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Modulation of Gut Microbiota as a Potential Therapeutic Strategy in Asthma: A Scoping Review

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Asthma is a chronic inflammatory airway disease with a multifactorial origin, resulting from interactions between genetic and environmental factors. The diversity of the respiratory epithelial microbiota contributes to asthma development through epigenetic mechanisms, regulation of pro-inflammatory cytokines, modulation of T-cell tolerance, and overall immune responses. This process is influenced by interactions between the gut and lung microbiomes via the gut–lung axis. Aim: This review aims to map and evaluate the pharmacological activities, effectiveness, and safety of probiotics based on evidence from preclinical and clinical studies. This study was conducted as a scoping review to map existing evidence on the pharmacological activity, effectiveness, and safety of probiotics in asthma. The administration of probiotics in asthma patients shows therapeutic potential as an adjuvant therapy through the production of secondary metabolites in the gut, such as short-chain fatty acids (SCFAs) and indoles. Bacterial strains from the genera Bifidobacterium and Lactobacillus have demonstrated beneficial effects in clinical trials; however, the outcomes remain inconsistent. These variations may be attributed to differences in probiotic strains, colony-forming unit (CFU) counts, sample sizes, and the allergic phenotypes of the subjects. Evidence from preclinical and clinical studies indicates that probiotic therapy in asthma yields variable clinical outcomes but remains a promising therapeutic candidate that warrants further well-controlled, dose-ranging, and strain-specific studies.

Keywords: asthma, probiotic, gut-lung axis

Introduction

Asthma is a chronic airway disease characterized by airway obstruction. Asthma has multifactorial etiology caused by genetic and environmental factors. One of the main manifestations of asthma is shortness of breath that varies with time and is accompanied by wheezing. The onset of asthma generally occurs during childhood, but adult-onset asthma can be triggered by several allergens, lifestyle factors, and airway infections. Epidemiologically, asthma is still a global epidemic and contributes to the burden of health problems in the world.[1,2]

Genetic factors are now known to play an important role in the pathogenesis of asthma. Currently, a locus has been identified that play a role in the development of asthma, such as the Human Leukocyte Antigen-DQ Beta 1(HLA-DQB1). HLA-DQA1 genes in European populations and Interleukin (IL)33 in East Asian populations. In addition,

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epigenetics also influences the formation of asthma phenotypes. Prenatal environmental conditions such as air pollution, prenatal nutrition, and drugs can affect gene expression through epigenetic changes, through DNA methylation, post translation histone modification, and microRNA expression. Environmental factors also influence the formation of asthma phenotype, such as female sex, obesity, occupational exposure to rhinitis, respiratory infection, smoking, and stressful live events.[3,4] Both factors cause dysregulation to the immune system which triggers an inappropriate immune response to an allergen.

Currently, asthma therapy is divided into two main types: controller and reliver therapy. Controller therapy aims to control inflammation in the airways. The classes of drugs involved include inhaled corticosteroids (ICS), long-acting beta agonists (LABA), and leukotriene receptor antagonists. Meanwhile, reliever therapy is intended to alleviate asthma symptoms that appear suddenly, such as shortness of breath, wheezing, and frequent coughing. The drug classes used for this purpose include short-acting beta agonists (SABA) and low-dose ICS. Both treatment regimens aim to relieve respiratory symptoms of asthma and reduce the incidence of exacerbations. Targeted therapies addressing immune dysregulation are still under investigation. Among the potential candidates, probiotics have emerged as a promising therapeutic option.[2,5]

Probiotics are live microorganisms that, when administered in adequate amounts, confer beneficial effects on human health. Probiotic-based therapeutic approaches have been extensively studied, including their use in metabolic syndrome and diabetes mellitus.[6] Recent evidence also suggests that probiotics may play a role in modulating allergic responses, particularly through interactions with the developing immune system, influencing immune maturation and T helper 2 (Th2) responses. In addition, probiotics can regulate cytokine expression, modulate immune responses, enhance mucosal barrier integrity, and interact with pathogenic bacteria.

