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Alleviation of Atopic Dermatitis Symptoms by Implementation of Standard and Alternative Treatments

Nika Sayvongsa

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Nika Sayvongsa

Eleanor Mann School of Nursing

College of Education and Health Professions

University of Arkansas Honors College

Dr. Kelly Young and Dr. Allison Scott

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Abstract

Atopic Dermatitis (AD) is a chronic dermatological disease caused by a combination of hereditary and environmental factors. This is a common condition that is primarily diagnosed among children, but can persist throughout adulthood. Twenty peer-reviewed articles are analyzed in this expanded literature review. Various methods were implemented throughout these studies, including randomized, double-blind, placebo-controlled, and single-blind studies; all of the studies shared the objective of evaluating AD alleviation with the use of either standard treatment modalities or alternative/ complementary therapies.

Introduction

AD is a chronic form of dermatitis that arises due to both genetic and environmental factors. There is a gene alteration that hinders the skin's protective functions regarding immunological barriers and moisture retention (Feldman et al., 2018). With this decreased protection, the skin becomes more susceptible to environmental factors, such as allergens, contact irritants, temperature, and weather. Common manifestations that can arise are objective signs such as inflammation, erythema, edema/ papulation, blistering, dryness, oozing/ crusts, and thickened/ cracked/ scaly skin; objective symptoms include pruritus and poor sleep quality due to sleep loss from constant itching. AD can cause numerous complications: asthma/ hay fever, skin infections, irritant hand dermatitis, and allergic contact dermatitis (Eichenfield et al., 2016). This is evidently a dermatological condition that impedes quality of life; however, there is no cure. In an attempt to alleviate AD, studies have been conducted to evaluate various methods that can aid in managing AD symptoms. Currently, nursing management of AD predominantly incorporates patient assessment with a SCORAD (SCORing Atopic Dermatitis) calculation, along with interventions such as daily cool baths/ cool compresses, application of moisturizing creams, or topical steroids/ anti-inflammatory creams, and wet dressings (Miller et al., 2011). The articles that will be discussed in this review evaluate the strategy of various standard and alternative/ complementary treatments in the reduction of AD symptoms.

Review of Literature

PICO Research Question

Among children with Atopic Dermatitis (AD), do standard treatment modalities have a greater influence on the alleviation of AD compared to alternative/ complementary treatment modalities?

Methods

Study Design

PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were utilized to review research articles found within the PubMed and CINAHL (Cumulative Index to Nursing and Allied Health Literature) databases. This is a systematic review of evidence from research studies that were implemented to analyze the alleviation of AD among children/ adolescents who received standard or alternative treatment modalities.

Three randomized, controlled research trials were implemented to analyze the alleviation of AD among children and adolescent patients who received skincare maintenance compared to those who do not receive this in their plan of care. Two research studies were implemented among patients who received topical treatments. Three randomized, controlled research trials were implemented among patients who received oral treatments. Four randomized, controlled research studies were implemented to analyze the alleviation of AD among children and adolescents who received probiotic intervention compared to those who do not receive this in their plan of care. Two studies were implemented among patients who received dietary supplements. Two studies were implemented among patients who received Chinese herbal medicine.

Information Sources

The PubMed and CINAHL Complete databases were utilized as electronic information sources when searching for relevant research studies. PubMed's MeSH (Medical Subject Heading) database contains evidence-based articles pertaining to medical and life sciences. CINAHL contains scholarly literature pertaining to nursing and allied health.

Search Strategies

To search for evidence-based literature relevant to the PICOT research question, a combined search was utilized, along with the Boolean connector "AND" between the keywords "atopic dermatitis," "treatment," and "children" (up to age 18). These limitations consist of the condition, treatment category, and population, which allowed for a narrower selection of articles within the PubMed and CINAHL Complete databases, to which the following articles were eventually selected for this systemic review, as shown in the Figure 2 flow chart. The search limiters utilized in both the PubMed and CINAHL Complete databases were English language, human subjects, peer-reviewed, evidence-based practice, randomized controlled trials, full text, and a publication date between 2009-2021.

