



ACTAS Dermo-Sifiliográficas

Full English text available at
www.actasdermo.org



ORIGINAL ARTICLE

Probiotics to Reduce the Severity of Atopic Dermatitis in Pediatric Patients: A Systematic Review and Meta-Analysis[☆]



A.F. Pachacama López, M.F. Tapia Portilla,* F. Moreno-Piedrahíta Hernández, S. Palacios-Álvarez

Pontificia Universidad Católica del Ecuador, Quito, Ecuador

Received 14 December 2020; accepted 21 June 2021
Available online 20 October 2021

KEYWORDS

Atopic dermatitis;
Probiotics;
Children;
Adolescents;
Scoring Atopic Dermatitis (SCORAD) tool;
Meta-analysis;
Therapy

Abstract

Background and objective: Probiotics, defined as live microbial dietary supplements that provide health benefits for the host, have been suggested as a treatment for atopic dermatitis based on a variety of proposed mechanisms of action. We analyzed evidence for the efficacy of probiotics to attenuate the severity of atopic dermatitis in pediatric patients younger than the age of 18 years.

Material and methods: Systematic review of trials of probiotics that included patients under the age of 18 years with a confirmed diagnosis of atopic dermatitis scored for severity using the Scoring Atopic Dermatitis (SCORAD) tool. We performed a meta-analysis of the randomized placebo controlled trials. The following databases were searched: MEDLINE, Web of Science, Scopus, ClinicalTrials.gov, Epistemonikos, Trip Medical Database, and the Spanish Virtual Health Library.

Results: Twenty trials were retrieved and included in the systematic review. Sixteen supported the use of probiotics to attenuate SCORAD-evaluated severity. Meta-analysis found an overall mean difference in effect between probiotics and placebo of -0.38 (95% CI, -0.63 to -0.14) in favor of probiotics. However, trial heterogeneity was high (I^2 statistic, 76%) due to clinical and methodological variability.

[☆] Please cite this article as: Pachacama López AF, Tapia Portilla MF, Moreno-Piedrahíta Hernández F, Palacios-Álvarez S. Uso de probióticos para disminuir la gravedad de la dermatitis atópica en población pediátrica: revisión sistemática y metaanálisis. Actas Dermosifiliogr. 2021;112:881–890.

* Corresponding author.

E-mail addresses: mafernanda1196@outlook.es, mafernanda1196@gmail.com (M.F. Tapia Portilla).

PALABRAS CLAVE

Dermatitis atópica;
 Probióticos;
 Niño;
 SCORAD;
 Metaanálisis;
 Terapia

Conclusion: In spite of clinical heterogeneity in trials attributable to different types of probiotic products and doses, and to the subjective variability of the SCORAD scale, we conclude that probiotics are beneficial for reducing the severity of atopic dermatitis as reflected by the SCORAD index.

© 2021 AEDV. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Uso de probióticos para disminuir la gravedad de la dermatitis atópica en población pediátrica: revisión sistemática y metaanálisis

Resumen

Introducción: Los probióticos, definidos como microorganismos vivos que proveen un beneficio para la salud del huésped, se han propuesto como una opción terapéutica para la dermatitis atópica (DA), habiéndose identificado varios mecanismos de acción. Se evaluó la eficacia del uso de probióticos para disminuir la gravedad de dermatitis atópica en pacientes pediátricos menores de 18 años.

Materiales y métodos: Se realizó una revisión sistemática y metaanálisis que incluyó ensayos clínicos aleatorizados en pacientes menores de 18 años con diagnóstico establecido de dermatitis atópica, cuya gravedad estuvo medida por el Scoring Atopic Dermatitis (SCORAD) comparando el efecto de probióticos con el placebo, mediante la investigación en bases de datos MEDLINE, Web Of Science (WOS), Scopus, ClinicalTrials.gov, Epistemonikos, Trip medical database, Biblioteca virtual en salud (BVS).

Resultados: Se obtuvieron 20 estudios que fueron incluidos en la revisión sistemática, de los cuales 16 apoyan el uso de probióticos para reducir la gravedad del SCORAD en la dermatitis atópica. En el metaanálisis se obtuvo como resultado global una diferencia de medias de $-0,38$, con un IC 95% de $-0,63$ a $-0,14$, a favor del uso de probióticos; sin embargo, se encontró una alta heterogeneidad en los estudios debido a la variabilidad clínica y metodológica, con un $I^2 = 76\%$.

Conclusiones: El uso de probióticos es beneficioso para reducir la gravedad de la DA medida según SCORAD, a pesar de la presencia de una alta heterogeneidad clínica, derivada de sus diferentes tipos, dosis y variabilidad de una escala subjetiva como es el SCORAD.

© 2021 AEDV. Publicado por Elsevier España, S.L.U. Este es un artículo Open Access bajo la licencia CC BY-NC-ND (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Atopic dermatitis (AD) is a chronic, recurring disease of the skin, associated with abnormal barrier function of the skin, immunologic sensitization, and other mechanisms.¹

The general prevalence of this disease has increased between 2-fold and 3-fold in recent decades. The disease manifests during the 1st year of life in approximately 60% of cases but may appear at any age. Its course may be continuous for long periods or may be recurrent. AD is mild in approximately 80% of children affected².

Probiotics are defined by the WHO as “live microorganisms which, when administered in adequate amounts, confer a health benefit on the host”³.

Multiple mechanisms have been proposed for how probiotics reduce atopy, including shifting the Th1/Th2 balance toward Th1 by inhibiting Th2 cytokines or increasing production of regulatory cytokines such as IL-10 through maturation of dendritic cells or their receptors⁴.

