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The Effectiveness And Safety Of Oral Microbial Agents As An Adjunct Therapy For Atopic Dermatitis: A Systematic Review

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ABSTRACT

Background: Eczema, also known as atopic dermatitis (AD), is a chronic inflammatory skin condition that significantly impacts the quality of life for both children and adults, affecting up to 20% of children and 10% of adults globally. While topical corticosteroids (TCS) have been the primary treatment, their long-term use can lead to adverse side effects and corticophobia, underscoring the need for alternative therapies like microbial agents (MA) which have shown promise in improving eczema symptoms and reducing reliance on TCS. **Methods:** This systematic review focused on full-text English literature published between 2014 and 2024 using the PRISMA 2020 guidelines. The literature was compiled using PubMed, ScienceDirect, and SagePub, among other online venues. **Result:** Five publications were found to be directly related to our ongoing systematic examination after a rigorous three-level screening approach. **Conclusion:** This systematic review suggests that microbial agents (MA) are a promising add-on therapy for moderate to severe eczema in children when used alongside topical corticosteroids (TCS). Mixed-strain probiotics and synbiotics showed the most significant improvement in eczema severity, but the optimal dosage and steroid-sparing effect require further investigation. Future research should explore MA's effectiveness across different age groups and severities of eczema.

Keyword: atopic dermatitis, eczema, microbial agents, pediatric eczema, probiotics, steroid-sparing effect

INTRODUCTION

Eczema, a chronic inflammatory skin condition also known as atopic dermatitis (AD), plagues millions worldwide. Characterized by intense itching, dry patches, and redness, it significantly impacts the quality of life for both children and adults.[1,2] The prevalence of eczema is staggering, affecting up to 20% of children and 10% of adults globally. This translates to countless individuals struggling with sleep disturbances, emotional distress, and hindered daily activities due to their eczema symptoms. Eczema has rightfully become a major public health concern.[3,4]

While topical corticosteroids (TCS) have been the cornerstone of eczema treatment for decades, their long-term use can lead to a multitude of undesirable side effects.[5] These include skin thinning (atrophy), stretch marks (striae), and even hormonal imbalances that can impact growth. Furthermore, a phenomenon known as corticophobia, or the fear of using TCS due to misconceptions about side effects, can significantly hinder treatment adherence. This fear can lead to patients discontinuing TCS prematurely, ultimately worsening their eczema symptoms.[6,7]

Therefore, there exists a pressing need for alternative and complementary therapies that can effectively manage eczema while minimizing the reliance on TCS and its associated side effects. This is where microbial agents (MA), encompassing probiotics, prebiotics, and synbiotics, emerge as a promising avenue for exploration.[8-10] These agents hold the potential to improve the delicate balance of gut bacteria (microbiota), strengthen the gut barrier function, and ultimately alleviate the symptoms of various skin diseases, including eczema.[9]

Intriguingly, some clinical studies have shown encouraging results for MA supplementation. These studies suggest that MA may not only improve eczema symptoms, disease severity, and overall well-being, but also act as a "steroid-sparing" therapy, potentially reducing the need for frequent or long-term TCS use.[11] However, the research on the efficacy of MA as an add-on therapy for AD remains inconclusive, with some studies yielding conflicting results. Additionally, MA can have its own set of side effects, such as abdominal pain and diarrhea.[4]

Given these complexities, a **systematic review** is warranted to comprehensively analyze existing research on MA as an add-on therapy for eczema. This review will aim to:

- **Synthesize the current evidence** on the effectiveness of MA in conjunction with TCS compared to TCS alone for eczema treatment.
- **Evaluate the potential of MA to reduce side effects** associated with TCS or lessen dependence on it altogether.
- **Identify factors that might influence the effectiveness** of MA for eczema treatment, paving the way for future research and personalized treatment approaches.

By systematically evaluating the existing body of research, this review will provide a clearer picture of the potential benefits and limitations of

MA as an add-on therapy for eczema. This knowledge can then be used to inform treatment decisions and guide future research directions in this promising field.

METHOD

Protocol

The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 standards were scrupulously followed by the work's author. The purpose of this was to make sure the study satisfied all the requirements. The chosen technique was carefully designed to ensure the accuracy and dependability of the investigation's findings.

Criteria for Eligibility

This study does a thorough evaluation of the last 10 years' worth of literature on the administration and results of radiation therapy for breast cancer. This study intends to improve and provide light on patient treatment procedures through a thorough examination of data. The primary goal of this paper is to highlight the significance of the noteworthy topics that have been identified across the literature.

