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Systematic Review (Pages: 11271-11285)

Probiotics for the Treatment of Asthma: A Systematic Review and Meta-Analysis of Randomized Trials

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Abstract

Background: Asthma is a growing problem worldwide and the limitations of the current therapy for allergic asthma highlight the need for novel therapeutics. We conducted a systematic review and meta-analysis to find out the role of probiotics in the treatment of Asthma.

Materials and Methods: In this systematic review, a comprehensive search of the major electronic databases was done till October 2017. Clinical trials comparing the effect of probiotics versus placebo on treating asthma were included. Trials focusing on prevention of asthma were not included. A predefined set of outcome measures was assessed. Continuous data were expressed as standardized mean difference with 95% confidence interval (CI). Dichotomous data were expressed as odds ratio with 95% CI. P-value < 0.05 was considered as significant.

***Results*:** 11 studies with 2,027 participants were included. Probiotic intake was associated with a significant improvement in pulmonary function test and slight benefits in asthma control test. Probiotics did not reduce asthma exacerbation and wheezing episodes although there was a high degree of heterogeneity in studies. It also has no significant effect on viral respiratory infection in asthmatics and no improvement in quality of life. Probiotic intake improved the following parameters: longer time free from episodes of asthma. Adverse events were not significant.

***Conclusion*:** Although trials showed promising effects of probiotics as an additive on therapy on some parameters of asthma, as this evidence was generated from only a few trials with high degree of heterogeneity, routine use of probiotics as an additive on therapy of asthmatic patients cannot be recommended at this time.

Key Words: Asthma, Probiotics, Treatment

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1- INTRODUCTION

The prevalence of non-communicable diseases (NCDs) including asthma has increased worldwide during recent decades. The common threads of immune dysfunction most often unite NCDs and chronic low-grade inflammation (1). Current treatment of asthma by inhaled corticosteroids that focus on controlling asthma symptoms has little effect on underlying pathophysiologic process or natural history of disease. Finding novel therapies with the ability to modulate the immune basis of disease that cuts the roots of the tree and change the natural history of disease has been an interesting area for research. The hygiene hypothesis suggests that exposure to microbial agents, especially during early life, determinates, in part, our gut microbiota, and can protect against the development of allergic diseases, asthma and autoimmune diseases by modulating the immune system and tolerance induction (2).

Probiotics, prebiotics and synbiotics seem to be attractive choices with the ability to change the T helper balance (Th1/Th2) from Th2 to Th1, induction of regulatory T cell and Invariant natural killer T (iNKT) lymphocytes and immune tolerance (3). Recent studies demonstrated that asthmatic patients have a different microbial pattern in their upper and lower respiratory system compared to normal individuals even in neonatal period. Several researchers have evaluated the preventive effects of probiotics and prebiotics on allergic disorders including asthma with the best prevention result demonstrated for atopic dermatitis. Few studies have evaluated therapeutic effects of probiotics and synbiotics on asthmatic patients with different and even paradoxical results. In this systematic review, we focused on treatment effects of probiotics, prebiotics and synbiotics on clinical and laboratory parameters of patients with the diagnosis of asthma.

2- MATERIALS AND METHODS

Scopus, Medline (via PubMed), and Google Scholar were searched with the following key words: (Asthma OR Hyperactive Airway OR Respiratory Allergy) AND (Probiotic OR Prebiotic OR Synbiotic OR Symbiotic OR Micro Biota OR Lactobacillus OR Bifidobacteria OR Fermented Milk OR Additive Therapy) AND (RCT OR Randomized Controlled Trial OR Randomized Controlled Clinical). All randomized clinical trials that evaluated effects of treatment with probiotic or prebiotic or synbiotic for at least 2 weeks on the clinical or paraclinical parameter of asthmatic patients were included. Asthma was defined by clinical history of reversible hyperactive airway disease or pulmonary function tests. Step of asthma (mild intermittent, mild persistent moderate persistent, severe persistent) was defined based on the Global Initiative for asthma (GINA) Guideline (https://ginasthma.org/).

We evaluated reference lists of the relevant studies for any possible missed study. We also reviewed cited article of each relevant study by "cited by" tools of Google scholar. Two authors evaluated relevant studies blindly. Any disagreement was solved by opinion of a third author. For multiple publications from the same group of researchers, the most recent publication was selected. Quality of the included studies was evaluated by Oxford Center for Evidence-Based Medicine for RCTs (https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/).

Pooling of the data across included studies was done by random-effect model. Heterogeneity was evaluated by Cochrane Q value, and $P<0.05$ was considered statistically significant. I^2 index was used to quantify the heterogeneity. Comprehensive Meta-analysis (CMA) Version 2.0 performed all analysis.