The objective of this study is to perform a systematic review and meta-analysis to determine whether oral administration of probiotics reduces the severity of atopic dermatitis based on the *Scoring Atopic Dermatitis* (SCORAD)

scale in patients under 18 years of age with an established diagnosis of AD.

Materials and Methods

We performed a systematic review that included randomized clinical trials published to 2020. The studies had to compare the effect of probiotics with a placebo in reducing the severity of atopic dermatitis. The study population was patients under 18 years of age with an established diagnosis of atopic dermatitis, the severity of which was measured using the SCORAD scale.

Studies that did not meet the inclusion criteria, inconclusive studies, those that presented conflicts of interest, narrative reviews, studies with results other than those sought, studies carried out on animals, studies with interventions other than the clinical interest of this study, and those with a population over 18 year of age were excluded.

The search was performed in the following databases: MEDLINE, Web Of Science (WOS), Scopus, ClinicalTrials.gov, Epistemonikos, Trip medical database, and Biblioteca virtual in salud (BVS). The search string was as follows: (((«Dermatitis, Atopic»[Majr]) AND «Probiotics»[Majr]))

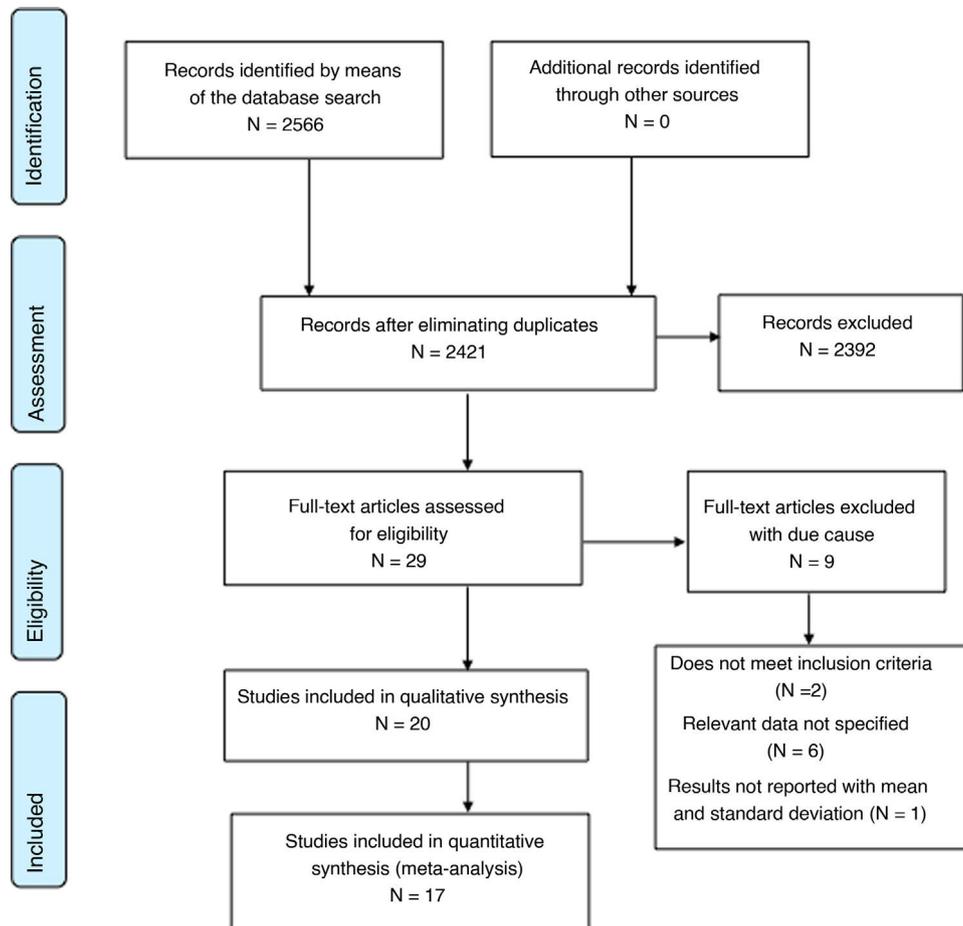


Figure 1 Flow chart of results.

AND (((«Child»[Mesh]) OR «Child, Preschool»[Mesh]) OR «Adolescent»[Mesh]).

A total of 2566 articles were found and after eliminating duplicates, we obtained 2412 articles, of which, when the inclusion criteria were applied, 29 articles were obtained, and 2392 records were excluded. The authors MFT and AFPL evaluated the 29 articles based on their level of evidence and discarded 9: 2 were excluded because they did not meet the inclusion criteria, 6 did not specify important data, and 1 did not include the necessary statistical results. Finally, 20 studies were included in the systematic review and 17 studies in the meta-analysis (Fig. 1).

Statistical Analysis

The information was extracted into databases using the programs Microsoft Excel and Review Manager (Rev Man), version 5.4. The results of studies were selected that made it possible to obtain the difference of means as a measure of the size of the continuous effect and its standard deviation with 95% confidence intervals (CI). Where possible, data was taken directly and in other cases, they were calculated using the Rev Man version 5.4 calculator. Clinical outcome was taken as the difference between the baseline SCORAD score and SCORAD score at the end of follow-up.