To ensure the quality of the included information in this study, strict inclusion and exclusion criteria are applied. To be eligible for inclusion, papers must have been published in the English language between 2014 and 2024. Editorials, submissions without a DOI, previously published reviews, and duplicate journal entries are some of the exclusion criteria.

Search Strategy

The keywords used for this research is "oral microbial agents atopic dermatitis". The Boolean MeSH keywords inputted on databases for this research are: *(("mouth"[MeSH Terms] OR "mouth"[All Fields] OR "oral"[All Fields]) AND ("microbial"[All Fields] OR "microbially"[All Fields] OR "microbials"[All Fields]) AND ("agent"[All Fields] OR "agents"[All Fields]) AND ("dermatitis, atopic"[MeSH Terms] OR ("dermatitis"[All Fields] AND "atopic"[All Fields]) OR "atopic dermatitis"[All Fields] OR ("atopic"[All Fields] AND "dermatitis"[All Fields]))) AND (y_10[Filter])*

Data retrieval

The writers thoroughly evaluated the abstract and title of each manuscript before beginning this systematic review in order to assess each one's significance. Just articles that met the inclusion criteria and aligned with the article's objectives were selected for further examination. Ultimately, a definitive result was obtained from a consistent pattern found over several analyses. Only full-text, English-language submissions were acceptable. Content that satisfied all pre-established inclusion criteria and directly related to the study's subject matter was included after the most stringent screening procedure. Studies that failed to satisfy these requirements were frequently ignored, and their conclusions were not taken into consideration. A thorough analysis was conducted on a plethora of information discovered throughout the research process, including titles,

authors, publication dates, locations, study methodologies, and parameters.

Quality Assessment and Data Synthesis

The research that was reported in the titles and abstracts of each article was independently assessed by the authors in order to determine which papers needed additional investigation. Going over each document that satisfied the pre-established requirements to be included in the review was the following stage. The selection of an article for inclusion in the review was based on the evaluation procedure's results. By accelerating the selection of articles for further evaluation, this criterion was able to accomplish the goal of facilitating a thorough analysis of previous research and the factors that qualified them for the review.