3- RESULTS

The literature search provided 941 studies but 867 articles were excluded by screening the abstracts and titles due to irrelevant subjects. **Figure.1** shows the literature search strategy (PRISMA flowchart). The full texts of the remaining 74 studies were evaluated in detail: 64 studies were excluded for being review articles, letters to editors or case reports. Finally, 11 relevant studies (**Table.1**) were included in our meta-analysis (4-14). We did not include murine studies or trials using probiotics for prevention of asthma and allergic diseases. We also did not evaluate trials with combined intervention such as probiotic added to laser acupuncture or combination of probiotic and fish oil or immunotherapy (15-17). **Table.2** shows the outcome measures of included articles (*Please see the tables at the end of paper*).

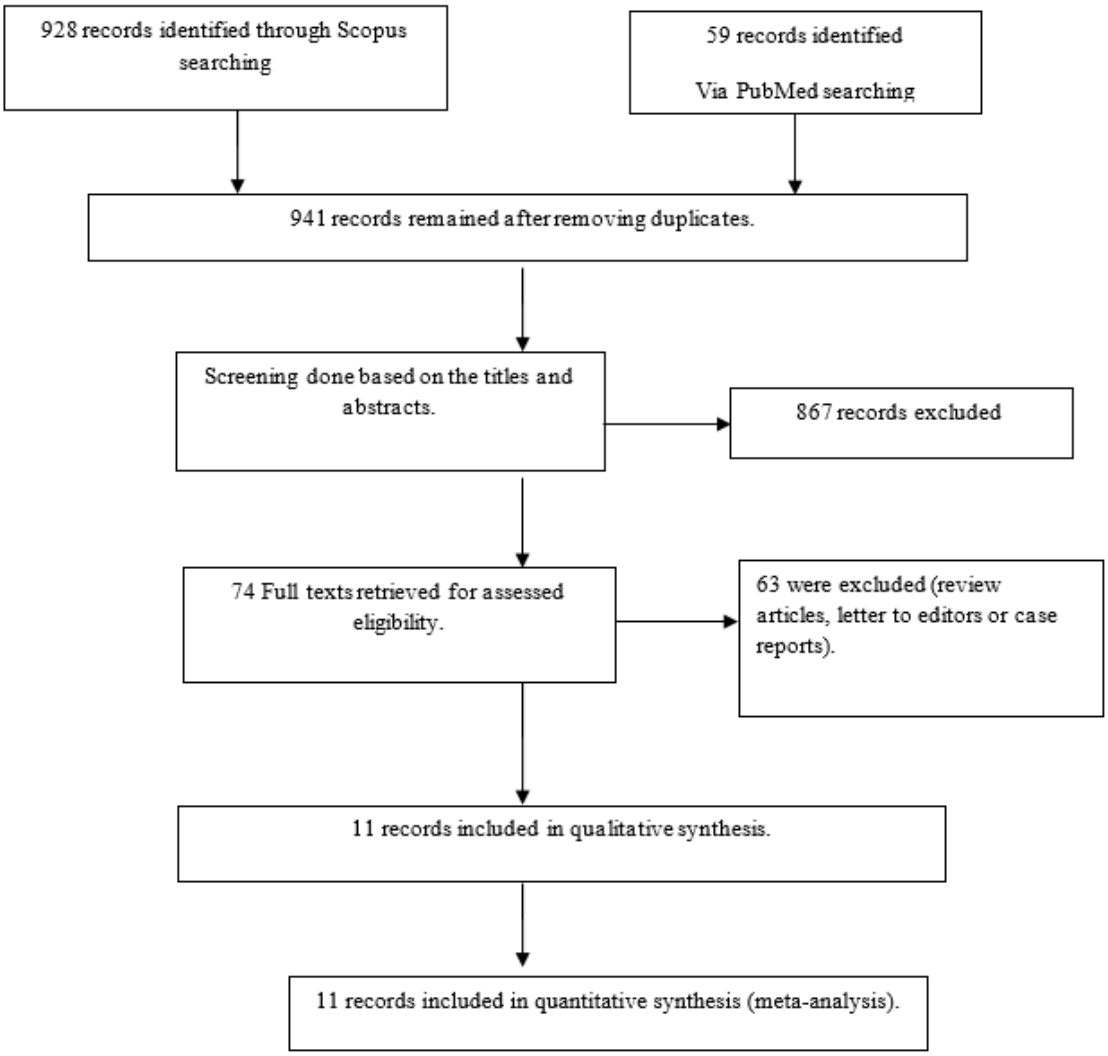


Fig.1: PRISMA flowchart of present study.

3-1. Asthma control tests and Asthma symptom scores

Asthma control is the main aim in the treatment of asthma. Data from two studies-using children asthma control test (c-ACT) were used for this analysis (**Figure.2**). Del Guidice at al. noted the absence of significant difference in c- ACT value at the beginning and at the end of the study period between probiotic and

placebo group (23.4±1.1 vs. 22.7±1) (9). Another study revealed a significant increase in the asthma control in both the probiotic and control groups (P <0.001), and the number of patients who had an improvement in the c-ACT score was higher in the probiotic group (33/49, 67.3%) than in the placebo group (33/56, 58.9%; P <0.05) (11). Finally, although probiotics may improve asthma control test, more studies are needed for any conclusion. In one study, there was no significant change in weekly allergic lung symptom between the two groups from baseline and during pollen season (7). After pollen season, the mean (95% CI) change in allergic lung symptom score in the intervention group was 0.8 (−1.7 to 3.2) and in the placebo group was 6.8 (−0.3 to 13.9) (P = 0.1). Another study noted that difference in asthma symptoms between two groups was not significant (10).