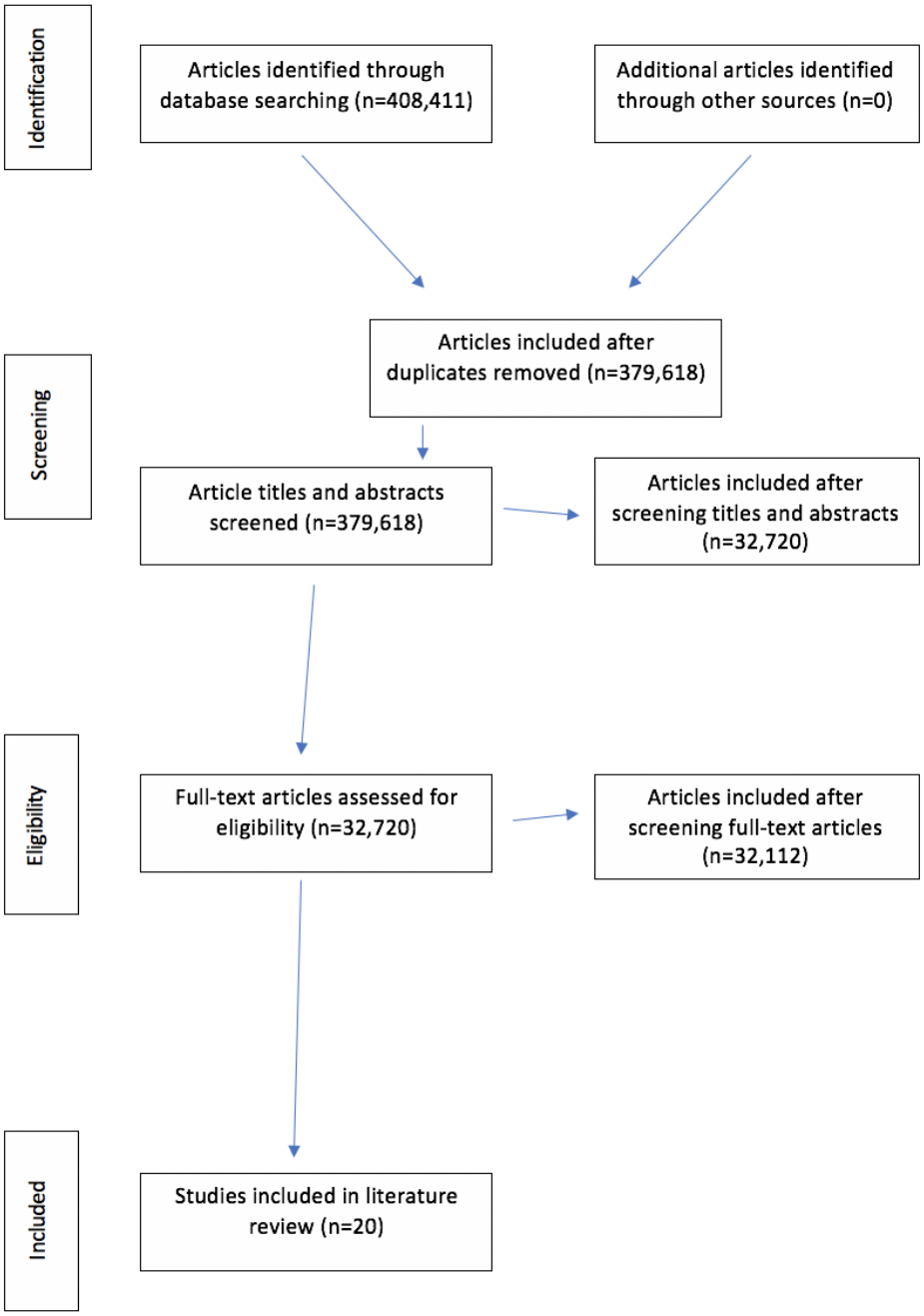
Figure 1

PRISMA Flowchart of Data Extraction

PubMed MeSH terms: “atopic dermatitis,” “treatment,” and “children”

CINAHL Complete subject headings: “atopic dermatitis,” “treatment,” and “children”

Search limiters: “English language,” “humans,” and a “2009-2021” publication date



Inclusion/ Exclusion Criteria

The inclusion criteria during the selection of these research articles were guided by the PICOT components: population, intervention, comparison, outcome, and sometimes time frame. The articles needed to contain the following elements: research conducted among children, and/ or adolescents (P), research implemented the administration of a standard treatment modality, or alternative/ complementary therapy (I), research compared the usage of a standard treatment or complementary/ alternative treatment with the absence of any treatment in the AD treatment plan (C), and outcomes are associated with the influence on AD alleviation (O). In this case, time frame was not utilized.

Data Extraction

For each of the peer-reviewed research articles, the following information was extracted: author(s), publication year, study design, sample size, study location, purpose of study, and outcomes.

Search Results

PubMed and CINAHL Complete databases were utilized to search for articles containing the key terms: “atopic dermatitis,” “treatment,” and “children/ adolescents.” The search limiters were “English language,” “humans,” and a “2009-2021” publication date. With this initial search, PubMed provided 408,411 articles, and CINAHL Complete provided 4 articles. 379,618 articles remained after duplicates were removed. The abstracts of these articles were screened for exclusion, then 32,112 of these articles were included. Twenty articles meeting the inclusion criteria were then selected for this literature review.

Results

Characteristics of Studies

Eleven studies analyzing standard treatment modalities are discussed in this literature review. These treatment categories include oral treatments, skincare maintenance, and topical treatments. Nine studies analyzing standard treatment modalities are discussed in this literature review. These treatment categories include dietary supplements, Traditional Chinese Medicine, and probiotics.