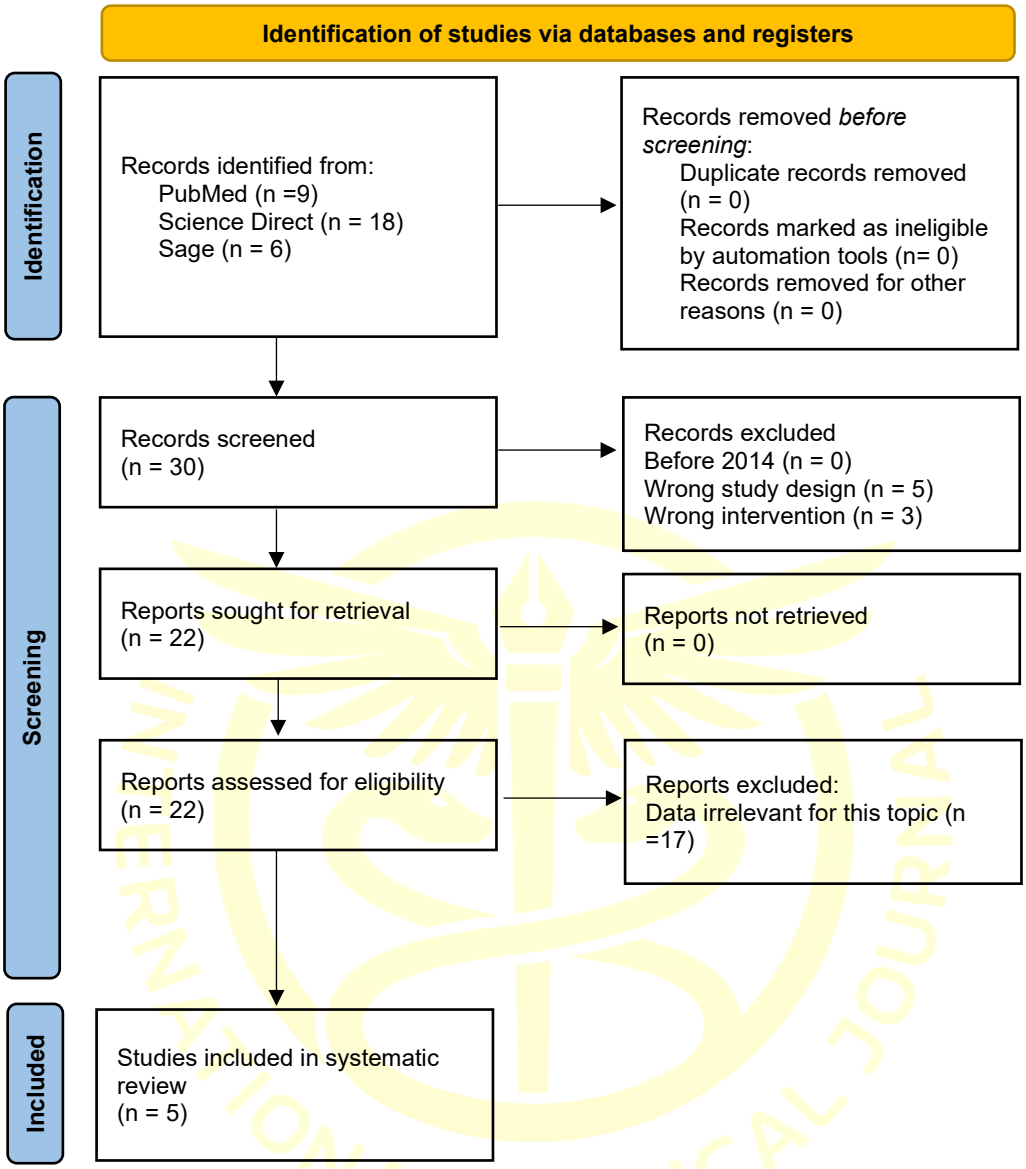

Figure 1. Article search flow chart

RESULT

Using reputable resources like Science Direct, PubMed, and SagePub, our research team first gathered over 100,000 publications. A thorough three-level screening strategy was used to identify only five papers as directly relevant to our ongoing systematic evaluation. Next, a thorough study of the entire text and further examination of these articles were selected. Table 1 compiles the literature that was analyzed for this analysis in order to make it easier to view.

Table 1. The literature included in this study

Author	Origin	Method	Sample	Result
Andrade et al., 2022.[12]	Brazil	Randomized Controlled Trial	Forty patients completed the study (24 probiotics, 16 placebo).	After treatment for six months, the clinical response was significantly better in the probiotics group; the SCORAD decreased [mean difference (MD) 27.69 percentage points; 95% confidence interval (CI), 2.44–52.94], even after adjustment for co-variables (MD 32.33 percentage points; 95%CI, 5.52–59.13), especially from the third month of treatment on. The reduction of the SCORAD in probiotic group persisted for three more months after the treatment had been discontinued, even after adjustment for co-variables (MD 14.24 percentage points; 95%CI, 0.78–27.70). Patients in the probiotics group required topical immunosuppressant less frequently at 6 and 9 months. No significant changes were found for IgE levels, SPT and cytokines.
Prakoeswa et al., 2017.[13]	Iran	A randomised double-blind placebo controlled trial	The trial included 22 AD children divided into intervention and control groups of n=12 and n=10 patients, respectively.	Scoring Atopic Dermatitis Index (SCORAD) and serum immunoglobulin E (IgE), interleukin (IL)-4, interferon gamma (IFN-γ), forkhead box P3 (Foxp3+)/IL-10, and IL-17 levels were assessed. Demographic and baseline characteristics were not significantly different between the two groups. SCORAD and levels of IL-4, IFN-γ, and IL-17 were significantly lower in the probiotic group than those in the placebo group, while the IgE levels were not significantly changed. The ratio of Foxp3+ to IL-10 was significantly higher in the probiotic group than that in placebo group.
Aldaghi, et al., 2020. [14]	Iran	double-blind, randomized	81 subjects with AD.	The mean age of subjects was 4.87±3.5 and 59.26% (n=48) were male. The mean SCOARD scores was substantially decreased in the synbiotic (bxy: -13.90, 95% CI, -20.99, -6.81; P <0.001) and vitamin