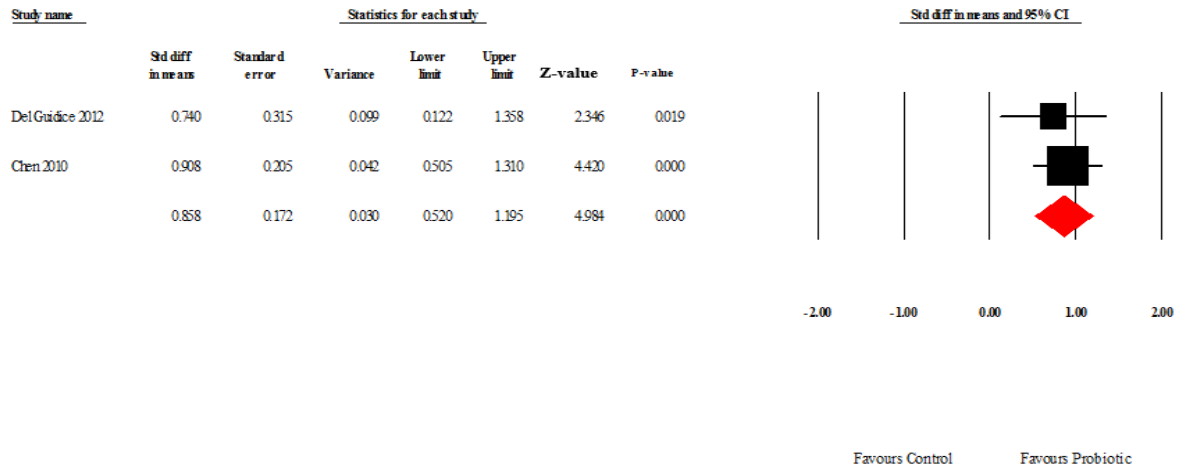


Fig.2: Changes in asthma control tests.

3-2. Asthma exacerbation and wheezing episodes

Number of asthma exacerbation or wheezing episodes were measured in five studies. As the heterogeneity of studies was high in the intervention (dose, duration, type and number of probiotic species, prebiotic usage, follow up, etc.), the outcomes (exacerbation, wheezing episode), and different statistical methods used in these trials, we could not do a meta-analysis of data in this item. Three studies reported no difference in asthma exacerbation between intervention and control groups (4, 8, 13). One of these studies, a community-based trial in 1,302 people with asthma found no evidence of probiotics mixture on asthma exacerbations (13). In Gutkowski et al.'s study, asthma exacerbation was significantly lower in probiotic group between visit 1 and 2, visit 2 and 3 and between visit 3 and 4 (5). Ahanchian et al. reported that there was no significant difference in outpatient visit or hospital admission between two groups of children treated with synbiotic and placebo (12). Giovannini et al. also measured mean duration of an episode, with mean difference (MD) (95%CI) −0.47 (−1.47 to 0.53) days, which was not significant (4). They also measured times free from episode of asthma with no significant difference between the two groups, mean (95% CI) time of 6.2 (5.0 to 7.4) months in the intervention group versus 5.1 (4.0 to 6.3) months in the control group (P = 0.4). Rose et al. (8) also noted that the number of days with wheeze was not statistically different between two groups. One study

(12) showed that the number of viral respiratory infections was lower in synbiotic group in comparison to placebo (0.69 ± 0.11 vs. 0.92 ± 0.15, P= 0.046).
In conclusion, no differences were found, between the intervention group with probiotic and the placebo group regarding asthma exacerbations and time free of asthma symptoms. Only one study reported lower respiratory infections in the symbiotic group.

3-3. Anti-asthma Drugs

This was measured in three studies. Rose et al. showed that probiotic group needed more inhalative betamimetics (median 17 vs. 10, P=0.03) (8). In one study, the total use of allergy and asthma medication increased more in the probiotic group, but the difference did not reach statistical significance (P = 0.06) (7). In one study, salbutamol use was the same in the two groups (9). Two studies showed lower Salbutamol usage in synbiotic group compared to control group (5, 12). It seems that now, it is difficult to make any conclusion regarding the effect of probiotics on the usage of quick reliever or controller drugs in asthmatic patients.