Oral Treatment

Among the four studies regarding oral treatments, two evaluated the usage of antihistamines, one evaluated the usage of immunosuppressants, and one evaluated the usage of dupilumab. In the assessment of antihistamines by He et al. (2017), double-blind, randomized trials were analyzed to determine its effect on AD treatment. Additionally, the prevalence of antihistamine usage was observed by collecting data on physician visits between 2003-2012 as provided by the National Ambulatory Medical Care Survey. In the other article by Matterne et al. (2019) regarding antihistamines, 8 studies involving a total of 1,941 children were discussed.

In the systematic review by Roekevisch et al. (2013), randomized controlled trials analyzing systemic immunomodulating treatments for moderate-to-severe AD among 1,653 patients

were reviewed. Clinical effectiveness was measured by assessing clinical signs, symptoms, quality of life, and the course of the condition.

Simpson et al. (2019) evaluates Dupilumab monotherapy among adolescents with moderate-to-severe uncontrolled AD. The study implemented a randomized phase 3 clinical trial

with 251 adolescents. Dupilumab 200 or 300 mg was administered every 2 weeks, and 300 mg was administered every 4 weeks for a total of 16 weeks.

Skincare Maintenance

Among the three research studies evaluating skincare maintenance, a total of 561 patients completed the research study. All three studies were randomized. In the study utilizing an over the counter (OTC) moisturizer, 39 subjects between the ages 2 to 17 participated. In the study utilizing an emollient bath additive, the trial was based in the United Kingdom, with two parallel groups of subjects between the ages of 1 to 11. In the study evaluating the effectiveness of bathing frequency, 40 patients between the ages of 6 months to 11 years were randomized in single-blind, crossover-controlled trial.

The purpose of the article by Miller et al. (2011) was to compare the clinical effectiveness and cost-effectiveness of three different OTC moisturizers, which are less expensive in comparison to FDA-approved prescription device moisturizers as monotherapy for mild-to-moderate AD among children aged 2-17 years. The OTC moisturizers used were glycyrrhetinic acid-containing barrier repair cream (BRC-Gly, Atopiclair®), a ceramide-dominant barrier repair cream (BRC-Cer, EpiCeram®) and an OTC petroleum-based skin protectant moisturizer (OTC-Pet, Aquaphor Healing Ointment®). The patients were randomized in a 1:1:1 ratio to receive one of the three OTC moisturizers. All three of these groups were provided with the same usage instructions. They applied their designated OTC moisturizer three times daily for a duration of three weeks. The severity and improvement of their AD were assessed at baseline, then day 7, and day 21 of the treatment plan.

The purpose of the article by Santer et al. (2018) was to measure the clinical efficacy and

cost-efficacy of emollient bath additives for AD alleviation. This was conducted as a pragmatic randomized open label superiority trial with two parallel groups in Wales and throughout western and southern England. The 482 patients aged 1 to 11 years who participated all met the United Kingdom's diagnostic criteria for AD. The patients in the intervention group utilized prescribed emollient bath additives for regular usage for a duration of 12 months. The analysis involved post-baseline POEM, 16 questionnaires provided at time points throughout the 12 months. The average POEM score was 7.5 for the intervention group, while the average POEM score was 9.5 for the control group receiving no bath additives. It was also determined that there was no difference in secondary results, economic results, or adverse effects between the intervention and control group.

The purpose of the article by Cardona et al. (2020) was to compare the clinical effectiveness of twice-daily soaking baths, immediately followed by the application of an occlusive moisturizer, (which is referred to as soak-and-seal, or SS), with twice-weekly soak-and-seal baths in AD alleviation. This was conducted as a randomized, single-blind, crossover-controlled research trial. The participants were children between the ages of 6 months to11 years. They were equally separated into two groups. The first group bathed twice-weekly for no longer than 10 minutes at a time for a duration of two weeks; they bathed twice-daily for 15 to 20 minutes for a duration of two weeks. All patients utilized the same moisturizer cleanser and low-potency topical corticosteroid (TCS).

Topical Treatment

Among the three research studies pertaining to topical treatments, more than 550 patients were analyzed in regard to AD management by topical ointments to manage their mild to moderate AD.

The objective of the article by Eichenfield et al. (2016) was to investigate the efficacy and safety of long-term Crisaborole Topical Ointment 2%, which is a nonsteroidal anti-inflammatory (NSAID) topical phosphodiesterase 4 inhibitor to manage their mild to moderate AD. A multicenter, open-label, pivotal, 48-week study was conducted among a pediatric group of 517 patients over 2 years of age.

In the article by Luger et al. (2021), eight countries (Belarus, China, Germany, Jordan, Russia, Turkey, Ukraine, and the United Arab Emirates) formed a topical treatment algorithm of TCIs pimecrolimus and tacrolimus, and TCS. Their results support pimecrolimus as the preferred option for sensitive skin areas in terms of efficacy, tolerability, and selectivity profile. TCS was labeled as the recommendation for short-term use in the case of severe flare ups.

The purpose of the article by Ohtsuki et al. (2018) was to provide support that TAC-O is clinically effective and tolerated by reviewing double-blind randomized controlled trials.

