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The effectiveness of *Lactobacillus plantarum* administration in patients with atopic dermatitis

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Abstract

Atopic dermatitis is a chronic and residual inflammatory skin disease with increased prevalence in every year. The medications that are often given can cause serious side effects if it given in the long-term. The treatment of *Lactobacillus plantarum* is expected to be safer long-term treatment option for patient with atopic dermatitis. The objective is to determine the effectiveness treatment of *Lactobacillus plantarum* in patients with atopic dermatitis. The research design was a Systematic Review with a qualitative approach using meta-synthesis analysis type. The search was conducted on 3 databases: PubMed, Science Direct, and Google Scholar. Total articles obtained were 239 with 16 duplicate data. 211 articles were included in the exclusion criteria and 5 articles were interventions with combination probiotics. So there are 7 articles included in the research with clinical trials, open trials, pilot studies, and 4 research using the randomized controlled trial Double Blind design. All results showed improvement in symptoms with the SCORAD index or Skindex-16. Several studies also measured IgE, IL-4, IL-10, IL-13, IL-17, the percentage of Th1, Th2, Treg, TGF- β , IFN- γ and obtained different results. Treatment of *Lactobacillus plantarum* in patients with atopic dermatitis is effective to reducing symptoms and as an immunomodulator.

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INTRODUCTION

Atopic Dermatitis (AD) is a chronic, residual inflammatory skin disease which is related to another allergic disease such as bronchial asthma and allergic rhino conjunctivitis. The complaints can be in the form of unusual itchiness, erythema, edema, vesicles, and acute stage wound; then the patient will undergo excoriations and lichenifications in the chronic stage¹. According to Indonesian Pediatric Dermatology Study Group (KSDAI), prevalence rate of AD cases is in the first rank of children's skin diseases top 10, which is about 611 cases or 23,67%². There are about 70% - 80% of AD patients with extrinsic type; in this form, there are environmental allergen sensitization is accompanied with IgE serum increase³.

Although, AD does not cause death but it causes a variety of problems such as health issues, physical issues, social relationship issues, environmental issues and psychological issues. Besides, the need of long term therapies can affect the economic condition of patients and their family⁴. AD therapy is intended to minimize the relapse frequency and reduce the duration and the degree of severity in relapse. Topical corticosteroids can be added in pharmacological therapy. However, for long term treatments, corticosteroids therapy causes side effects, it leads systemic effects even further⁵. Patients can use moisturizers for skin barrier function improvement and for decrease topical steroid usages. Nevertheless, one of frequently used moisturizer is *Sodium Lauryl Sulfate* (SLS), which is reported as irritant⁶. Another therapy that can be used is probiotics therapy; it has a unique role in AD treatments or preventions⁷.

Moreover, probiotics are used to help the host from pathogenic bacteria and the usage of probiotics for children's diseases is increased^{8,9}. The role of probiotics toward atopic dermatitis disease is supported by some researches that showed variety of the results¹⁰. As in Navarro-Lopez et al. and Wang and Wang, the administration of probiotics is able to decrease the SCORAD index and decrease the topical steroid usage on AD patients^{11,12}. While, in Gore et al., there is no significant SCORAD differences in the all group¹³. Some of lactic acid bacterial species are good probiotics; some of those are from *Bifidobacterium* genera, *Lactobacillus* genera, *Bacillus coagulans*, etc.⁷. In addition, one of them is *Lactobacillus plantarum*. The *Lactobacillus plantarum* growth will produce anti-bacterial substances such as *hydrogen peroxide*, organic acids and bacteriocin. Many researches about the effect of *Lactobacillus plantarum* administration in AD patients is experimental research. Therefore, this research wants to do analytical review studies toward the previous studies that have been done with assessing the effectiveness of *Lactobacillus plantarum* administration in AD patients.

METHODS

This research design is a Systematic Review with a qualitative approach using a meta-synthesis type of analysis which aims to answer research questions by summarizing various research results (meta-aggregation). This research has been approved by the Health Research Ethics Committee Faculty of medicine of Universitas Muhammadiyah Surakarta with No. 3155 / C.1 / KEPK-FKUMS / XI / 2020.

The search was conducted on 3 databases: PubMed, ScienceDirect, and Google Scholar using the keywords "*Lactobacillus plantarum*" AND "atopic dermatitis" with a limit of 2005-2020 and in

Indonesian and English. The process of searching for articles was carried out on Friday, December 4, 2020 and data synthesis to be used was carried out on Saturday, December 5, 2020 using the Mendeley application. In the initial search, a total of 239 results were obtained from several databases, namely PubMed (n = 31), Science Direct (n = 69), Google Scholar (n = 139). After the process of deleting duplicated articles, 223 articles were obtained. A total of 211 articles were excluded because they did not meet the criteria and 5 articles used a combination probiotic supplement as an intervention. So that there are 7 articles that according to the inclusion criteria for data analysis.