The χ^2 test was used to determine heterogeneity, which was considered for $P < .05$, and the coefficient of inconsistency between studies (I^2), considering heterogeneity if this coefficient is $> 40\%$. The random effects model was used to carry out the meta-analysis and a funnel plot was drawn up to assess the risk of publication bias.⁵

Risk-of-Bias Assessment

The risk of selection, performance, detection, attrition, and notification bias was analyzed for each study based on the criteria proposed by the Cochrane Handbook for Systematic Reviews of Interventions. This analysis can be seen in Figs. 2 and 3, which show the individual risks of bias based on the criteria of both researchers.

Results

Twenty studies included in the systematic review were analyzed (Table 1), of which 16 supported the use of probiotics to reduce the SCORAD severity in atopic dermatitis. With regard to the type of probiotic, 7 studies used combinations of strains and 13 used single strains; the most commonly used genus was *Lactobacillus*, species *rhamnosus*. The frequency of administration of the probiotic varied from 1 to

Table 1 Studies Included.

Study	Population	Probiotics (Genus, Species, Strain)	Duration	Study Conclusion
1 Navarro-López et al. ⁴ , 2018	47 children aged 4 to 17 years with AD, moderate SCORAD	<i>Bifidobacterium lactis</i> CECT 8145, <i>B longum</i> CECT 7347, and <i>Lactobacillus casei</i> CECT 9104	12 wk	Use of probiotics is useful in reducing SCORAD
2 Prakoeswa et al. ⁶ , 2017	22 children aged 0 to 14 years with AD	<i>Lactobacillus plantarum</i> IS-10506	12 wk	The use of probiotics is a potential treatment for AD in children
3 Wang y Wang ⁷ , 2015	212 children aged 1 to 18 years AD and at least 1 positive skin prick or IgE antibody test specific to common allergens	<i>Lactobacillus paracasei</i> GMNL-133, <i>Lactobacillus fermentum</i> GM090	12 wk	The mix of probiotics is associated with clinical improvement of AD
4 Wu et al. ⁸ , 2017	67 children aged 4 to 48 months AD, SCORAD \geq 15	<i>Lactobacillus rhamnosus</i> (MP108)	8 wk	The use of probiotics reduces all SCORAD parameters in children with AD
5 Han et al. ⁹ , 2012	83 children aged 1 to 13 years with AD, SCORAD between 20 and 50	<i>Lactobacillus plantarum</i> CJLP133	16 wk	Probiotic supplements are beneficial for the treatment of AD
6 Gore et al. ¹⁰ , 2012	137 children aged 3 to 6 months with AD, SCORAD \geq 10	<i>Lactobacillus paracasei</i> CNCM I-2116 or <i>Bifidobacterium lactis</i> CNCM I-3446	12 wk	No benefit was found for the use of probiotics in the treatment of AD
7 Woo et al. ¹¹ , 2010	75 children aged 2 to 10 years with AD, SCORAD > 25	<i>Lactobacillus sakei</i> KCTC 10755BP	14 wk	The use of probiotics is associated with clinical improvement of AD in children
8 Weston ¹² , 2005	53 children with a diagnosis of AD and SCORAD \geq 25	<i>Lactobacillus fermentum</i> VRI-033 PCC	16 wk	The probiotic supplement is beneficial in reducing the extension and severity of SCORAD
9 Sistek et al. ¹³ , 2006	49 children aged 1 to 10 years and at least 1 positive skin prick or specific IgE antibody test, or a RAST test positive for common allergens	<i>Lactobacillus rhamnosus</i> and <i>Bifidobacterium lactis</i>	18 wk	Probiotics improved clinical signs and symptoms of AD only in patients with food sensitivities
10 Grüber et al. ¹⁴ , 2007	102 children aged 3 to 12 months with AD, moderate to severe SCORAD	<i>Lactobacillus rhamnosus</i> GG	12 wk	No therapeutic effect for reducing the severity of AD was found
11 Brouwer et al. ¹⁵ , 2006	50 children aged under 5 months with AD	<i>Lactobacillus rhamnosus</i> (NP-Lrh), <i>Lactobacillus</i> GG (NP-LGG)	12 wk	No statistically significant effect of probiotic supplements on SCORAD, inflammatory parameters, or cytokine production
12 Fölster-Holst et al. ¹⁶ , 2006	54 children aged 1 to 55 months with moderate to severe AD	<i>Lactobacillus rhamnosus</i> strain GG (LGG)	8 wk	No significant differences were found between the groups in terms of clinical symptoms (SCORAD, pruritus, sleep loss)
13 Rosenfeldt et al. ¹⁷ , 2003	43 children aged 1 to 13 years with AD	Lyophilized <i>Lactobacillus rhamnosus</i> (19070-2) and <i>Lactobacillus reuteri</i> (DSM 122460)	6 wk	A combination of probiotics was beneficial in the treatment of AD

Table 1 (Continued)