Dietary Supplementation

Melatonin supplements were administered in a double-blind, placebo-controlled crossover study of 73 pediatric patients between the ages of 1 to 18 years by Chang et al. (2016) in Taiwan. The patients had physician-diagnosed AD of at least 5% of their total body surface area. 48 patients were randomly separated into two groups to either receive melatonin or a placebo treatment. 38 of them finished the cross-over period. Melatonin 3mg daily or placebo was administered for a total of 4 weeks, followed by a 2-week washout period, then a crossover to the alternate treatment for another 4 weeks. AD severity was evaluated by the SCORAD index; additionally, secondary outcomes such as sleep variables were accounted for.

Melatonin supplements were administered for 70 pediatric patients between age 6 to 12 years in a randomized, double-blinded, placebo-controlled trial by Ardakani et al. (2018) in order

to determine its effects on AD severity and sleep quality. 35 patients received melatonin 6 mg daily, while the other 35 patients received a placebo for a total of 6 weeks. SCORAD indices were utilized to measure disease severity. Sleep quality was measured by the Children's Sleep Habits Questionnaire (CSHQ).

Traditional Chinese Medicine

Randomized, placebo-controlled trials comparing Chinese herbal medicine (CHM) were reviewed by Gu et al. (2013); they assessed eczema management by oral ingestion and topical applications of CHM.

The effect of Traditional Chinese Medicine (TCM) on the quality of life in pediatric patients with moderate to severe AD was assessed among a small sample of 13 children by Thanik et al. (2018). Medication use, SCORAD indices, Dermatology Life Quality Index (DLQI) scores, safety monitoring lab results, and IgE levels were analyzed. The TCM approach consisted of Phellodendron chinensis formula herbal bath additive and cream, and internal tea.

Probiotic Treatment

Among four of the five studies regarding probiotic treatment, a total of 426 patients participated. Two of the studies involved patients residing in South Korea, and the other two involved patients residing in Taiwan. The age range of these patients were between 4 months to 18 years old. All four studies were randomized, double-blind, placebo-controlled studies.

The objective of the article by Jeong et al. (2020) was to assess the therapeutic effectiveness and safety of administration of the probiotic *Lactobacillus rhamnosus* (RHT3201) among pediatric patients (aged 1 to 12 years) with moderate AD. This was conducted as a randomized, double-blind, placebo-controlled 12-week study in South Korea. 1.0x 10^10 CPU/d of RHT3201 was given to 33 patients of the variable group, while the placebo was given to the

other 33 patients of the control group. With the RHT3201 group, the SCORAD score change from baseline to the final 12th week of the study was significantly greater in comparison to the control group; this is supported with the mean and standard deviation values of the RHT3201 group being -13.89 ± 10.05, compared to the control group at −8.37 ± 9.95. Furthermore, eosinophil cationic protein (ECP) and interleukin (IL)-31 displayed decreases with the RHT3201 group. In regard to safety of administration, 50 patients from each group were analyzed by assessing full body physical examinations, vital signs, body weight, complete blood cell count, blood chemistry, and a urinalysis at baseline and the 12th week. Because 27 patients of the RHT3201 group experienced adverse effects, and 29 patients of the control group experienced adverse effects, there was not a significant statistical difference between them. Additionally, these were either temporary adverse effects, or unrelated allergic issues.

The objective of the article by Wang (2015) was to evaluate the therapeutic effectiveness of Live probiotics: *Lactobacillus paracasei* (LP) and *Lactobacillus fermentum* (LF) among pediatric patients (aged 1-18 years) with AD. This was a randomized, double-blind, placebo-controlled 16-week study in Taipei, Taiwan. After excluding patients who did not fit criteria, 159 patients in the treatment group and 53 patients in the control group were able to be analyzed. 55 LP, 55 LF, and 55 LP+LF were randomly assigned among the patients in the treatment group. Patients of both groups recorded the severity of AD, health issues, and medication usage each week for 3 months. The SCORAD score decreased after treatment was received in each of the three treatment groups. By the third month, patients in the control group revealed higher SCORAD scores. However, there was not a significant statistical difference in the SCORAD scores between the treatment and control groups.

The objective of the article by So et al. (2020) was to assess the clinical and immunological therapeutic effects of *Lactobacillus pentosus* among 82 pediatric patients (aged 2-13 years) with mild to moderate AD. This randomized, double-blind, placebo-controlled 12-week study was conducted in South Korea. For the 41 patients in the treatment group, their average SCORAD value at baseline was 30.4 ± 8.6, while those in the control group were at 34.3 ± 8.3. The treatment group displayed significantly lower SCORAD indices compared to the control group (P=0.040). By the 12th week, the indices were 23.6 ± 11.0 for the treatment group, and 23.1± 8.3 for the control group. Thus, both groups exhibited decreases in SCORAD indices. However, there is no significant statistical difference in indices between the groups.