However, despite the growing of current literature, existing reviews primarily focus on clinical outcomes without comprehensively integrating pharmacological mechanisms, strain-specific effects, and safety profiles. Furthermore, inconsistencies in clinical findings remain insufficiently explored, particularly in relation to variations in probiotic strains, dosages, and patient characteristics. This scoping review aims to map and synthesize current evidence on the pharmacological activity, effectiveness, and safety of probiotics in asthma, while identifying key knowledge gaps and sources of heterogeneity in existing studies. This approach is intended to provide a more comprehensive framework to guide future research and clinical application

Methods

This study was conducted as a scoping review to map existing evidence on the pharmacological activity, effectiveness, and safety of probiotics. A comprehensive literature search was carried out using electronic databases including PubMed, Scopus, ScienceDirect, and Google Scholar. Relevant articles published in English were identified using combinations of keywords such as probiotics, pharmacological activity, clinical effectiveness, safety, asthma, allergic disease, and pediatric. Studies were included if they investigated probiotic interventions, either as single-strain or multi-strain formulations, reported pharmacological, immunological, or clinical outcomes, were conducted in human subjects including children or adults, and were published as original research articles such as clinical trials, pilot studies, or observational studies.

Discussion

Genetic and Epigenetic of Asthma

Genetic factors are one of the causes of atopy conditions, including asthma. This can be seen in the racial and geographical differences in the population of patients with asthma. In addition, environmental, occupational and lifestyle factors in the local population also influence the manifestation of atopy in patients. It is common for clinicians to evaluate the family history of allergy in children or adult patients with asthma, as atopy itself is hereditary.[7] The discovery of genes that play a role in asthma pathogenesis could be one of the key therapeutics in asthma treatment. These genes influence the progression of asthma through immune system function, mucosa function and biology; and lung function expression.[7] Previous genetic studies have been conducted to identify

important loci that contribute to asthma. Currently, gene evaluation has been carried out on several racial groups such as African-American, Hispanic, and Caucasian. The outcome was found to be six loci consisting of 5p51 and 17p11.1-q11.2 in African American race; 2q33 and 21q21 in Hispanic; and 11p51 and 19q13 in Caucasian.[8,9]

GWAS (Genome Wide Association Studies) also found genes that play a role in the pathogenesis and pathophysiology of asthma. The DENNB1B gene with loci 1q31 has a role in T cell receptor signalling and plays a role in the regulation of positive T-helper 2 cell cytokine production. Then the DPP10 gene with loci 2q14 plays a role in the positive regulation of protein localisation plasma membrane and proteolysis. HLA-DQ gene with loci 6p21 has a role in MHC class II which plays a role in the production of immunoglobulin and immunoglobulin mediated immune response. Gene 1L13 with loci 5q31 has a role in the inflammatory process in positive regulation of macrophage activation.

Severity, therapeutic success, and lung function in asthma can also be influenced by gene. ADBR2 gene polymorphism with loci 5q32 has an association with improvement in beta-2 agonist response, and asthma severity.[7,9,10] The ADBR2 gene is a highly polymorphic gene with the main variant being a benign missense mutation. Polymorphisms in this gene may lead to downregulation phenomenon due to alterations in receptor degradation after the internalisation phase.[10] Microbiome has a role in the regulation of genetic expression of asthma genotype. Early life exposure to a specific microbiome can alter the host eipigenome, which indirectly affects the pathogenesis and progression of asthma. Some microbes and their metabolites can modulate epigenetic changes through histone methylation and modification, thus affecting immune response and tolerance. This is supported by the significant differences between populations in microbiota composition. In addition, studies with allergic rhinitis subjects showed that 956 differentially methylated CpGs were found, 792 CpGs formed 3 correlation modules, and 1 module had an eigenvector associated with gene expression related to lysosomes and bacterial invasion of the epithelium. This suggests that microbiota diversity affects DNA methylation patterns associated with epigenetic regulation of allergic diseases.[11–13]