3-4. Pulmonary function tests

Data of five studies reporting the result of spirometry values or peak expiratory flow rates (PEFR) were used for this analysis (**Figure.3**). In one study, lung function (FEV1/FVC) in probiotic group during the observation period was statistically improved, but was unchanged in the placebo group (5). Chen et al. showed significant improvement in the pulmonary function tests (FEV1, FVC, FEV1/FVC, and MEF), and PEFR in the intervention group. The peak expiratory flow (PEF) significantly improved over time in the synbiotics group (morning P=0.003, evening P=0.011), compared to placebo and the change in morning and evening PEF differed significantly between both groups (10). Two other studies noted there was no statistically significant difference between probiotic and control groups in FEV1 value (6, 18). In conclusion, majority of clinical trials demonstrated the beneficial effect of probiotics on spirometric (FEV1, FVC, FEV1/FVC, and MEF) or peak flow values, although a few studies failed to show any benefits.

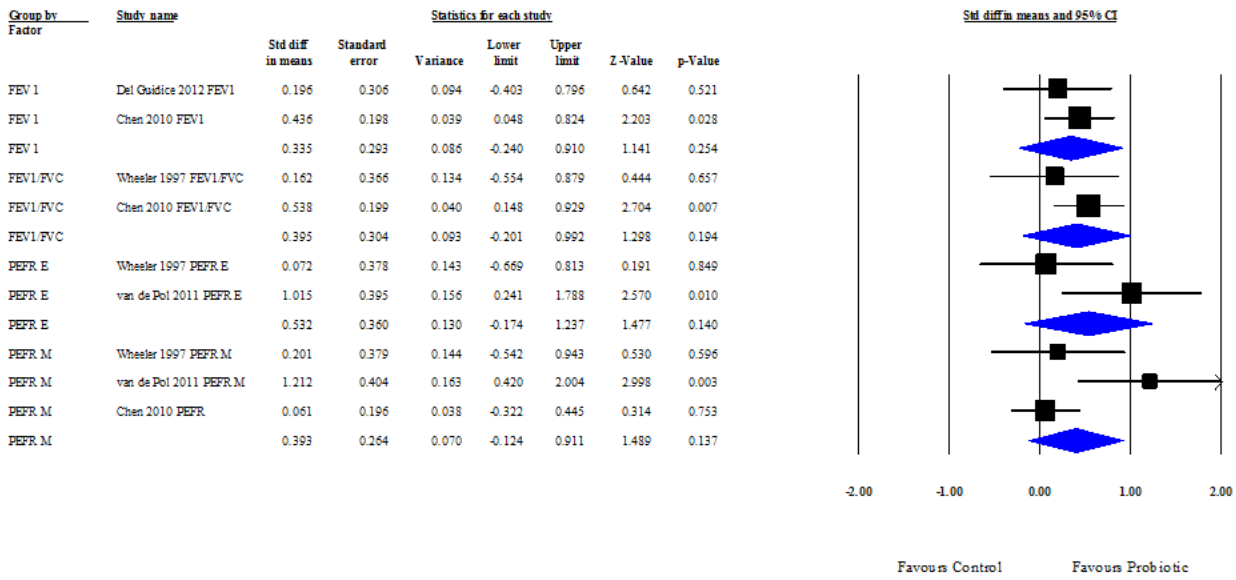
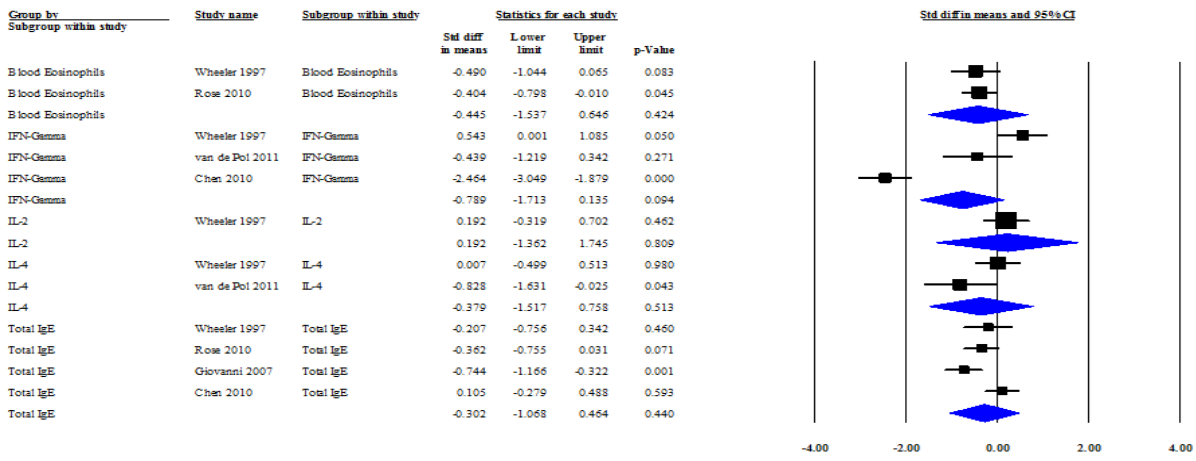


Fig.3: Changes in Pulmonary function tests.