In the article by Wu et al. (2017), the aim of the study was to assess the therapeutic effectiveness and safety of administering *Lactobacillus rhamnosus* among pediatric patients (aged 4-48 months) with AD, as diagnosed according to Hanifin and Rajka criteria and a SCORAD of at least 15 at baseline. This two-center, randomized, double-blind, placebo-controlled 8-week study occurred in Taiwan. The patients in the treatment group received one ComProbi capsule of the probiotic daily, while those in the control group received a placebo capsule daily. The average SCORAD change from baseline to the 8th week group was -21.69 ± 16.56 within the treatment, and -12.35 ± 12.82 within the control group.

In the fifth article comparing different probiotic strains in AD prevention among pediatric patients by Tan-Lim et al. (2021), data was extracted from randomized, placebo-controlled trials. The total sample was 5,406 children diagnosed by clinicians or who met the diagnostic criteria.

Discussion

Oral Treatment

Oral antihistamines are commonly prescribed to reduce pruritis. However, there is insufficient evidence to prove the degree of their efficacy. The results found by He et al. (2017) displayed sedating and non-sedating oral antihistamines as ineffective in treating AD-associated pruritis. Limitations within this study were inaccuracy of AD diagnoses and medication recording.

In the article by Matterne et al. (2019), results also revealed that the usage of H1 antihistamines were ineffective for eczema therapy. One limitation was a failure to report the severity of eczema at baseline.

The results of the systemic review by Roekevisch et al. (2013) indicate that cyclosporin A is effective as first-line treatment for short-term use, azathioprine is less effective as second-line treatment, and methotrexate can be administered as third-line treatment. Mycophenolate, montelukast, IV immunoglobulins, and systemic glucocorticosteroids are not clinically effective for AD treatment due to insufficient evidence.

The findings for dupilumab monotherapy exhibited at least 75% improvement from baseline values in the eczema severity index. Therefore, dupilumab led to significant improvement in AD signs, symptoms, and quality of life with an acceptable safety profile as well.

Skincare Maintenance

The results of the study conducted by Miller et al. (2011) displayed that all three moisturizers proved to be clinically effective in AD alleviation. There was no statistically

significant difference between the three OTC moisturizers at any of the assessment times. OTC-Pet was found to be greater than 47 times more cost-effective than BRC-Gly and BRC-Cer.

The results of the study conducted by Santer et al. (2018) displayed no significant clinical efficacy of the incorporation of emollient bath additives as standard management for AD. With this evidence, it can be indicated that further research is necessary in order to determine clinically effective emollient and soap substitutes for AD alleviation.

The results of the study conducted by Cardona et al. (2020) were based on the evaluation of AD severity in accordance to the SCORAD index. Additional assessments included a caregiver assessment of AD severity (Atopic Dermatitis Quickscore/ ADQ), quality of life, Staphylococcal aureus colonization, skin hydration, moisturizer, and TCS usage. The SCOARD score of the second group who underwent twice-daily baths decreased by a value of 21.2 in comparison with the first group who underwent twice-weekly baths. Upon a secondary analysis, the SCORAD score improved by greater than 30%. Furthermore, the ADQ decreased by 5.8, so this was a significant improvement. In conclusion, twice-daily baths exhibited significant clinical effectiveness.

Topical Treatment

In the article by Eichenfield et al. (2016), a sample of pediatric patients over the age of 2 with mild to moderate AD applied Crisaborole Topical Ointment, 2%. They were assessed for AD severity every 4 weeks. Treatment emergent adverse events (TEAEs) were analyzed throughout the treatment period; it was concluded that there is favorable safety to its efficacy as long-term topical treatment. The results displayed treatment related adverse events among 10.2% of this sample group; the adverse reactions mostly consisted of atopic dermatitis, application site

pain, and application site infection. There were seven TEAEs that resulted in the study; however, they were not treatment related.

In the article by Luger et al. (2021), topical calcineurin inhibitors (TCI) pimecrolimus and tacrolimus (at different strengths for different age groups) as first-line treatment and management for mild-to-moderate AD (and those with severe flares) were effective in alleviating AD symptoms. Their results displayed TCI to be the preferred treatment over topical steroids (TCS), with pimecrolimus having greater clinical efficacy and tolerability over tacrolimus for application over sensitive areas (such as the head, neck, axilla, inguinal, and genital area).

In the article by Ohtsuki et al. (2018), the results of 19 studies analyzing the clinical effectiveness of TCIs tacrolimus (TAC-O) and pimecrolimus were reviewed. TAC-O 0.03% and 0.1% were more effective in alleviation of AD than other topical ointments such as hydrocortisone 1%, or pimecrolimus 1% cream. TAC-O 0.03% was similar to medium-to-high-potency TCS in terms of strength. It is also emphasized that TAC-O significantly relieves pruritus by desensitizing cutaneous sensory neurons. Furthermore, in another study of 30 pediatric patients who a 4-week long therapy of TAC-O ointment had shown a significant improvement in quality of life, erythema/ papulation scores, pruritus, and sleeplessness.