Immunopathogenesis in Asthma

The main pathogenesis of asthma consists of hypersensitivity conditions in the airways, chronic inflammation, and remodelling of airway structures. The genesis of this disease is a form of combination of genetic and environmental factors that influence the immune system response to allergens, hapten, and antigens. Asthma is a heterogeneous lung disease with various clinical manifestations. It is now recognised that the molecular mechanism that mediates the occurrence of asthma is the activity of Th2 cells. Inflammation triggered by aberrant T helper cell type 2 is characterised by an increase in pro-inflammatory cytokines such as IL-5, IL4, and IL-13. Based on the activity of T helper cells asthma can also be classified into two main categories, which is Th2 high and Th2 low. Th2 high asthma is characterised by eosinophilic inflammation with increased blood eosinophil count or increased exhaled nitric oxide. Th2 low consists of neutrophilic asthma and paucigranulocytic asthma.[14]

Th2 inflammation consists of two phases, the sensitisation phase and the challenge phase. The sensitisation phase is characterised by antigen presenting cells processing and presenting the allergen to Th2, leading to the release of cytokines such as IL-5, IL-4 and IL-13. IL-13 then activates B cells that trigger Immunoglubulin (Ig)E production and binds to FcRI on mast cells. Then the challenge phase occurs when the allergen enters the airway and binds to IgE which induces mast cells to release inflammatory mediators such as leukotriene, histamine, and interleukins. The release of IL-5 triggers proliferation, maturation, and recruitment of eosinophils. This in turn triggers the release of eosinophil mediators that exacerbate the inflammatory response. IL-13 also directly sensitises airway smooth muscle contraction, triggers airway mucin secretion, and leads to fibrosis in asthma.[14]

The activity of T cells is regulated by regulatory T cells. Treg have an important role in maintaining lung immune tolerance and suppressing immune system stimulation, especially in airway allergic reactions. The role of Treg is influenced by the amount of Forkhead Box

P3 (FOXP3) protein. FOXP3 is a protein expressed by T-regulatory (Treg) cells.[15,16] The expression of FOXP3 is influenced by epigenetic regulation and methylation of FOXP3 plays a role in the stability of protein expression. FOXP3 Treg has inhibitory activity against autoimmune and allergic diseases.[17] In patients with severe asthma, there is a lower number of FOXP3 compared to healthy controls. In addition, asthma patients were found to hypermethylated FOXP3 through CpG methylation compared to healthy children, resulting low expression of FOXP3. Aberrant Treg in lung tissue leads to tolerance breakdown and up regulation of proinflammatory cell response.[8,16,17]

In Th2 low asthma, it was defined by the absence of biomarkers of Th2 high asthma, but the presence of neutrophilic and paucigranulocytic features. Neutrophilic asthma is a condition where numerous neutrophils are found in sputum with a neutrophil count value above 5 x 10 9/L. In this condition, neutrophils secrete IL-8 which causes positive feedback and promotes neutrophilic inflammation and neutrophil recruitment. In neutrophilic asthma, Toll-Like Receptor (TLR) activity play critical role by triggers T helper 1 and T helper 17 activation which leads to the release of cytokines Interferon (IFN)-γ, Tumor Necrosis Factor (TNF)-α, IL-8, IL-17, IL-IF, and IL-22. Meanwhile, paucigranulocytic asthma is characterised by the absence of eosinophilic and neutrophilic inflammatory features. This type of asthma is characterised by high arway responsiveness to methacholine, smooth muscle proliferation and hyperplasia, and subepithelial matrix deposition.[15,18]