RESULTS

There are 7 clinical trials that are required with several research designs, namely *clinical trials*, *open trials* and *pilot study*. Furthermore, there are 4 researches that used *randomized controlled trial double blind* research design and 3 of them are from Indonesia. There are 6 researches that used SCORAD as AD measuring instrument and 1 research used Skindex-16 for assessing patients' life qualities in the term of skin diseases. In addition, there are 6 researches that measured the IgE levels and there is only one research that took measurements with SCORAD. Measurements of IL-4 levels were found in 3 studies, measurement of IFN- γ in 2 studies, measurement of IL-10, IL-13, IL-17, percentage of Th1, Th2, Treg, TGF- β , each in 1 study.

All studies resulted in a significant reduction in symptoms based on the SCORAD index and Skindex-16 in the *Lactobacillus plantarum* group. Some studies show meaningless results toward total IgE levels decrease but there are symptom improvements in patients with high IgE levels in the experimental group and placebo group.

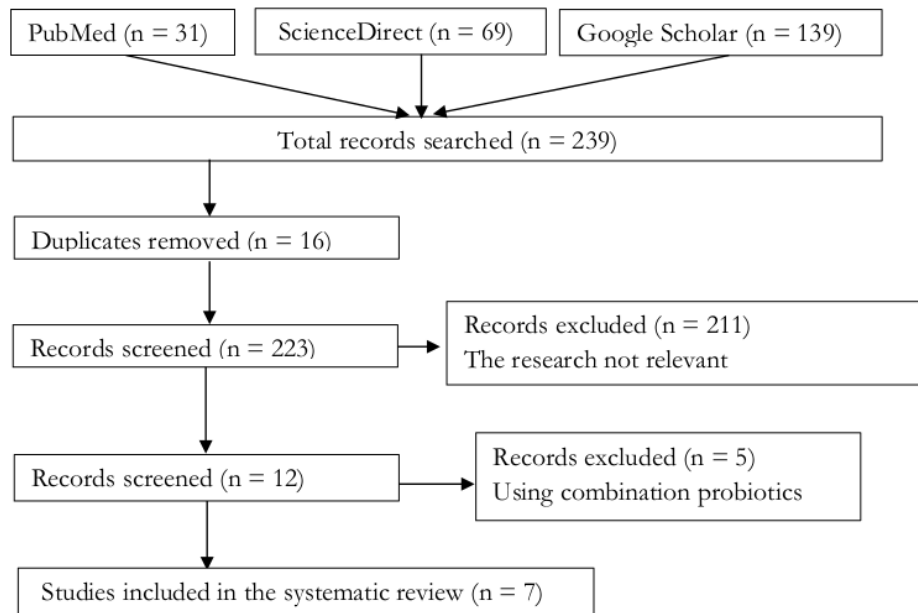


Figure 1. PRISMA flowchart (Source: personal data, 2020)

Table 1. The results of data extraction

RCT DB = Randomized Controlled Trial Double Blind, CT = Clinical Trials, OT = Open Trials, PS = Pilot Study, LP = Lactobacillus plantarum, cfu = colony forming unit, SCORAD = SCORing Atopik Dermatitis, IgE = Immunoglobulin E, IL = interleukin, IFN = interferon, TGF = transforming growth factor, DLQI = Dermatology Life Quality Index, ECP = eosinophil cationic protein

Author (year)	Study Design	Population	Intervention (Dose/duration)	Result
Karim,A, et al.(2019) ¹⁴	RCT DB	Adult	LP IS-10506 (2x10 ¹⁰ cfu/day, 8 week)	Reducing SCORAD index in LP group more significant.
Bonita, L., et al. (2019) ¹⁵	RCT DB	Adult	LP IS-10506 (2x10 ¹⁰ cfu/day, 8 week)	Reducing SCORAD index in LP group more significant and no significant difference in decreasing IgE level serum.
Prakoewa, C.R.S., et al. (2017) ¹⁶	RCT DB	Children	LP IS-10506 (10 ¹⁰ cfu/day, 12 week)	Reduce clinical symptoms by a decrease in SCORAD index, IL-4, IL-7, and IgE but not significant. Increase Foxp3+ to IL-10 level ratio.
Han, Y., et al (2012) ¹⁷	RCT DB	Children	LP CJLP133 (0.5x10 ¹⁰ cfu, twice daily, 12 week)	Reducing the clinical severity, SCORAD score, total eosinophil count, IFN-γ and IL4.
Kim, J., et al (2017) ¹⁸	CT	Children	LP CJLP133 (1x10 ¹⁰ cfu/day, 12 week)	Reducing SCORAD index, eosinophilia, high total IgE levels, increased TGF-β mRNA, and high proportion of CD4 ⁺ CD25 ⁺ Foxp3 ⁺ in Treg cells (associated with good clinical response).
Harima Mizusawa, N., et al. (2016) ¹⁹	2 OT	Adult	LP0132- <i>fermented juice</i> (6x10 ¹⁰ cells/100 ml, 8 week)	Reducing Skindex-16 in both trials, ECP, total IgE, specific IgE (Japanese cedar and cypress pollen) significantly attenuated in Trial 2, no significant changes in persentase of Th1, Th2, Th1/Th2, Treg during the trials.
Fang, Z., et al. (2019) ²⁰	PS	Adult	LP CCFM8610 (10 ⁹ cfu/day, 8 week)	Decreased SCORAD index, improved DLQI index, upregulation of IL-10 expression, not showed any significant differences in IgE, IL-4 and IL-13.