Traditional Chinese Medicine

Most of the studies reviewed by Gu et al. (2013) displayed a greater number of patients who showed significant improvement, especially by decreased pruritis and improved quality of life scores. However, it is emphasized that this may be low quality evidence.

The conclusion of the study by Thanik et al. (2018) is in support for the possibility of Traditional Chinese Medicine being a complementary therapy for moderate to severe AD when weaning off corticosteroids. However, this study had the most limitations; it was unblinded,

uncontrolled, and had a small sample size. Traditional Chinese Medicine remedies for AD management is relatively new, so more studies are needed in order to determine its clinical efficacy.

Dietary Supplementation

The crossover study by Chang et al. (2016) demonstrated that melatonin supplementation is clinically effective and safe in improving sleep and AD severity among pediatric patients. The SCORAD index reduced by 9.1. Sleep-onset latency shortened by 21.4 minutes with melatonin treatment.

At the end of the 6-week melatonin supplementation plan conducted by Ardakani et al. (2018), there was significant improvement in the SCOARD indices, serum total IgE levels, and CSHQ. There was not significant improvement in pruritus scores, high-sensitivity C-reactive protein, sleep-onset latency, total seep time, or BMI.

Probiotic Treatment

The primary findings throughout four of the five articles evaluating probiotic treatment focused on the change from baseline to the final week of evaluation in SCORAD scores, which objectively measured the alleviation of AD among patients between the ages of 4 months and 18 years. Additional outcomes were evaluated as well. Eosinophil and cytokine levels were measured in the articles by Jeong et al. (2020), Wang (2015), and So et al. (2020). Serum immunoglobulin E was measured in the article by Wang (2015). Two articles incorporated subjective questionnaires for their patients to complete. Wang (2015) utilized Children's Dermatology Life Quality Index (CDLQI) and Family Dermatology Life Quality Index (FDLQI); Wu et al. (2017) utilized Infants' Dermatitis Quality of Life Index (IDQOL) and

Dermatitis Family Index (DFI). These questionnaires are designed to assess how quality of life is impacted in regard to dermatological conditions/ diseases, which was AD in this case.

The conclusions of the by Jeong et al. (2020) exhibit *L. rhamnosus* treatment group displayed a statistically significant decrease in the SCORAD score from baseline to week 12 in comparison to the control group. Furthermore, this same result occurred with an evaluation after 50 months. Additional immunologic parameters were assessed, which revealed a reduction in serum eosinophil (eosinophil cationic protein) and regulatory cytokine (interleukin-31) levels among the treatment group. There were multiple limitations of this study: inability to entirely cease usage of emollients/ topical corticosteroids (used for AD management), and inability to measure IFN-γ, because of a lack in blood samples. However, interleukin-31 was measured as an immunological parameter instead.

The conclusions of the study by Wang (2015) exhibit a statistically significant decrease in SCORAD scores (with a $P < 0.05$), as well as decreased serum cytokine (interleukin-4), IgE, and eosinophil levels among the *L. paracasei* and *L. fermentum* treatment group; this indicates that the severity of AD was alleviated with probiotic treatment from week 12 to baseline, especially among younger children and mite sensitization. A limitation in this study is the variation in resident microbiota, genetic, lifestyle, and diet among the patients. These factors influence how a patient will respond to probiotic usage. However, this study was randomized to combat these confounding variables. A second limitation is that the patients were not required to entirely cease any current use of Fluticasone propionate (topical corticosteroid), which are also used in AD therapy; this was due to the possibility of severe flares, which these patients would use their prescribed TCS for.

In the article by So et al. (2020), the *L. pentosus* treatment group displayed a significant reduction in SCORAD scores after 12 weeks in comparison to the control group. However, the control group did exhibit improved SCORAD scores as well. Additionally, this study also evaluated the effect of probiotics on the gut microbiota, to which no significant changes were discovered; this result was attributed to age. Because the immune system is not yet fully developed in infants, the immunologic effects of probiotics could be minimal compared to older children. A limitation of this study is the additional consumption of fermented foods outside of the study. Although this study was randomized, another limitation was the lower average SCORAD scores at baseline in the treatment group; this issue was fixed prior to completing the statistical analyses.

The results displayed by Wu et al. (2017) show the *L. rhamnosus* treatment group reported a consistent, significant decrease in SCORAD scores throughout 8 weeks of treatment in comparison with the placebo group ($p < 0.05$). Furthermore, the subjective questionnaires, IDQOL and DFI, resulted in improved scores for both the treatment and placebo group; however, the decreases were not of statistical significance. A limitation in this study is the absence of a long-term evaluation, because AD severity is known to fluctuate frequently. Another limitation is the variation in TCS usage throughout the entire study; however, the amount and frequency used by patients was documented, and no significant statistical differences were shown.