Study	Population	Probiotics (Genus, Species, Strain)	Duration	Study Conclusion
14 Yeşilova et al. ¹⁸ , 2012	40 children aged 1 to 13 years with AD	<i>Bifidobacterium bifidum</i> , <i>Lactobacillus acidophilus</i> , <i>L casei</i> , <i>L salivarius</i>	8 wk	The use of probiotics is effective in reducing the SCORAD score in patients with AD
15 Nakata et al. ¹⁹ , 2019	59 children aged 10 months to 3 years with AD	<i>Lactobacillus acidophilus</i> L-92 (L-92)	24 wk	Consuming a specific quantity of L-92 functions as a complementary treatment for AD
16 Han et al. ⁹ , 2012	124 children aged 2 to 13 years with mild to moderate AD	<i>Lactobacillus pentosus</i>	4 wk	The SCORAD scores for the probiotics group improved significantly compared to the placebo group in AD
17 Gøbel et al. ²⁰ , 2010	50 children aged 7 to 24 months with AD	<i>Lactobacillus acidophilus</i> NCFM, <i>Bifidobacterium animalis</i> ssp. <i>lactis</i> Bi-07	8 wk	No clinical or general immunologic effect was shown by probiotic supplements in children with AD
18 Chernyshov ²¹ , 2009	58 children aged 2 months to 4 years with AD	<i>Lactobacillus rhamnosus</i> R0011, <i>L helveticus</i> R0052	4 wk	The use of the probiotic <i>Lactobacillus acidophilus</i> is associated with a larger number of patients who achieved marked clinical improvement and a greater corticosteroid-saving effect
19 Isolauri et al. ²² , 2000	27 children with a mean age of 4.6 months with AD	<i>Bifidobacterium lactis</i> Bb-12, <i>Lactobacillus</i> strain GG	8 wk	A significant improvement occurred in the general condition of the skin in patients who received formulae supplemented with probiotics, compared to the non-supplemented group
20 Viljanen et al. ²³ , 2005	230 children aged 1.4 to 11.9 months with AD	<i>Lactobacillus</i> GG (LGG), <i>L rhamnosus</i> LC705 (LC705), <i>Bifidobacterium breve</i> Bbi99, <i>Propionibacterium freudenreichii</i> ssp. <i>shermanii</i> JS (<i>Propionibacterium</i> JS)	4 wk	Treatment with LGG shows a greater reduction of the SCORAD score than the placebo group in infants suffering from AD associated with IgE

Abbreviations: B indicates *Bifidobacterium*; AD, atopic dermatitis; IgE, immunoglobulin E; L, *Lactobacillus*; SCORAD, Scoring Atopic Dermatitis.

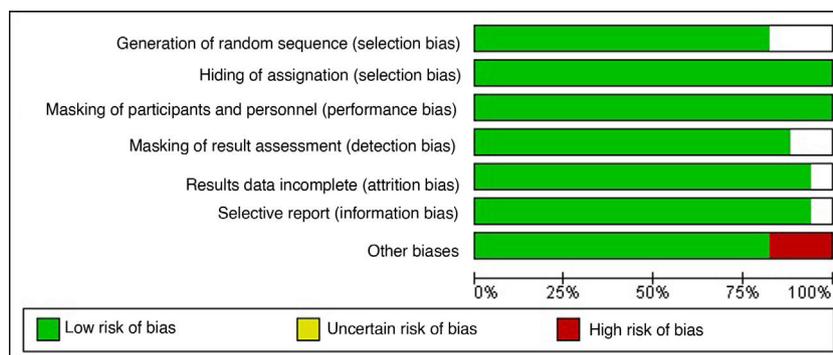


Figure 2 Risk-of-bias assessment: review based on the judgement of the authors of the risk of bias, presented as a percentage of all the articles included.

	Generation of random sequence (selection bias)	Hiding of assignment (selection bias)	Masking of participants and personnel (performance bias)	Masking of result assessment (detection bias)	Results data incomplete (attrition bias)	Selective report (information bias)	Other biases
Ahn 2019	+	+	+	+	+	+	+
Brower 2006	+	+	+	+	+	+	+
Chernyshov 2009	+	+	+	+	+	+	+
Fölster-Holst 2006	+	+	+	+	+	+	+
Gore 2012	+	+	+	+	+	+	-
Grüber 2007		+	+		+	+	+
Gøbel 2010	+	+	+	+	+	+	+
Han 2012	+	+	+	+	+		-
Nakata 2019	+	+	+	+	+	+	+
Navarro-López 2018	+	+	+	+	+	+	+
Prakoeswa 2017		+	+	+	+	+	+
Rosenfeldt 2003	+	+	+	+	+	+	+
Wang 2015	+	+	+	+		+	+
Weston 2005	+	+	+	+	+	+	-
Woo 2010	+	+	+	+	+	+	+
Wu 2017		+	+		+	+	+
Yeşilova 2012	+	+	+	+	+	+	+

Figure 3 Risk-of-bias assessment: review based on the judgement of the authors of the risk of each one of the articles included.

2 times per day and duration of treatment in the studies varied between 4 and 12 weeks.

The meta-analysis included 17 studies and the global result found a difference in measurement of -0.38 , with a 95% CI of -0.63 to -0.14 , in favor of the use of probiotics; however, high heterogeneity was found in the studies due to

clinical and methodological variability, with $I^2 = 76\%$ and χ^2 with $P = .00001$ (Fig. 4).