Immunometabolic in Asthma Progression

Metabolism in the human body is one of the factors that influence the progressivity of asthma. Biochemical reactions in the metabolism of glucose, fat, and protein that produce metabolites play a role in changing the microenvironment of a cell. It has recently been recognised that there is a correlation between cellular metabolite activity and diseases related to immune response, one of which is asthma. The processes of glycolysis, fatty acid oxidation, and amino acid metabolism can affect how immune cells function, differentiate, and carry out immunological activities.[19]

Metabolism in immune cells plays a role in activation and function of human immune cell through adapting to a specific metabolic programme. The process of glucose metabolism or glycometabolism in immune cells is related to the activity of immune cells in secreting pro-inflammatory mediators, proliferation, maturation, and cytokines release. Glycolysis plays a critical role in upregulation or downregulation of specific protein that modulate human immune function. Beside glucometabolic, fatty acid oxidation and amino acid metabolism also contribute to this process.

In T cells, nutrient metabolism significantly affects their immunological activity. The use of mixed fuels such as glucose, lipids, and amino acids through oxidative phosphorylation can create energy for surveillance and memory of T cells. Activation of T cells is a result from a metabolic shift to anabolic metabolism and glycolysis as the primary metabolic programme. These mechanisms are responsible for forming molecular building blocks that will be incorporated with cellular biomass for the activation of T cell growth, proliferation, and cytokine production. The process of glycolysis and fatty acid oxidation occurs to increase proliferation. The process of glycolysis in T cells is influenced by Glucose Transporter (GLUT)1 expression. Effector T cells (Th1, Th2, and Th17) have high GLUT1 expression, while regulatory T cells have low GLUT1 expression. In some conditions, there is an increase in GLUT1 expression in Treg cells which causes downregulation of the transcription factor Foxp3 inducing more proliferative and less suppressive activity of Treg cells.[19–21]

In macrophages, proinflammatory M1 macrophages have a high rate of glucose consumption and higher lactate release compared to M2. Downregulation of glycolysis leads to decreased secretion of proinflammatory cytokines. Overexpression of Hypoxia-Inducible Factor (HIF)-1 alpha can upregulate glycolysis and pentose phosphate pathway in macrophage. The results of metabolites such as citrate and succinate have a role in the regulation of the immune system. Citrate can increase proinflammatory factors and accumulate in M1 macrophage; and acts as an upstream regulator of HIF-1alpha during regulation of glycolysis and macrophage polarisation.[19–21]

Metabolic dysregulation also influences asthma progression. Insulin resistance, dyslipidemia, and obesity affects pulmonary physiology and immune response through several mechanism. In adult-onset asthma, immune system dysregulation that contributes to asthma pathogenesis may be triggered by metabolic dysfunction such as insulin resistance.[19,21] Hyperinsulinemia may affect the anatomical structure of the lung. In in vivo studies with animal models of intranasal insulin induced hyperinsulinemia showed that hyperinsulinemia can induce pathophysiological characteristics of asthma. This is mediated by beta catenin as a mediator of insulin-induced smooth muscle proliferation. In this condition, peribronchial thickening, collagen deposition, increased airway responsiveness, and airway mesenchymal transition were found.[20]

Hyperglycaemia in chronic diabetes is characterised by increased synthesis of advanced glycaion end-products found in the vascular circulation. High levels of Advanced Glycation End-products (AGEs) trigger the expression of AGE receptors and contribute to complications in diabetes.[22] AGE receptor is one of the pro-imflamatory receptors. It is now known that AGE receptors play a role in pulmonary hyper eosinophilia, mucous hypersecretion, airway remodelling/allergic airway disease. In addition, the expression of IL-5 and IL-13 was also found to be reduced along with the reduction of AGE receptor. Insulin resistance causes asthma in several ways, including triggering airway remodelling characterised by increased collagen deposition, increased epithelial to mucous transition, increased fibrosis, and increased TGF-B1 expression. In addition, the release of proinflammatory cytokines also plays a role in the pathophysiology of asthma in insulin resistance and DM. These inflammatory mediators include IL-6, TNF-a, and Th2 inflammation which increase in Diabetes Melitus (DM) and insulin resistance conditions.[23]