Source: Personal data, 2020

DISCUSSION

This research is systematic review research with 7 researches results from many countries. Even though, all researches are from experimental studies but there are different methods used for identifying the effects, measurements results, criteria of samples, types, doses and the duration of *Lactobacillus plantarum* administration. The researches subjects in some of these trials were more women than men. It is in line with the previous research, that AD frequently occurs in women than men with the ratio of 1,3 : 1. It states that the ratio of AD patients for women and men is 2,6 : 1. The differences in every country are caused by the differences in environmental interactions, genetics and immunological factors. Most of the researches subjects are acute exacerbation of chronic AD patients; it is appropriate with a research that mentioned that, AD is chronic residual, so the patients often relapse¹.

Lactobacillus plantarum growth in digestive tract will produce organic acids (acetic acid and lactic acid), hydrogen peroxide and bacteriocin that will give protection effects because they are antibacterial. Their roles in immune status can be modulated by intestinal barrier increase. It can be responsible for decreasing allergic events and severity of AD¹⁸. Moreover, there is glycoprotein isolates from *Lactobacillus plantarum* isolation that has anti-inflammatory effects and anti-allergy¹⁹. *Lactobacillus plantarum* can reduce inflammation with pro-inflammatory cytokines, IL-4, IL-6, TNF α , INF- γ decrease, high sensitivity C reactive protein (hsCRP); and increase IL-10 expression¹⁸. AD patients are dominated by Th2 cells that secrete IL-4 and increase IgE production. Those play an important role in skin allergen presentation in the Th2. *Lactobacillus plantarum* can help the gut microbiota stimulation with modulating toll-like receptors (TLR) and introducing proteoglycan protein in enterocytes; it can activate dendritic cells and Th1 response and will suppress the Th2¹¹. It can increase Th1 cytokines regulation such as INF- γ , IL-2, and IL-12. Besides, it can suppress the Th2 cell's production especially cytokine IL-4²⁰. Those can produce the balance between the Th1 cells and Th2 cells. Therefore, *Lactobacillus plantarum* administration in AD patients shows symptoms and immunological improvements.

Atopic dermatitis is divided into 2 types there are intrinsic and extrinsic type. A patient of intrinsic type or non-allergenic AD is marked with normal specific IgE levels and does not have any correlation with respiratory disease. While, in extrinsic type, there is specific IgE serum increase toward environmental allergen or foods. However, both types can be accompanied with eosinophilia. From the obtained results, there is a research that enclose eosinophil measurements, Han et al. shows significant decrease in the end of intervention at the LP CJLP133 0.5×10^{10} cfu twice a day for 12 weeks administrated group¹⁴. Moreover, in Harima-Mizusawa et al., there are specific IgE measurements in the *Japanese cedar and cypress pollen*, mites and house dust that are not decreased significantly¹⁶. Normal levels of IgE vary in a population that is affected by many factors such as genetic factors, for example there is polymorphism, environment interaction, age, race (American-African and Filipino descent have higher IgE levels), gender (which can be higher in men), and seasons (allergy sufferers will have higher IgE levels in autumn). In dominant researches results, there is no change in total IgE levels both in the adults or children. There is can cause by the short time intervention.

In the extrinsic AD, the memory T cells express *skin homing receptor, cutaneous lymphocyte-associated antigen (CLA)* so there is Th2 cytokines increase as IL-4 and IL-13 that induce IgE synthesis, also

IL-5 that has a role in eosinophil development and resistance. A research conducted by Prakoeswa et al. and Han et al. show the IL-4 levels decrease significantly in the experimental group^{13,14}. Meanwhile, in a research by Fang et al., there is no significant change in IL-4 levels. It is because of the different type of *Lactobacillus plantarum*, doses, and the duration of administration¹⁷.

Most clinical trials results used SCORAD index for assessing clinical symptoms in patients. People with severe AD were rarely sampled because severe AD patients still got standard therapy which was in the form of systemic corticosteroids that can confound variables in a research. All researches' results obtained mentioned that, patients who got topical corticosteroid, antihistamines, systemic immunosuppressive, phototherapy and another probiotic for 4 weeks were excluded because they can increase bias that might be happened in the research.

All results did not mention about the side effects that caused by *Lactobacillus plantarum* administration. However, in Harima-Mizusawa, N., et al., it is mentioned that there are no listed subjects that undergo bad effects or has change in their diet or life style during the trial¹⁶. Similar thing is mentioned in the Bonita, L., et al., there are no side effects in all treatments during monitoring and evaluation. It is also mentioned that in some RCT studies, there are some side effects that happened after consuming probiotics such as flatulent, abdominal discomfort, nausea and diarrhea, which those effects can improve on their own¹².

CONCLUSION

Lactobacillus plantarum is effectively given to AD patients for symptomatic or immunological improvement. It is hoped that further research can use the same for types of *Lactobacillus plantarum*, dosage and duration of administration.

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