Subgroup analyses were performed according to type of strain (Fig. 5) and follow-up time (Fig. 6) for the use of probiotics to reduce the SCORAD; nevertheless, high heterogeneity was found in both analyses. With regard to the

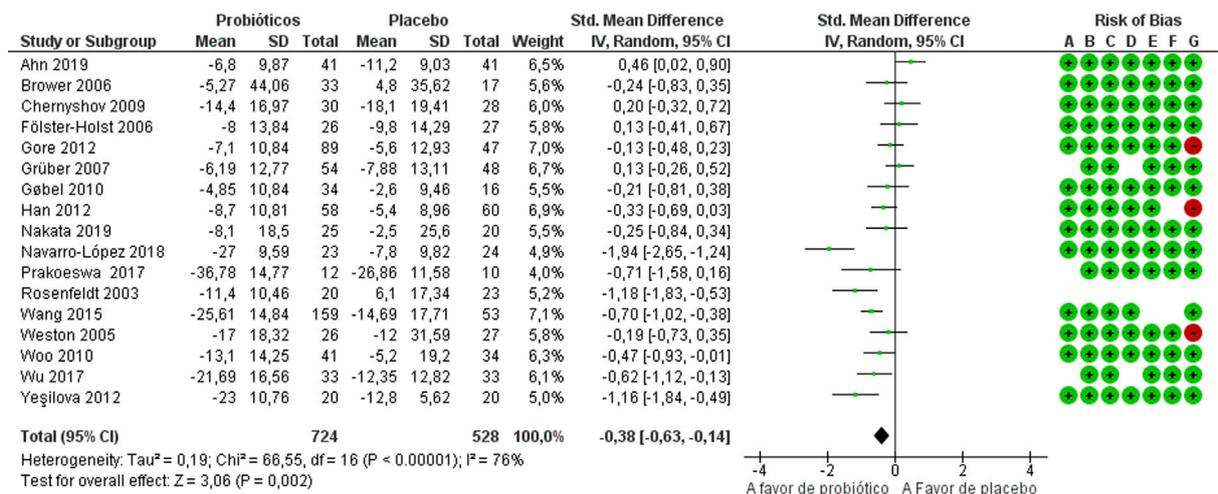


Figure 4 Forest plot: efficacy of probiotics vs. placebo in reducing the severity of AD measured by SCORAD.

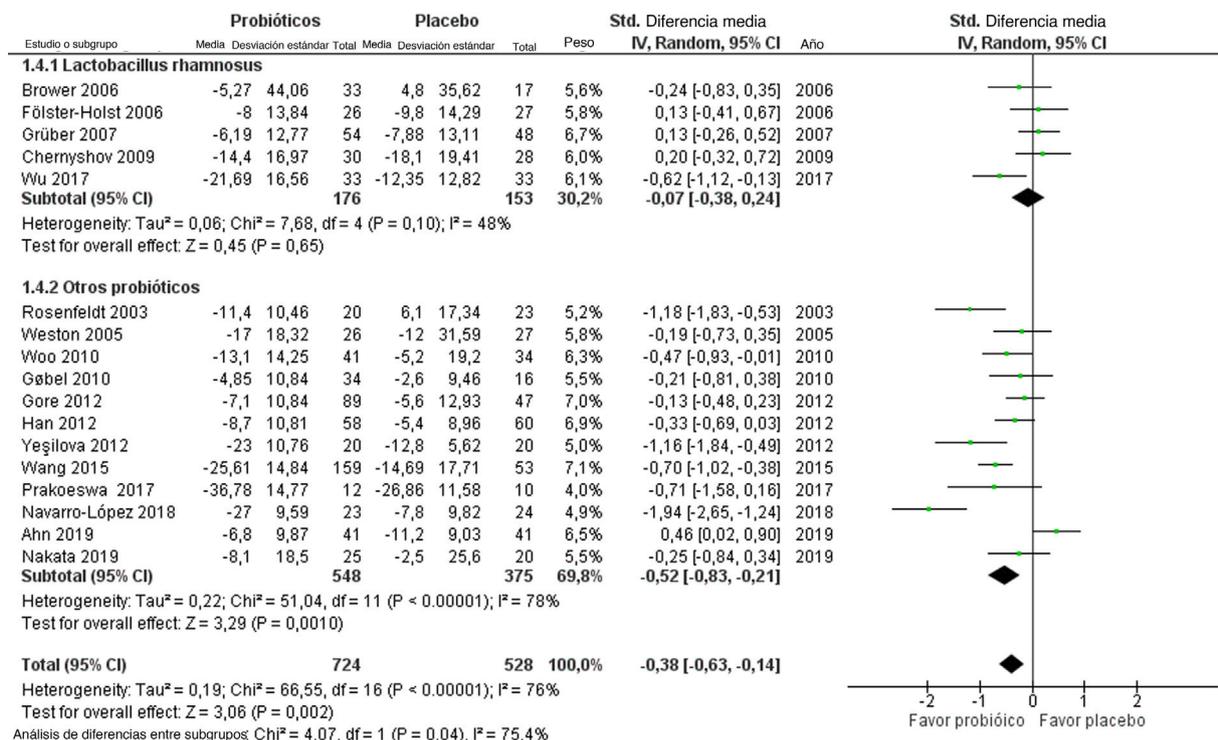


Figure 5 Forest plot: efficacy of *Lactobacillus rhamnosus* and other probiotics vs. placebo in reducing the severity of AD measured by SCORAD.

strain, greater benefit was not found with the use of *Lactobacillus rhamnosus* in comparison with the other probiotic strains. Based on the time of administration, a greater benefit was found after administration of probiotics for 12 weeks.