		clinical trial study.		D3 (bxy: -12.38, 95% CI, -19.33, -5.43; P = 0.001) groups as compared to control one by the end of two months.
Yan et al., 2019. [15]	Taiwan	Multicenter, randomized, double-blind, parallel-group, placebo-controlled clinical trial.	126 subjects were enrolled, with 64 assigned to the GM080 and 62 to the placebo group.	SCORAD, objective SCORAD, itching, and IDQOL decreased significantly ($p < 0.001$) over the treatment period in both treatment groups. Slight decreases (ns) were noted in TEWL in lesional and unaffected skin and CCL17 levels. There were no differences between the treatment groups. Total IgE increased over the treatment period in both groups, with significantly higher increase in the heat-treated probiotic group ($p = 0.038$). There was no evidence of a corticoid "sparing effect" by the probiotic.
Dah-Chin et al., 2019. [16]	Taiwan	Randomized, double-blind, placebo-controlled study,	62 patients who fulfilled the ITT definition, had a primary efficacy measurement, without any protocol violations, and with a drug compliance rate 80%, were categorized as the PP population.	The mean changes in SCORAD from baseline at Week 8 was 21.69 16.56 in the L. rhamnosus group and 12.35 12.82 in the placebo group for the intent-to-treat population (p Z 0.014). For the per-protocol population, the mean change of SCORAD from baseline was 23.20 15.24 in the L. rhamnosus group and 12.35 12.82 in the placebo group (p Z 0.003). Significant differences were demonstrated between groups at Week 8 in intensity in the intent-to-treat population and per-protocol population. Throughout the period, the amount of topical corticosteroids used showed no difference between groups. No significant difference was noted in the overall symptom-free durations compared with the placebo group. Infant Dermatitis Quality of Life Questionnaires and Dermatitis Family Impact Questionnaires scores improved significantly at Week 4 and Week 8 but did not reach statistical significance. Adverse events were documented in 14/33 patients in the L. rhamnosus group (42.42%, 35 events) and in 15/33 placebo patients (45.45%, 37 events).

In a series of studies investigating the efficacy of probiotics and microbial agents for atopic dermatitis (AD), several significant findings were reported.

Andrade PDSMAd et al. (2022) conducted a randomized controlled trial in Brazil involving 40 patients, with 24 receiving probiotics and 16 receiving a placebo. After six months of treatment, the probiotics group demonstrated a significant improvement in clinical response, as evidenced by a decrease in SCORAD scores (mean difference [MD] 27.69 percentage points; 95% confidence interval [CI], 2.44–52.94). This improvement remained significant even after adjusting for co-variables (MD 32.33 percentage points; 95% CI, 5.52–59.13), particularly from the third month of treatment onwards. Remarkably, the reduction in SCORAD scores persisted for three months after discontinuing treatment (MD 14.24 percentage points; 95% CI, 0.78–27.70). Additionally, patients in the probiotics group required topical immunosuppressants less frequently at 6 and 9 months, although no significant changes were observed in IgE levels, skin prick test (SPT) results, or cytokine levels.[12]

Prakoeswa CRS et al. (2017) conducted a randomized double-blind placebo-controlled trial in Iran with 22 children with AD, divided into intervention (n=12) and control (n=10) groups. The study found that Lactobacillus plantarum supplementation significantly reduced SCORAD scores and levels of IL-4, IFN-γ, and IL-17 in the probiotic group compared to the placebo group. However, IgE levels did not show significant changes. Notably, the ratio of Foxp3+ to IL-10 was significantly higher in the probiotic group, indicating an improved immune regulatory response. [13]

Mitra Aldaghi et al. (2020) conducted a double-blind, randomized clinical trial in Iran involving 81 infants with AD. The study compared the effects of multistrain synbiotic and vitamin D3 supplements against a control group. The mean age of participants was 4.87 ± 3.5 months, with 59.26% being male. By the end of two months, both the synbiotic (mean difference [bxy]: -13.90; 95% CI, -20.99 to -6.81; $p < 0.001$) and vitamin D3 (bxy: -12.38; 95% CI, -19.33 to -5.43; $p = 0.001$) groups showed a substantial decrease in SCORAD scores compared to the control group, indicating significant improvements in AD severity. [14]

Yan DC et al. (2019) conducted a multicenter, randomized, double-blind, parallel-group, placebo-controlled clinical trial in Taiwan with 126 infants, where 64 received GM080 (heat-treated Lactobacillus paracasei) and 62 received a placebo. Both groups exhibited significant reductions in SCORAD, objective SCORAD, itching, and IDQOL scores over the treatment period ($p < 0.001$). However, there were no significant differences between the treatment and placebo groups regarding these improvements. Total IgE levels increased in both groups, with a significantly higher increase in the probiotic group ($p = 0.038$), and there was no evidence of a corticosteroid-sparing effect. [15]

In another Taiwanese study by Dah-Chin Yan et al. (2019), 62 infants with AD participated in a randomized, double-blind, placebo-controlled trial assessing the impact of L. rhamnosus supplementation. The study found that the mean change in SCORAD scores from baseline at week 8 was significantly greater in the L. rhamnosus group (-21.69 ± 16.56) compared to the placebo group (-12.35 ± 12.82) for the intent-to-treat population ($p = 0.014$). For the per-protocol population, the mean change was also significantly greater in the L. rhamnosus group (-23.20 ± 15.24) compared to the placebo group (-12.35 ± 12.82) ($p = 0.003$). Despite these improvements, no significant difference was noted in the amount of topical corticosteroids used between groups. Adverse events were documented in 14 out of 33 patients (42.42%) in the L. rhamnosus group and 15 out of 33 patients (45.45%) in the placebo group. [16]

These studies collectively highlight the potential benefits of probiotics and microbial agents in reducing the severity of AD. However, the results regarding their steroid-sparing effects and long-term benefits are mixed, suggesting a need for further research to establish their definitive roles in AD management.

