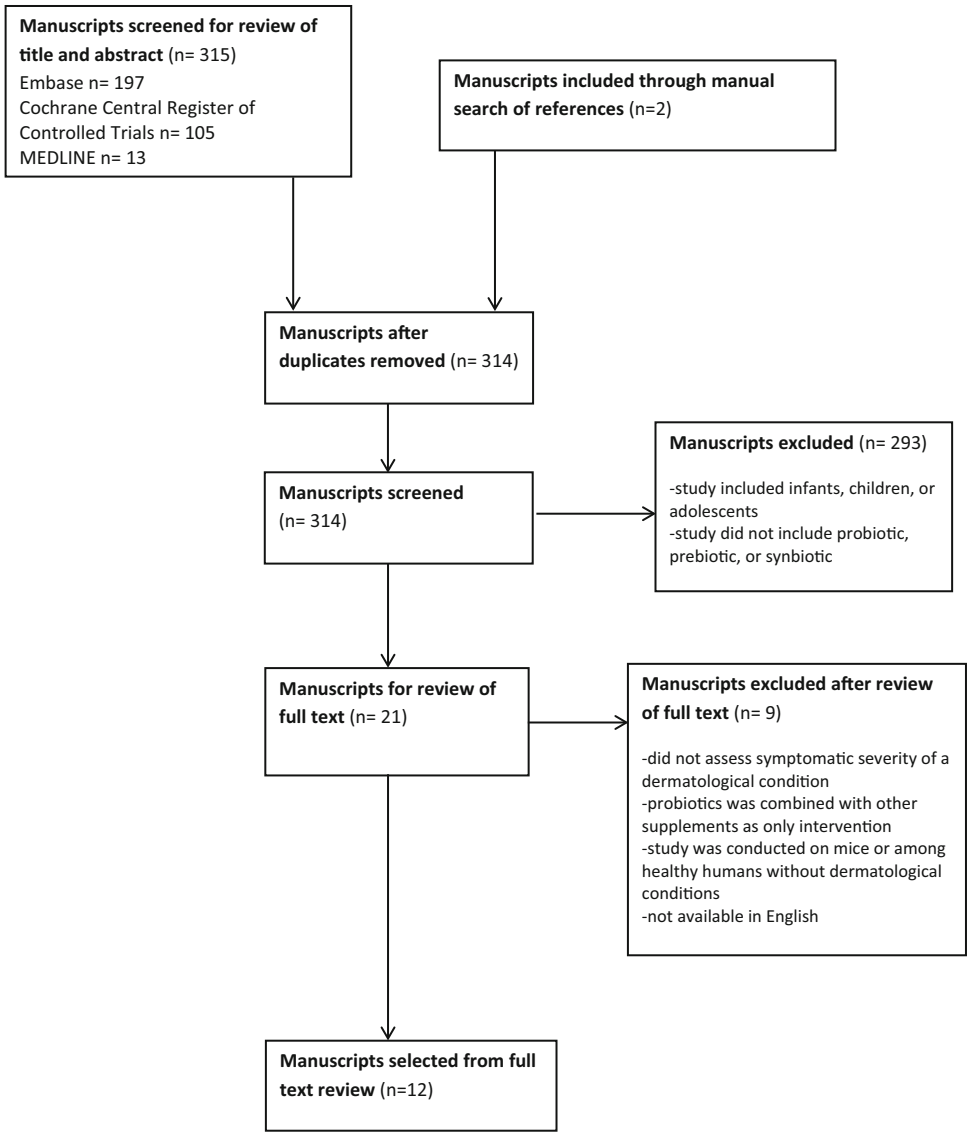

Fig. 1 Study selection process

5 Discussion

On the basis of this systematic review, certain probiotic supplements and mixtures may be helpful in the treatment of AD in adults over the age of 18 years [9, 10, 12, 14, 16, 18, 20]. Many studies included small sample sizes, which affected their generalizability. Overall, there were a limited number of studies regarding the treatment of AD, and even fewer regarding acne, psoriasis, and wound care. The differences in study methodology, dose, type and duration of probiotic, and duration of follow-up may be responsible for the variations in outcomes.

Our systematic review demonstrated there is a limited amount of research into the use of probiotics in adults with dermatological diseases such as AD. Probiotics are thought to benefit the immune system by reducing the adherence of pathogenic bacteria, assisting with the maintenance of tight junctions to reduce gut permeability, helping with the development of gut-associated lymphoid tissue (GALT), stimulating intestinal production of IgA, and downregulating Th2 cytokines through the stimulation of IL-12 and IFNγ [25].

AD has been linked to the 'hygiene hypothesis'. Early exposure to microbial agents can assist in the maturation of the Th1 cell response. In addition, this reduces the Th2 cell response which contributes to the development of allergic disease [14]. In pregnant women and newborns, probiotics are thought to prevent and treat AD by promoting the differentiation of naive T cells to mature Th1 cells [12]. In adults, the mechanisms are not clear, although there appear to be several possible modes of action. Beyond immune modulation, different gut bacteria populations differentially correlate with the presence of long-chain saturated fatty acids (LCFA) and short-chain fatty acids (SCFA) [26, 27].

LCFA and SCFA appear to interact with the immune system either by LCFA-based stimulation of TLRs [28] or by modulation of regulatory T-cell function [29]. While these hypotheses have been put forth with correlative findings, more mechanistic studies are needed to prospectively assess how probiotics and prebiotics may interface with the immune system and inflammation in ways that would be relevant to the skin.

Probiotics may be a useful adjunct to antibiotics in the treatment of acne [22]. Researchers postulated the improvement in the minocycline plus probiotic arm was due to modulation of the immune system by probiotics, and the combined anti-inflammatory effects of both agents. Larger-scale studies need to be conducted to determine if probiotics have a therapeutic role in the treatment of acne.

Further work needs to be conducted in the area of topical probiotics with regard to wound management. Specifically, more strains need to be evaluated for efficacy and long-term outcomes.

Of the 12 studies included, eight did not report on the incidence of side effects. Of the remaining four studies, one reported tolerable pain on topical application of a probiotic [23], one reported a case of diarrhea [9], and two reported no side effects related to the study agent [14, 16].

Our searches identified one study each for wound healing, acne, and psoriasis, and no studies were identified investigating other dermatological diseases associated with systemic inflammation, such as hidradenitis suppurativa. The studies using probiotics that we identified all utilized different strains (except two studies) and had differing methodology, making a statement regarding their overall efficacy in the treatment of dermatological diseases difficult. No studies regarding the use of prebiotics or synbiotics in adults were identified. Meta-analyses have shown evidence for a significant improvement with synbiotics for the treatment of pediatric AD [30]. A meta-analysis of four studies of probiotics in adults with AD [12, 14, 18, 19] found an improvement in the SCORAD index (−8.26, SD: −13.28, −3.25) [31]; however, this only involved a small number of studies and a small number of patients.

6 Conclusions

More research needs to be conducted into the effects of probiotics, prebiotics, and synbiotics in adults with dermatological diseases before any recommendations can be made. As research into this area grows, these findings will contribute to our knowledge regarding the interaction between the gut and the skin, and may provide a new therapeutic tool to benefit patients with chronic dermatological diseases.

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Compliance with Ethical Standards

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Conflict of interest Manisha Notay, Negar Foolad, and Alexandra R. Vaughn have no conflicts of interests to declare. Raja K. Sivamani serves as a scientific advisor for Dermveda.

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