Analysis of Sensitivity and Reporting Bias

A sensitivity analysis was performed, and no variations were found after repeatedly reviewing the data, and the results suggested no important changes. Reporting bias was

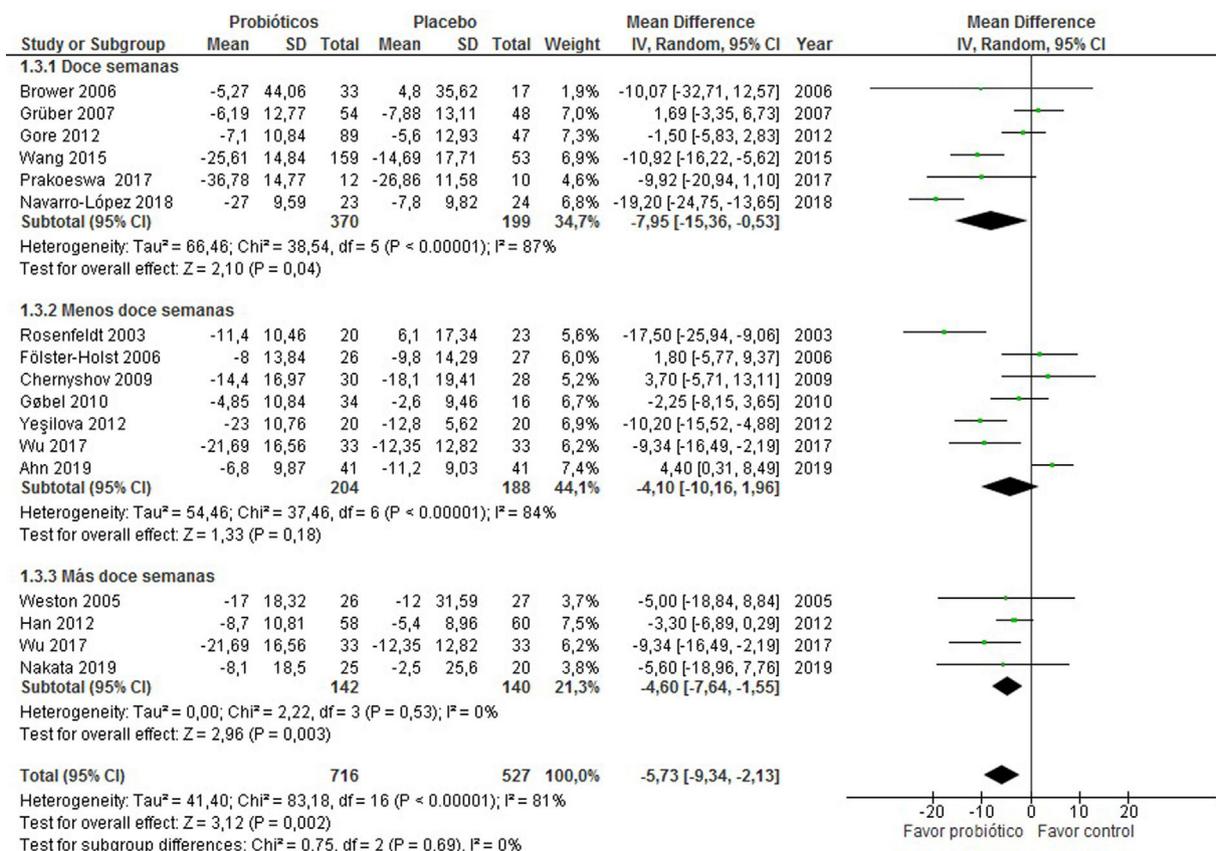


Figure 6 Forest plot: efficacy of probiotics vs. placebo in reducing the severity of AD by follow-up time.

assessed using a funnel plot (Fig. 7) and was corroborated using the trim-and-fill method²⁴, where a symmetric distribution of the studies can be observed, approaching a funnel shape, which makes it possible to rule out publication bias.

Discussion

The results of this systematic review indicated that probiotics have a beneficial effect in pediatric patients with atopic dermatitis.

These results are supported by the results obtained in the meta-analysis, in which the global results support the use of probiotics to reduce the SCORAD. The heterogeneity of the studies, however, does not make it possible to determine the real magnitude of the degree to which the probiotics reduce the severity of AD as measured by SCORAD.

This heterogeneity is due to the different interventions in each study, resulting from the use of different strains, the doses of probiotics, different duration of the treatments, and the subjectivity of the SCORAD scale for evaluating the severity of the AD.

Given the heterogeneity of the characteristics of the populations between the different studies, the analysis by subgroups does not show potentially real results, except for follow-up, in which case it was established that the efficacy of the use of probiotics is observed following administration for more than 12 weeks.

Makrgeorgou et al²⁵ performed an update of a systematic review similar to ours, based on a previous review

carried out in 2017. That review included 39 articles that, although they provided a significant sample, did not specifically analyze the pediatric population and included the use of symbiotics. The study concluded that probiotics reduce SCORAD severity but with a very low score for determining a significant change in the symptoms of atopic dermatitis.

The systematic review carried out by Huang et al²⁶ found that more evidence was required to recommend probiotics in a generalized manner. This is because the articles included covered small and heterogeneous populations, which reduced the power of evidence of the review, unlike this review, which includes a larger number of studies and with larger populations.

The limitations of this systematic review include the use of different strains of probiotic, which may lead to different results and individual conclusions in each study. Moreover, several major differences exist between the participants in the clinical trials: in some, it was established that the participants should follow a strict diet with no fermented foods, restriction of the use of antibiotics, and other requirements that were not present in all the clinical trials.