3-5. Immunological and blood Parameters

Total Immunoglobulin E (IgE) was measured in three studies (**Figure.4**). In one study (8), there was no significant change in the course of the study: 14.7 (12.3–190.5) vs. 11.3 (8.7–62.8). Regarding the cumulative specific IgE, levels of aero-allergen specific IgE in serum were lower in the LGG group after 6 months of supplementation (0.526 vs. 10.3; P = 0.011), and after 6 months of follow-up (1.03 vs. 15.6; P = 0.002). Giovannini et al. noted that no overall statistical difference was found at baseline or at 12 months of intervention between intervention and control groups for any examined immunologic variable including IgE, IgG, IgM, and IgA (4). Another study showed that although the serum levels of total IgE decreased slightly in both the probiotic-treated and control groups at the end of the study period, the difference was not statistically significant (11). Wheeler also reported no significant difference in total IgE (6). In conclusion, there was not any significant change in serum IgE made by probiotics in comparison with placebo. Three studies reported serum or mucus Eosinophils with no significant differences between intervention and control groups (6, 8, 10). In a study, airway inflammation monitored by exhaled nitric oxide (FeNo), showed that probiotic group had significantly lower FeNO values than patients in placebo group (20.7±4.1 vs. 30.8±14.1, P= 0.005) (18). This study also noted that Exhaled breath IL-10 significantly increased and exhaled breath IL-2 significantly decreased in probiotic group while there were no differences in IL-4 levels in all experimental groups. Chen et al. observed a significant decrease in the Tumour Necrosis Factor alpha (TNF alpha), and IL-13 production by the peripheral blood mononuclear cells (PBMCs) that were incubated with medium alone and by the Der p-stimulated peripheral blood mononuclear cells (for TNF-a), and by the PHA- and Der p-stimulated PBMCs (for IL-13), following the ingestion of Lactobacillus Gasseri capsules for 8 weeks as compared to those of control group (P <0.05). They also observed that after probiotic treatment, the production of Th1 cytokines, such as IFN-g and IL-12, production by the PBMCs stimulated with PHA or Der p allergen decrease significantly as compared to those of control group (P<0.05). They also found that the percentage $CD4^{+}$ $CD25^{high}$ $FoxP3^{+}$ T lymphocytes (natural Treg [T cells]) among the PBMCs before (0.42 _ 0.39%), and after (0.41 _ 0.37%) the probiotic treatment did not differ significantly, although the natural Treg function improved after the treatment (11).



Group by Subgroup within study	Study name	Subgroup within study	Statistics for each study: Std diff in means	Lower limit	Upper limit	p-Value
Blood Eosinophils	Wheeler 1997	Blood Eosinophils	-0.490	-1.044	0.065	0.083
Blood Eosinophils	Rose 2010	Blood Eosinophils	-0.404	-0.798	-0.010	0.045
Blood Eosinophils			-0.445	-1.537	0.646	0.424
IFN-Gamma	Wheeler 1997	IFN-Gamma	0.543	0.001	1.085	0.050
IFN-Gamma	van de Pol 2011	IFN-Gamma	-0.439	-1.219	0.342	0.271
IFN-Gamma	Chen 2010	IFN-Gamma	-2.464	-3.049	-1.879	0.000
IFN-Gamma			-0.789	-1.713	0.135	0.094
IL-2	Wheeler 1997	IL-2	0.192	-0.319	0.702	0.462
IL-2			0.192	-1.362	1.745	0.809
IL-4	Wheeler 1997	IL-4	0.007	-0.499	0.513	0.980
IL-4	van de Pol 2011	IL-4	-0.828	-1.631	-0.025	0.043
IL-4			-0.379	-1.517	0.758	0.513
Total IgE	Wheeler 1997	Total IgE	-0.207	-0.756	0.342	0.460
Total IgE	Rose 2010	Total IgE	-0.362	-0.755	0.031	0.071
Total IgE	Giovanni 2007	Total IgE	-0.744	-1.166	-0.322	0.001
Total IgE	Chen 2010	Total IgE	0.105	-0.279	0.488	0.593
Total IgE			-0.302	-1.068	0.464	0.440

Fig.4: Changes in immunologic and blood parameters.