The systematic review and meta-analysis by Tan-Lim et al. (2021) demonstrated that there is insufficient evidence that Lactobacillus paracasei ST11, Bifidobacterium longum BL999, Lactobacillus paracasei ssp paracasei F19, and Lactobacillus rhamnosus GG, or Bifidobacterium animalis ssp lactis Bb-12 are effective in preventing atopic dermatitis prior to the manifestation of symptoms.

Limitations

It is important to note that confounding variables, such as age, genetic/ cultural backgrounds, diet, initial AD severity, allergic comorbidities, dosages, combinations of interventions, and the study design itself can influence the outcomes measured in all of the articles in general. For instance, with probiotic treatment, regular consumption (for a minimum duration of 2 months) has a therapeutic, alleviating effect on mild to moderate AD. However, there are articles that present opposing findings; one example is the process of change that intestinal microbiota undergo with age, meaning the effectiveness of probiotics would consequently differ with age. Due to the existing number of studies with opposing results, additional studies are needed to eliminate gaps in literature and determine the therapeutic effectiveness of probiotics in the alleviation AD symptoms. It would be beneficial to conduct similarly designed studies to minimize confounding variables, as well as test for different strain(s) of probiotics to identify which would be most effective in treatment. As the amount of evidence-based research regarding probiotic treatment in AD alleviation increases, compiled results could potentially provide sufficient evidence to determine whether or not probiotic treatment should be integrated as a typical intervention of AD treatment/ management.

Conclusion

Based on the evidence-based, peer-reviewed articles evaluated in this expanded literature review, some interventions belonging to either standard or alternative/ complementary treatment modalities have proven to be clinically effective in the alleviation of AD at varying degrees. Oral antihistamines, emollient bath additives, and Traditional Chinese Medicine did not have sufficient evidence in the ability to alleviate symptoms of AD; cyclosporin A, dupilumab, OTC moisturizers, soak and seal baths, Crisaborole Topical Ointment 2%, TCIs pimecrolimus and

tacrolimus, melatonin, and probiotics did alleviate symptoms of AD. Rather than adhering to one category of interventions, a combination of both standard and alternative/ complementary treatment modalities may be more clinically-effective in the alleviation of AD symptoms among pediatric patients.

References

Ahn, S. H., Yoon, W., Lee, S. Y., Shin, H. S., Lim, M. Y., Nam, Y. D., & Yoo, Y. (May 11, 2020). Effects of *Lactobacillus pentosus* in Children with Allergen-Sensitized Atopic Dermatitis. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7211510/

Atopic dermatitis (eczema) (June 12, 2020). https://www.mayoclinic.org/diseases-conditions/atopic-dermatitis-eczema/symptoms-causes/syc-20353273

Cardona, I. D., Kempe, E. E., Lary, C., Ginder, J. H., & Jain, N. (2020). Frequent versus infrequent bathing in pediatric atopic dermatitis: A randomized clinical trial. *Journal of Allergy and Clinical Immunology.in Practice, 8*(3), 1014-1021.doi:http://dx.doi.org/10.1016/j.jaip.2019.10.042

Chang, Y.-S., Lin, M.-H., Lee, J.-H., Lee, P.-L., Dai, Y.-S., Chu, K.-H., Sun, C., Lin, Y.-T., Wang, L.-C., Yu, H.-H., Yang, Y.-H., Chen, C.-A., Wan, K.-S., & Chiang, B.-L. (2016). Melatonin supplementation for children with atopic dermatitis and sleep disturbance. *JAMA Pediatrics*, *170*(1), 35. https://doi.org/10.1001/jamapediatrics.2015.3092

Eichenfield, L., Call, R., Forsha, D., Fowler, J., Hebert, A., Spellman, M., … Tschen, E. (November 11, 2016). *O064 Long-term safety of crisaborole topical ointment, 2%, in atopic dermatitis*. Annals of Allergy, Asthma & Immunology. https://www.sciencedirect.com/science/article/pii/S1081120616310523?via=ihub

Eric L. Simpson, M. D. (January 1, 2020). *Dupilumab in Adolescents With Uncontrolled*

Moderate to Severe Atopic Dermatitis. JAMA Dermatology. https://jamanetwork.com/journals/jamadermatology/article-abstract/2753673

Gu, S., Pang, C., Xue, C. C., Li, C. G., Yang, A. W. H., Zhang, W., & Williams, H. C. (2010). Chinese herbal medicine for atopic eczema. *Cochrane Database of Systematic Reviews*. https://doi.org/10.1002/14651858.cd008642

He, A., Feldman, S. R., & Fleischer, A. B. (January 6, 2018). *An assessment of the use of antihistamines in the management of atopic dermatitis*. Journal of the American Academy of Dermatology. https://www.sciencedirect.com/science/article/pii/S0190962218300203?via%3Dihub

Jeong, K., Kim, M., Jeon, S. A., Kim, Y., & Lee, S. (May 31, 2020). A randomized trial of Lactobacillus rhamnosus IDCC 3201 tyndallizate (RHT3201) for treating atopic dermatitis. https://onlinelibrary.wiley.com/doi/full/10.1111/pai.13269