In the statistical analysis for the meta-analysis, heterogeneity was found between the populations of the different studies. This constituted a limitation when analyzing the results, as it made it impossible to determine the reduction in the SCORAD score expected in patients with AD following administration of the probiotic. Another limiting factor involves the association of pharmaceutical companies and food manufacturers in the manufacture of probiotics for

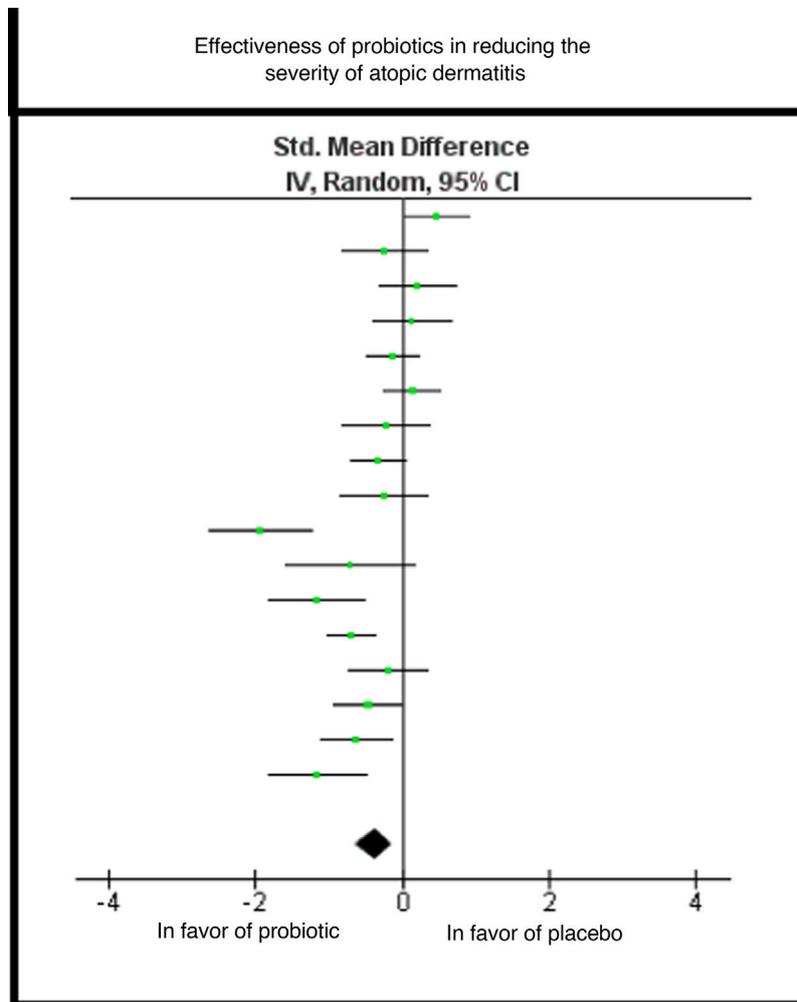


Figure 7 Funnel plot: use of probiotics vs. placebo to reduce the SCORAD score.

the trials, which may be a potential source of conflicts of interest.

The use of probiotics has been studied for several years, with a particular focus on diseases linked to the digestive system. Given that a wide range of probiotics exists on the market in our country, we may begin to use them as coadjutant treatment in AD.

Conclusion

Oral probiotics, especially strains of bacteria of the genus *Lactobacillus*, are useful for reducing the severity of atopic dermatitis but more homogeneous studies are required to determine the magnitude of this benefit.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

The authors would like to thank the Pontificada Universidad Católica del Ecuador for encouraging this study.

References

1. Leung D, Eichenfield L, Boguniewicz M. Dermatitis atópica (eccema atópico). In: Fitzpatrick Dermatología En Medicina General. 8th ed; 2014. p. 165–82.
2. Weidinger S, Novak N. Atopic dermatitis. Lancet. 2016;387:1109–22, [http://dx.doi.org/10.1016/S0140-6736\(15\)00149-X](http://dx.doi.org/10.1016/S0140-6736(15)00149-X).
3. Cipriani F, Dondi A, Ricci G. Recent advances in epidemiology and prevention of atopic eczema. Pediatr Allergy Immunol. 2014;25:630–8, <http://dx.doi.org/10.1111/pai.12309>.
4. Navarro-López V, Ramírez-Boscá A, Ramón-Vidal D, Ruzafa-Costas B, Genovés-Martínez S, Chenoll-Cuadros E, et al. Effect of oral administration of a mixture of probiotic strains on SCORAD index and use of topical steroids in young patients with moderate atopic dermatitis. JAMA Dermatol. 2018;154:37, <http://dx.doi.org/10.1001/jamadermatol.2017.3647>.
5. Higgins J, Green S. Manual Cochrane de Revisiones Sistemáticas de Intervenciones. Barcelona Cent Cochrane Iberoam. 2012, versión 5. <http://www.cochrane.es/?q=es/node/269>.
6. Prakoeswa CRS, Herwanto N, Prameswari R, Astari L, Sawitri S, Hidayati A-N, et al. *Lactobacillus plantarum* IS-10506 supplementation reduced SCORAD in children with atopic dermatitis. Benef Microbes. 2017;8:833–40, <http://dx.doi.org/10.3920/BM2017.0011>.