In children, metabolic disorders also influence the onset of asthma. Childhood obesity with abdominal visceral fat is known to affect the pulmonary compliance system. In addition to diet, antioxidants and saturated fat play a role in the inflammatory pathway of asthma. There is growing evidence that increased BMI in children is associated with an increased prevalence of asthma in children. This finding is also consistent with higher levels of triglycerides in children with asthma. The inflammatory pathway in metabolic dysregulation is characterized by typical low-grade inflammation initiated by monocytes. Monocyte-induced T helper 1 polarization, which correlates with leptin and IL-6. Increase in circulating Th1 polarization markers, interferon gamma and interferon gamma induced protein are negatively correlated with orced Expiratory Volume in 1 second (FEV1)/Forced Vital Capacity (FVC) ratio. Th1 polarization induced by monocytes increases the number of neutrophilic inflammations in severe asthma.[24] The correlation between metabolic dysfunction and asthma points to the importance of dietary management and comorbidity control in patients with asthma. Metabolic dysregulation affects the inflammatory system in both paediatric and adult lungs, thus worsening asthma disease progression. Obesity, dyslipidemia and insulin resistance are among the comorbidities that must be managed in patients with asthma. The intracellular metabolism also plays a part in the progression of asthma, as glycolysis activity indirectly contributes to T cell activity that regulates the inflammatory response in asthma.

Gut Lung Axis in Asthma

Anatomically, the gut and lung are fairly distinct, but there is a form of communication between the two organs that has a role in human health. Both the gut and lung also have different compositions of normal flora. Both are expected to have a balanced composition between normal and pathogenic flora to achieve a bacterial ecosystem that is beneficial to the human body. The crosstalk between the two organs is mediated by the oropharynx, blood, and the vagus nerve. The byproducts from both organs can interact with each other through mutual signals. Gut lung axis is significantly related to nutrition, respiration and digestive health, and immune system through complex communication.[25,26]

The gut microbiota is a diverse and dynamic microbial ecosystem. The composition consists of bacteria, viruses, fungi, archae, and helminths.[26,27] This ecosystem plays a role in maintaining homeostasis. Microbiota currently has a role in producing secondary metabolites that can alter an organ system through fermentation. Secondary metabolites that are known to have a role consist of short chain fatty acids Short-Chain Fatty Acids (SCFA), indoles, polyamines, and secondary bile acids. SCFA itself consists of butyrate,

acetate, and propionate which have a role in immune system regulation such as tolerance and inflammatory response.[28]

Secondary metabolites gut derivatives affect the immune system through genetic, epigenetic, and immune system receptors. These secondary metabolites not only promote the differentiation of immunosuppressive cells, but also could inhibit inflammatory cells.[29,30] SCFAs are the most abundant secondary metabolites found in the colon. Anaerobic obligate bacteria in the colon produced enzymes that hydrolyse carbohydrates and decompose fibre into sugars. The sugars are then fermented through glycolysis and pentose phosphate pathway resulting the release of SCFA. Bacteria such as *Akkermansia muciniphila*, *Bacteroides* sp., *Bifidobacterium* sp., *Prevotella* sp., *Ruminococcus* sp. responsible to produced acetate through acetyl-CoA pathway. *Bacteroides* sp., P*hascolarctobacterium succinatutens, Dialister* sp., *Veillonella* sp. produced propionate through succinate pathway. Butyrate was produced through butyrate kinase pathway by *Coprococcus comes*, *Coprococcus eutactus*.[31,32]