Luger, T., Adaskevich, U., Anfilova, M., Dou, X., Murashkin, N. N., Namazova-Baranova, L., Nitochko, O., Reda, A., Svyatenko, T. V., Tamay, Z., Tawara, M., Vishneva, E. A., Vozianova, S., Wang, H., & Zhao, Z. (May 07, 2021). Practical algorithm to inform clinical decision-making in the topical treatment of atopic dermatitis. *The Journal of Dermatology*, *48*(8), 1139–1148. https://doi.org/10.1111/1346-8138.15921

Matterne U, Böhmer MM, Weisshaar E, Jupiter A, Carter B, Apfelbacher CJ. Oral H1 antihistamines as 'add-on' therapy to topical treatment for eczema. Cochrane Database of Systematic Reviews 2019, Issue 1. Art. No.: CD012167. DOI:10.1002/14651858.CD012167.pub2

Miller DW, Koch SB, Yentzer BA, et al. An over-the-counter moisturizer is as clinically effective as, and more cost-effective than, prescription barrier creams in the treatment of children with mild-to-moderate atopic dermatitis: a randomized, controlled trial. J Drugs Dermatol 2011; 10:531

Ohtsuki, M., Morimoto, H., & Nakagawa, H. (June 21, 2018). *Tacrolimus ointment for the treatment of adult and pediatric atopic dermatitis: Review on safety and benefits*. Wiley Online Library. https://onlinelibrary.wiley.com/doi/full/10.1111/1346-8138.14501

Roekevisch, E., Spuls, P. I., Kuester, D., Limpens, J., & Schmitt, J. (October 24, 2013). *Efficacy and safety of systemic treatments for moderate-to-severe atopic dermatitis: A systematic review*. Journal of Allergy and Clinical Immunology. https://www.sciencedirect.com/science/article/pii/S0091674913013006?via%3Dihub

Santer, M., Ridd, M. J., Francis, N. A., Stuart, B., Rumsby, K., Chorozoglou, M., … Little, P. (May 3, 2018). *Emollient bath additives for the treatment of childhood eczema (BATHE): multicentre pragmatic parallel group randomised controlled trial of clinical and cost effectiveness*. The BMJ. https://www.bmj.com/content/361/bmj.k1332

SCORAD. (2009). https://dermnetnz.org/topics/scorad/

Srivastava, K., Yang, N., Uzun, S., Thanik, E., Ehrlich, P., Chung, D., … Li, X.-M. (February 24, 2020). *Effect of Traditional Chinese Medicine (TCM) in moderate-to-severe eczema in clinic and animal model: beyond corticosteroids*. Journal of Allergy and Clinical Immunology. https://www.sciencedirect.com/science/article/pii/S0091674919319931

Taghavi Ardakani, A., Farrehi, M., Sharif, M. R., Ostadmohammadi, V., Mirhosseini, N., Kheirkhah, D., Moosavi, S. G., Behnejad, M., Reiter, R. J., & Asemi, Z. (2018). The effects of melatonin administration on disease severity and sleep quality in children with

atopic dermatitis: A randomized, double-blinded, placebo-controlled trial. *Pediatric Allergy and Immunology*, *29*(8), 834–840. https://doi.org/10.1111/pai.12978

Tan-Lim, C. S., Esteban-Ipac, N. A., Recto, M. S., Castor, M. A., Casis-Hao, R. J., & Nano, A. L. (2021). Comparative effectiveness of probiotic strains on the prevention of pediatric atopic dermatitis: A systematic review and Network meta-analysis. *Pediatric Allergy and Immunology*, *32*(6), 1255–1270. https://doi.org/10.1111/pai.13514

Thanik, E., Wisniewski, J. A., Nowak-Wegrzyn, A., Sampson, H., & Li, X.-M. (2018). Effect of traditional Chinese medicine on skin lesions and quality of life in patients with moderate to severe eczema. *Annals of Allergy, Asthma & Immunology*, *121*(1), 135–136. https://doi.org/10.1016/j.anai.2018.03.004

The Royal Children's Hospital Melbourne (2018) https://www.rch.org.au/rchcpg/hospital_clinical_guideline_index/Eczema_management/

Van Zuuren EJ, Fedorowicz Z, Christensen R, et al. Emollients and moisturisers for eczema. Cochrane Database Syst Rev 2017; 2:CD012119

Wang, I.-J., & Wang, J.-Y. (2015). Children with atopic dermatitis show clinical improvement after*lactobacillus*exposure. *Clinical & Experimental Allergy*, *45*(4), 779–787. https://doi.org/10.1111/cea.12489

Wu, Y., Wu, W., Hung, C., Ku, M., Liao, P., Sun, H., . . . Lue, K. (November 27, 2015). Evaluation of efficacy and safety of Lactobacillus rhamnosus in children aged 4–48 months with atopic dermatitis: An 8-week, double-blind, randomized, placebo-controlled study. https://www.sciencedirect.com/science/article/pii/S1684118215008981?via=ihub