7. Wang I-J, Wang J-Y. Children with atopic dermatitis show clinical improvement after *Lactobacillus* exposure. Clin Exp Allergy. 2015;45:779–87, <http://dx.doi.org/10.1111/cea.12489>.
8. Wu Y-J, Wu W-F, Hung C-W, Ku MS, Liao P-F, Sun H-L, et al. 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. J Microbiol Immunol Infect. 2017;50:684–92, <http://dx.doi.org/10.1016/j.jmii.2015.10.003>.
9. Han Y, Kim B, Ban J, Lee J, Kim B-J, Sun B, et al. A randomized trial of *Lactobacillus plantarum* CJLP133 for the treatment of atopic dermatitis. Pediatr Allergy Immunol. 2012;23:667–73, <http://dx.doi.org/10.1111/pai.12010>.
10. Gore C, Custovic A, Tannock GW, Munro K, Kerry G, Jhonson K, et al. Treatment and secondary prevention effects of the probiotics *Lactobacillus paracasei* or Bifidobacterium lactis on early infant eczema: randomized controlled trial with follow-up until age 3 years. Clin Exp Allergy. 2012;42:112–22, <http://dx.doi.org/10.1111/j.1365-2222.2011.03885.x>.
11. Woo S-I, Kim J-Y, Lee Y-J, Kim N-S, Hahn Y-S. Effect of *Lactobacillus sakei* supplementation in children with atopic eczema-dermatitis syndrome. Ann Allergy Asthma Immunol. 2010;104:343–8, <http://dx.doi.org/10.1016/j.anai.2010.01.020>.
12. Weston S. Effects of probiotics on atopic dermatitis: A randomised controlled trial. Arch Dis Child. 2005;90:892–7, <http://dx.doi.org/10.1136/adc.2004.060673>.
13. Sistek D, Kelly R, Wickens K, Stanley T, Fitzharris P, Crane J. Is the effect of probiotics on atopic dermatitis confined to food sensitized children? Clin Exp Allergy. 2006;36:629–33, <http://dx.doi.org/10.1111/j.1365-2222.2006.02485.x>.
14. Grüber C, Wendt M, Sulser C, Lau S, Kulig M, Wuahn U, et al. Randomized, placebo-controlled trial of *Lactobacillus rhamnosus* GG as treatment of atopic dermatitis in infancy. Allergy. 2007;62:1270–6, <http://dx.doi.org/10.1111/j.1398-9995.2007.01543.x>.
15. Brouwer ML, Wolt-Plompen SAA, Dubois AEJ, Van der Heide S, Jansen D-F, Hoijer M-A, et al. No effects of probiotics on atopic dermatitis in infancy: A randomized placebo-controlled trial. Clin Exp Allergy. 2006;36:899–906, <http://dx.doi.org/10.1111/j.1365-2222.2006.02513.x>.
16. Fölster-Holst R, Müller F, Schnopp N, Abeck D, Kreiselmair I, Lenz T, et al. Prospective, randomized controlled trial on *Lactobacillus rhamnosus* in infants with moderate to severe atopic dermatitis. Br J Dermatol. 2006;155:1256–61, <http://dx.doi.org/10.1111/j.1365-2133.2006.07558.x>.
17. Rosenfeldt V, Benfeldt E, Nielsen SD, Michaelsen KF, Jeppesen DL, Valerius NH, et al. Effect of probiotic *Lactobacillus* strains in children with atopic dermatitis. J Allergy Clin Immunol. 2003;111:389–95, <http://dx.doi.org/10.1067/mai.2003.389>.
18. Yeşilova Y, Çalka Ö, Akdeniz N, Berktaş M. Effect of probiotics on the treatment of children with atopic dermatitis. Ann Dermatol. 2012;24:189, <http://dx.doi.org/10.5021/ad.2012.24.2.189>.
19. Nakata J, Hirota T, Umemura H, Nakagawa T, Kando N, Futamura M, et al. Additive effect of *Lactobacillus acidophilus* L-92 on children with atopic dermatitis concomitant with food allergy. Asia Pac Allergy. 2019;9:E18, <http://dx.doi.org/10.5415/apallergy.2019.9.e18>.
20. Gøbel R, Larsen N, Mølgaard C, Jakobsen M, Michaelsen KF. Probiotics to young children with atopic dermatitis: A randomized placebo-controlled trial. Int J Probiotics Prebiotics. 2010;5:53–9.
21. Chernyshov PV. Randomized, placebo-controlled trial on clinical and immunologic effects of probiotic containing *Lactobacillus rhamnosus* R0011 and *L. helveticus* R0052 in infants with atopic dermatitis. Microb Ecol Health Dis. 2009;21:228–32, <http://dx.doi.org/10.3109/08910600903444234>.
22. Isolauri E, Arvola T, Sutas Y, Moilanen E, Salminen S. Probiotics in the management of atopic eczema. Clin Exp Allergy. 2000;30:1605–10, <http://dx.doi.org/10.1046/j.1365-2222.2000.00943.x>.
23. Viljanen M, Savilahti E, Haahtela T, Juntunen-Backman K, Korpela R, Poussa T, et al. Probiotics in the treatment of atopic eczema/dermatitis syndrome in infants: a double-blind placebo-controlled trial. Allergy. 2005;60:494–500, <http://dx.doi.org/10.1111/j.1398-9995.2004.00514.x>.
24. Linyu S, Lifeng L. The trim-and-fill method for publication bias: practical guidelines and recommendations based on a large database of meta-analyses. 2019, <http://dx.doi.org/10.1097/MD.00000000000015987>.
25. Makrgeorgou A, Leonardi-Bee J, Bath-Hextall FJ, Murrell DF, Tang M, Roberts A, et al. Probiotics for treating eczema. Cochrane Database Syst Rev. 2018, <http://dx.doi.org/10.1002/14651858.CD006135.pub3>.
26. Huang R, Ning H, Shen M, Li J, Zhang J, Chen X. Probiotics for the treatment of atopic dermatitis in children: A systematic review and meta-analysis of randomized controlled trials. Front Cell Infect Microbiol. 2017;7:392, <http://dx.doi.org/10.3389/fcimb.2017.00392>.