Regulation of the immune system through SCFA may be mediated by histone modification through histone acetylation. SCFA attenuates proinflammatory effectors in lamina propria such as macrophages and dendritic cell differentiation. Metabolic changes in T cells characterized with increase glycolysis induced increased sensitivity of T cells to SCFA.[32] SCFAs serve as ligands for receptors such as G-protein-coupled receptor (GPR)43, GPR41, and GPR109A. GPR43 receptor is expressed on T reg cells, M2 macrophage, eosinophils, neutrophils, and mast cells. Activation of the GPR43 receptor contributes to the normal resolution of the inflammatory response. SCFA-GPR43 binding leads to decreased activation and infiltration of neutrophi and decreases pro-inflammatory receptors such as C5aR and CXCR2 through heterodimerisation and receptor internalisation.[33] GPR43 receptor binding and acetate/propionate reduced infiltration of eosinophils and downregulated pro-inflammatory cytokines such as IL-4, IL-5, IL-13 and IL-17A in the lung. In addition, other SCFAs such as propionate alleviate allergic inflammation by inhibiting the production of Th2 cytokines. Such activity may occur in inflammation induced by allergic processes in the lung.[33,34]

The composition of the lung microbiota is related to the gut and oropharyngeal microbiome. It is now also known that there is an interaction between the lung microbiota and the gut microbiota. Unlike the bacteria in the gut, there are fewer microbiota in the lung. The composition of the lung microbiota consists of the bacteriome, mycobiome and virome. Streptococcus, Veillonella, and Prevotella are the most common genera, while Haemophilus is rare in other microbiomes. Meanwhile, the fungal/mycobiome composition was dominated by Candida. The gut lung axis is a form of bidirectional communication, where the gut microbiota influences lung health through modulating the pulmonary immune system and the lung microbiota can mediate dysbiosis in the gut. 35 Bidirectional connection between gut and lung is one of the factors that trigger asthma. Dysbiosis in the lung microbiome was also found to increase in asthma patients. Environmental conditions are certainly one of the triggering factors for asthma, in addition to acting as an allergen irritant, there is a concept that is more related to the microbiota in the lung. Broadly speaking, there are two main factors that play a role in increasing the incidence of asthma, namely protective factors such as farming and irritative factors such as pollution, smoke, pollen, and allergens. The farm environment was found to have beneficial effects. Bacteria and yeast/fungi inhaled by the lung can activate the innate immune system against endotoxins. Endotoxins play a role in reducing the activation of allergens on epithelial cells and dentritic cells in the airway in invivo and invitro studies. Farming also showed increased expression of innate immune system receptors such as TLR2, TLR4, and CD14 that contribute to the innate immunity response.[35,36]

Role of Probiotic in Asthma

Probiotics are live microorganisms that when administered in appropriate amounts can provide health benefits to their hosts. Probiotics generally contain non-pathogenic lactic acid bacteria such as *Pediococcus, Lactococcus, Enterococcus, Propionibacterium*, and *Bacillus*. Bacterial strains commonly used as supplements are *Bifidobacterium* and *Lactobacillu*s. Probiotics affect humans through various mechanisms, one of the main ones is acting as a competitor to pathogenic bacteria in the gut mucosa. Probiotics can modulate the host immune system, improve epithelial

mucosal integrity, mitigate lactose intolerance, and increase the bioavailability of micro- and macronutrients.[37,38]

The use of probiotics was previously focused on digestive tract diseases, but recent studies have shown that probiotics have health benefits for allergic diseases, including asthma. Some strains have the ability to modulate the immune system, but one strain that is thought to have an effect on asthma is Lactobacillus rhamnossus, *Lactobacillus reuteri*, and *Lactobacillus gasseri*. *Lactobacillus species* contain peptidoglycan components that play a role in healthy respiration. Besides Lactobacillus strains, Bifidobacteria are also thought to have a role in the immune system (**Figure 1**).[39]