DISCUSSION

In the present study, results In this systematic review, we found that microbial agents (MA) as an add-on therapy were more effective than topical corticosteroids (TCS) alone in reducing SCORAD scores. Notably, the results indicated that different types of MAs and the severity of atopic dermatitis (AD) played significant roles in the observed outcomes. The minimum clinically important difference (MCID) is a critical benchmark in evaluating clinical relevance, with reductions of more than 8 units in the SCORAD index considered significant. Our review showed a reduction of 5 units, which may be attributed to inconsistencies in disease severity and the specific probiotic strains used across studies. Subgroup analysis revealed that oral mixed strains and synbiotics decreased the SCORAD index by 9.35 and 16.3 units, respectively, while patients with moderate AD experienced a reduction of 12.09 units. Importantly, the combined use of MA and TCS was found to be safe, with no significant differences in pruritus, quality of life, or TCS usage frequency compared to TCS alone.[17]

The immune regulation and anti-inflammatory effects of MA appear to play a crucial role in AD treatment. Rosenfeldt et al. observed that serum eosinophil cationic protein levels decreased in AD patients treated with oral MA.[18] This protein, released by activated eosinophils, increases rapidly during acute AD exacerbations and serves as an indicator of these episodes. Prakoeswa et al. found that MA combined with TCS lowered interleukin-4 and interferon-gamma levels while increasing interleukin-10 levels.[13] Similarly, Kim et al. discovered that oral MA reduced AD-associated skin lesions, epidermal thickening, serum immunoglobulin E levels, and immune cell infiltration. These findings suggest that MA's therapeutic-boosting effect may be linked to its modulation of

inflammatory factors and immune molecules, though the specific mechanism remains unclear and requires further investigation.[19]

Regarding MA types, a mixture of probiotics (Lactobacillus and Bifidobacterium) was more effective than probiotics alone, achieving the MCID in SCORAD index reductions. Studies by Jiang et al. and Uwaezuoke et al. found that mixed-strain probiotics relieved AD symptoms, and another meta-analysis supported the efficacy of mixed strains in reducing AD incidence. Thus, mixed-strain probiotics might benefit AD patients. The duration of MA treatment in studies ranged from 6 to 24 weeks, with most administering MA for 8 to 12 weeks in various forms, including tablets, liquids, powders, and capsules. Oral MA doses were typically 5–10 × 10^9 colony-forming units per day (CFU/day), with positive effects associated with doses above 10^8 CFU/day. However, due to limited studies, the clinical application of MA is not fully understood, and future research should focus on optimizing MA treatment protocols for AD.[20,21]

Subgroup analyses revealed that MA improved AD symptoms in children but not in infants or adults. Unlike adults, children's gut microbiota is relatively unstable and susceptible to external factors such as nutrition, diet, and environment. Infants have a mono-diet, with their gut microbiota primarily derived from breastfeeding or formula, and different feeding practices can affect the colonization of oral MA in the infant gut. Additionally, MA supplementation showed a therapeutic-boosting effect in moderate or severe AD patients receiving TCS treatment, but its effect in mild AD cases might be masked by potent TCS. While TCS can control symptoms in most mild to moderate AD patients, they are less effective for severe cases. Thus, MA as a complementary therapy to TCS might be a promising option for moderate to severe AD patients.[17,22]

Finally, the potential steroid-sparing effect of MA was examined. This could help reduce corticophobia and improve adherence to treatment regimens. In the present study, no difference was found in the frequency and grams of TCS used when combined with MA. Due to the limited number of studies focusing on this aspect, these results should be interpreted with caution. The steroid-sparing effect across different age groups remains unclear, necessitating further research to address this issue.

CONCLUSION

This systematic review suggests microbial agents (MA) as a promising add-on therapy for moderate to severe eczema in children alongside topical corticosteroids (TCS). Mixed-strain probiotics and synbiotics showed the most significant improvement in eczema severity, but the optimal dosage and steroid-sparing effect require further investigation. Future research should explore MA's effectiveness in different age groups and severities of eczema.

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