4- DISCUSSION

The main conclusion of this systematic review is that probiotics may be beneficial in increasing asthma control scores and pulmonary function test parameters. There was no significant effect on asthma exacerbation or eosinophils counts. Asthma is a growing problem worldwide and the limitations of the current therapy for allergic asthma highlight the need for novel therapeutics with long-term benefits and greater asthma and inflammation control (19). Currently, inhaled corticosteroids therapy alone or in combination with long-acting β -agonists is aimed at targeting the chronic inflammatory process. Considering the fact that asthma is a chronic disease, poor adherence to inhaled steroids, long-term side effects and symptomatic therapy with no effect on natural history of disease are the disadvantages of current therapies. Microbiota and human microbes are key players in host immune responses and immunomodulation (20). Perturbation in the structure of the complex microbial communities, also known as dysbiosis, affects health and may impair immune system development. Regarding the microbiome–immune system interaction, probiotics, prebiotics and synbiotics are potential novel candidates for inducing immunnomodulation needed for prevention or treatment of asthma and allergic diseases. Probiotics as our "old friends" exert their immunomodulatory properties after recognition by the innate immune system by inducing regulatory dendritic cells, which in turn drive polarization of T cells to Treg cells rather than Th1 or Th2 cells and suppression of inflammatory responses. In addition, gut content antigens and allergens are processed resulting in downregulation of allergies, autoimmunity and inflammatory bowel disease (IBDs) (21). This systematic review showed that clinical trials had different results and even paradoxical conclusions. In addition to heterogeneity of the intervention (dose, duration, type etc.), and the outcomes, the fact that microbiota are unique in every subject poses critical challenges in the results of trials and future development of therapeutic or prophylactic approaches to promote a healthy microbiota (22). In addition to reducing inflammation and immunomodulation, probiotics may also exert benefits in asthmatic patients by reducing viral respiratory infections and asthma exacerbation. In 2015, a Cochrane review by Hao et al. concluded that probiotics were better than placebo in reducing the number of acute upper respiratory infections, mean duration of an episode and the antibiotic consumption (23). Viral respiratory infections are the most common cause (80-85%) of pediatric asthma exacerbations and more than half of asthma attacks in adults (24, 25). Recent studies have shown that the airway's epithelial cells in asthmatics can produce less anti-viral interferons including Interferon lambda (IFNλ), and Interferon beta (IFN-β), making them potentially susceptible to viral infections (26). Synbiotics can reduce respiratory viral infection by modulation of the Th1/Th2 responses in the lungs and also reduce the duration of viral infections in healthy school-children and reduce Th2 cytokine in asthmatic children (27-30).

5- CONCLUSIONS

This systematic review has shown probiotics may be effective at increasing asthma control and pulmonary function tests. Regarding the heterogeneity of studies, further research needs to be done before probiotics should be considered as a strategy for treatment of asthma symptoms such as wheeze or prevention of asthma exacerbation or respiratory infection in asthmatic patients. This research may include studies that examine different mixture of probiotics or synbiotics,

different dose and duration and different age or asthma severity. As recent studies demonstrated, asthma as a syndrome with different phenotype and endotype, future research on asthma subgroups will be an interesting area for research.

6- CONFLICT OF INTEREST: None.

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Table-1: Characteristics of included studies in the systematic review.

Name	Design	Sample size case	Sample size control	Target population	Intervention	Control	Notes
Giovini, 2007	Randomized Clinical Trial	92	95	Asthmatic children 2-5 years	Fermented milk containing Lactobacillus bulgaricus (107cfu/ml), Streptococcus thermophylus (108cfu/ml), Lactobacillus casei (108cfu/ml) daily for 12 month	Milk	Exclusion criteria: cow's milk allergy, lactose intolerance, severe food allergy, other severe chronic diseases, perinatal respiratory disorder, antibiotic use in recent 4 weeks, before intervention
Gutkowski, 2010	Randomized Clinical Trial	22	24	Children 4-10 years with mild to moderate atopic asthma and positive prick test and elevated IgE level	Trilac capsule containing 6.1×10^9 microorganisms consisted of lactobacillus acidophilus, bifid bacterium bifidium lactobacillus Delbrucki, subsp. Bulgaricus twice daily for 12 weeks	Placebo	NA
Wheeler, 1997	Crossover double-blinded Clinical Trial	15	15	Adult patient with moderate asthma and positive prick test for aerosol allergen	Yogurt containing Lactobacillus acidophilus lactobacillus Bulgaricus streptococcus thermophilus at average concentration 7.6×10^8,3.3×10^8 and 3.7×10^8bacteria per gram of yogurt, 225gram yogurt twice daily for one month	Same yogurt without Lactobaeillus acidophilus	Exclusion criteria- History of clinical allergy or intolerance to milk product or actively smooking within 3 month of study or receiving antibiotic or immunotherapy in 3 months ago
Helin, 2002	Randomized Clinical Trial	18	18	14-36 year old patients with allergy to birch and mild asthma	Capsule containing 5×109 lactobacillus rhamnosus daily for 5.5 months	Placebo	Exclusion criteria-Exclusion criteria-other pollen allergies, smoking, pregnancy and lactation, use of immunotherapy or long-term medication or antibiotics and probiotic product
Rose, 2010	Randomized Clinical Trial	65	65	Children 6-24 months old with two or more episodes of wheezing >3days necessitating bronchodilator that at least one of them occurred during 3 months before enrolment	Lactobacillus rhamnosus ATLL 53103 (10^{10} CFU) twice daily for 6 months.	Placebo	6 months follow up. Exclusion criteria: GG preterm birth ((<37 weeks) at gestational age) other systemic or chronic disease congenital anomaly, current antibiotic therapy, history of probiotic intolerance
Del Guidice, 2012	Randomized Clinical Trial	25	25	Children 6-14 years old with mild persistent asthma	Lactobacillus reuteri (10^8cfu=5 drop per day) daily for 60 days	Placebo	Exclusion criteria-History of previous immunotherapy or systemic or inhaled steroid therapy 8 weeks before other respiratory