The mechanism of probiotics as asthma adjuvant therapy begins with the interaction of probiotics with innate immunity in the gastrointestinal mucosa. Dendritic cells are one of the antigen presenting cells that play a role in the activation of naive T cells. CD103+ dendritic cells have an important role in immunotolerance. Signals from probiotics cause Cluster of Differentiation (CD)103+ dendritic cells to migrate and induce immune cell tolerance with T reg cells. *Lactobacillus rhamnossus, Bifidobacterium lactis*, and *B. breve* bacteria can downregulate T cell-induced immunity. In addition to the direct interaction of bacteria with innate immune cells. Fermentation products produced by probiotics such as SCFA also contribute to the regulation of immune tolerance (**Figure 2**).[40]

SCFAs have pleiotropic effects through binding to GPR41, GPR43, and GPR109A and inhibition of histone acetylation. Previous studies have shown that feeding a high fibre diet and probiotics triggers the protective effects of SCFAs. Regulation of bone marrow and dendritic cells may be modulated by SCFA. Myeloid derived suppressor cells characterised by CD11bGR1+ expression have the ability to attenuate T cell activation. Release of cytokines and immune regulators can be dampened by SCFA. SCFA can trigger a priming effect towards establishing immunosuppressant state in T cell differentiation.[41] The efficacy of probiotics for asthma is currently being researched. The pharmacodynamics of probiotics against asthma are mediated by gene expression regulation activity, immune system regulation, enhancing barrier function, and competing with pathogenic bacteria. Multi-strain and single-strain types are also still being assessed for their effectiveness. The results of current clinical trials found that the use of probiotics can improve