							cardiovascular or systemic disorders, or anatomical anomaly
Van de pol, 2011	Randomized Clinical Trial	14	15	Adult patient 21-51 years old with mild persistent asthma	Synbiotic containing Bifidobacterium breve (10^{10}cfu) combined with prebiotic twice daily for 4 weeks	Placebo	Exclusion criteria: History of previous immunotherapy, respiratory tract infection within previous 6 weeks, history of smoking in previous 6 months, significant change in environmental allergen in previous 6 months and during study.
Chen, 2010	Randomized Clinical Trial	49	56	Children 6-12 years old with mild to moderate persistent asthma	Lactobacillus Gasseri as (>2×10^{9}CFU) daily for 8 weeks	Placebo	Exclusion criteria-History of immunotherapy corticosteroid usage, other respiratory disease anatomical abnormality of the upper respiratory tract, congenital cardiovascular disease
Ahanchian, 2016	Randomized Clinical Trial	36	36	Children 6-12 years old with mild persistent asthma	Synbiotic containing 1 billion CFU/Capsule of 7 probiotic strains and Fructooligosaccharide daily for 2 months	Placebo	Exclusion criteria-Congenital abnormality or syndrome, antibiotic or probiotic consumption during 2 previous weeks, any underlying disease
Smith, 2016	Randomized Clinical Trial	652	650	5 years and older asthmatics	2 strains of Lactobacillus acidophilus, Bifidobacterium bifidum and B animalis at a total 2.5×10^{10} CFU for 6 months	Placebo	-----

CFU: Colony forming unit, IgE: Immunoglobulin E.

Table-2: The outcomes of included studies.

Author /date	Outcomes	Probiotics vs. Placebo	P- value
Giovannini, 2007	Time free episode of asthma cumulative number of episode of asthma Mean duration of an episode change in immunological profile IgA (mg/dl) IgG (mg/dl) IgM (mg/dl) IgE (U/ml)	4.1(3.1 to 5) vs 3.3(2.4 to 4.3) months No differences Mean difference -0.47(-1.47 to 0.53) day 102.8 (92.7;114.0) vs 96.5 (83.6;111.3) 945.1 (892.4;1000.9) vs 923.6 (871.1;979.0) 98.8 (89.8;108.8) vs 95.8 (87.3;105.1) 255.0 (181.8;357.7) vs 252.9 (176.5;362.6)	0.231 NS NS 0.507 0.533 0.695 0.913
Gut Kowski, 2010	Asthma exacerbation (number) Visit1/Visit2 Visit2/Visit3 Visit3/Visit4 FEV1/FVC Bronchodilator(Visit 3/Visit 4)	 12.9 vs. 20.4 21.1 vs. 23.3 34.9 vs. 27	 Statistically Significant Statistically Significant Statistically Significant Statistically Significant
Helin, 2002	Lung symptoms (% of participant) During pollen season After pollen season Inhaled medication During pollen season After pollen season	 17.2(7.2 to 41.6) vs 32.7(6.6 to 58.3) 4.4(9.4 to 17.7) vs 37.7(1.6 to 77.2) +2.7 (+1.6 to +3.7) vs +1.2(+0.05 to +2.4) +0.9(-0.05 to +1.9) vs +0.9 (-0.50 to +2.4)	 0.37 0.10 0.06 0.98
Ahanchian, 2016	Viral respiratory infection First month Second month Total Salbutamol usage, number Outpatient visit, number Hospital admission, number Oral prednisolone, number	 0.44 ± 0.1 vs. 0.74 ± 0.12 0.74 ± 0.12 vs. 0.5 ± 0.8 0.69 ± 0.11 vs. 0.92 ± 0.15 16 vs. 26 1 vs. 3 14 vs. 21 0 vs. 1	 0.007 0.641 0.o46 0.017 0.303 0.099 0.314
Rose, 2010	Number of wheezing episodes median (±95% CI) Number of rescue free days median (±95% CI) Number of symptom free days median (±95% CI) Days with wheeze Asthma symptom score Asthma symptom score in aeroallergen-sensitized patients	1 (0.66-1.34) vs. 1(0.60-1.40) 168.5 (158.4–178.6) vs. 177.5 (172.0–183.0) 133.0 (123.4–142.6) vs. 126.5 (115.7–137.3) 7.50(1.32-13.7) vs. 6.50(0.80-12.2) 19.8 (0.93–38.6) vs. 9.81 (6.34–26.0) 22.9 vs. 42.5	NS NS NS NS NS NS

		13.5 (3.39–23.6) vs. 13.0 (8.11–17.9)	0.04
	Days on inhalative Salbutamol	16.0 (7.29–24.7) vs. 9.50 (1.99–17.0)	0.03
	Days on inhalative steroids		
		13.6(6.5-109.1) vs. 20/2(16.2-81.3)	NS
	IgG (IU/mL)	3(2.2-3.9) vs. 3(2.5-3.6)	NS
	Eosinophils (%)(min, max)	15.6(1.98-29.2) vs. 24.4(16.6-34.1)	NS
	ECP (mg/ML) mean (min, max).		
Del Giudice, 2012	FEV1(mean ± SD)	95.8±9 vs. 92.5±8.9	0.8
	Children Asthma control test (C- ACT): (mean ± SD)	23.4±1.1 vs. 22.7±1.1	NS
	FeNO (mean ± SD)	20.7±4.1 vs. 30.8±14.1	0.005
	Exhaled breath IL10	Significantly increased in probiotic group	<0.05
	Exhaled breath IL2	Significantly reduced in probiotic group	<0.05
	Exhaled breath IL4	----	NS
Chen, 2010	Change in PFT from baseline to visit 5		
	FEV1	9.05±2.25 vs. 1.80±0.61	0.028
	FVC	8.14±1.85 vs. 0.77±1.71	0.035
	PEFR	8.80±5.85 vs. 7.76±3.16	0.754
	FEV1/FVC (%)	1.01±0.43 vs. 1.1±0.23	0.007
	MEF 25-75	1.39±0.91 vs. 1.74±0.41	0.211
	Post bronchodilator FEV1 change	-60.46±21.61 vs. 16.85±10.61	<0.001
	serum total IgE (IU)	853.2+1103.2 vs 843.2+1397.2	NS
	Patient with improved daily symptom/total patients	37/49 vs. 35/56	<0.05
	with improved night symptom/total patients	32/51 vs. 33/56	NS
	Patient with improved ACT score/total patients	33/49 vs. 33/56	<0.05
	Decrease in TNFα, IL 13 production by PBMCs		<0.05
	IL 10 production by PBMCs		NS
	Decrease in IFN γ, IL 12 production by PBMCs		<0.05
Van de pol, 2011	Asthma symptom score		Not significant
	Change in Peak expiratory flow (PEF)		
	Morning	30 vs. 15	0.003
	Evening	13 vs. -10	0.011
	Sputum Eosinophils (×104/gr)	9.5 vs. 9.5	0.998
	Sputum neutrophils (104/gr)	44 vs. 26.4	0.295
	Eosinophilic cationic protein (ng/gr)	138 vs. 65	0.403
	Myeloperoxidase (ng/gr)	884 vs. 582	0.500
		2.4 vs. 16.5	0.055

	Serum IL 5 Regulatory T cells (CD4+CD25+/IL7R- T cells Expression of FoxP3 in CD4/CD25 high T cells		 NS NS
Wheeler, 1997	Peak Expiratory flow (PEF) Morning Evening FEV1/FVC (%) PEF 25-75% Eosinophils (number/mm^3) Total IgE (IU/ml) Cytokine production after lymphocytes stimulation IL 2 Il 4 Interferon gamma	 335 vs. 352 364 vs. 368 *72* vs. 72 2.07 vs. 1.84 224 vs. 209 163 vs. 187 252 vs. 296 40 vs. 40 61 vs. 46	 0.60 0.85 0.66 0.52 0.09 0.47 0.47 0.98 0.058
Smith, 2016	Antibiotic consumption Respiratory tract infection Asthma exacerbation	27.7% vs. 26.9% (odds ratio = 1.04; 95% CI, 0.82-1.34) 29.5% vs. 28% 10.5% vs. 11.1%	NS NS NS
Del Giudice, 2017	Nasal symptom (TSS score) Quality of life Rescue medication Cetirizine Salbutamol	(T0 = 9.3 ± 2.1; T1 = 3.5 ± 1.7) vs. (T0 =8.4 ± 2; T1 = 11 ± 1.3) (T0 = 37.6 ± 8.4; T1 = 11.9 ± 5.2) vs. (T0 = 32.4 ± 8.9; T1 = 47.5 ± 7.1) 31 ± 8 days vs. 33 ± 7 days 19 ± 7 puffs vs. 22 ± 4 puffs	< 0.005 < 0.001 NS NS

NS: not significant, ECP: Eosinophilic cationic protein, FeNO: Fraction of exhaled nitric oxide, c-ACT: Childhood Asthma Control test, IgA: Immunoglobulin A, NS: Not significant, FEV1: Forced expiratory value in one score, FVC: Forced vital capacity, SD: Standard deviation, TSS: Training Stress Score, PEFR: Peak expiratory flow rate, CI: Confidence Interval, ECP: Eosinophil cationic protein, MEF 25-75: mean expiratory flow *25–75*%, ACT: Asthma control test, TNFα: Tumor necrosis factor alpha, in TNFα , IL 13: Interleukin 13, PBMCs: Peripheral blood mononuclear cells.