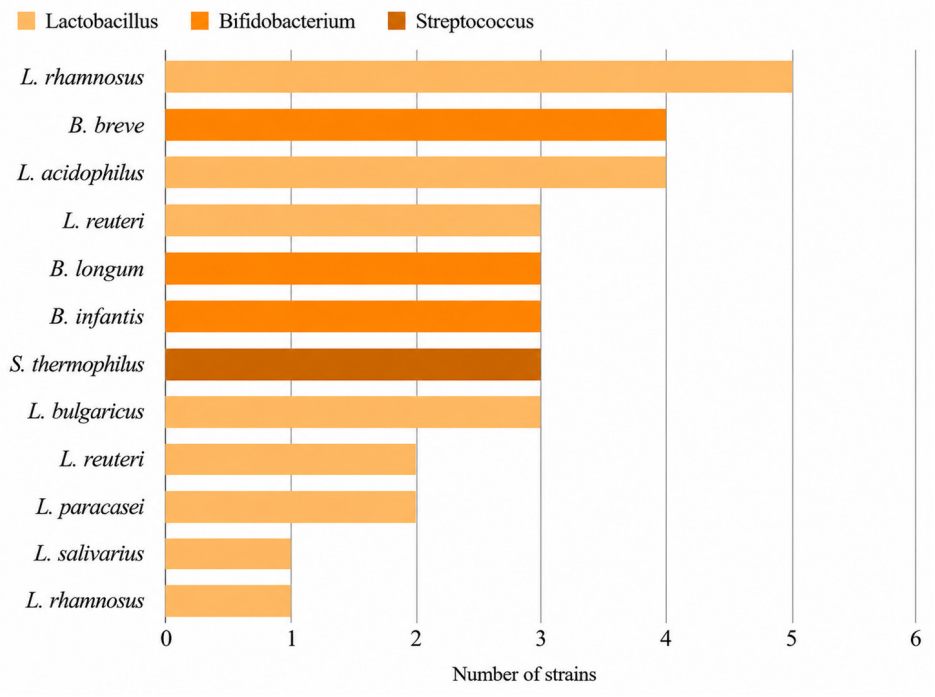


Figure 1. Number of Bacteria Studied

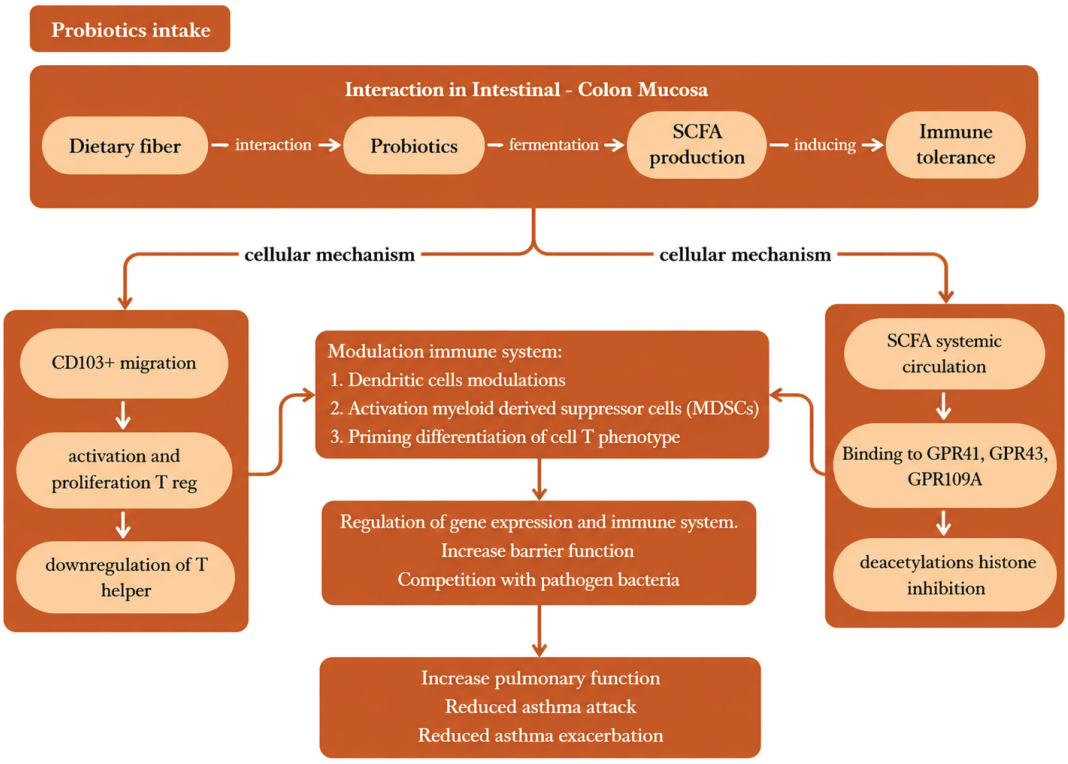


Figure 2. Mechanism of probiotic in asthma modulation

the lung function of asthma patients characterised by improvements in lung function including FVC, FEV1, PEFR, and FEV1/FVC ratio. Furthermore, the clinical incidence of acute asthma exacerbation was found to be lower in subjects who received probiotics (**Table 1**).

Probiotics exert their effects in asthma through multiple immunomodulatory mechanisms that influence key pathways involved in airway inflammation. These include modulation of antigen-presenting cell activity, regulation of T cell differentiation, and suppression of pro-inflammatory signaling pathways. Several studies demonstrate that probiotics can alter dendritic cell function, promote regulatory T cell (Treg) responses, and rebalance Th1/Th2 immune profiles, thereby reducing allergic inflammation. In addition, probiotics have been shown to downregulate innate immune receptors and inflammatory mediators, contributing to decreased airway hyperresponsiveness and immune activation. The principal pharmacodynamic mechanisms identified across preclinical studies are summarized in **Table 2**. Mapping the Mechanistic Pathways of Probiotics in Asthma

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Probiotics Immunodulation Action in Asthma

Probiotics and synbiotics particularly those containing multi-strain combinations and SCFAs act on the gut mucosa to trigger a comprehensive cascade of immunomodulatory actions spanning from innate to adaptive immunity. Innate immune cells serve as the

Table 1. Current clinical study of probiotics

Population	Probiotic Strain(s) & Dose	Outcomes	Main Findings
Children with asthma, 6–17 years[42]	Lactobacillus reuteri 10^8 CFU/day	Lung function (FVC, FEV1), clinical symptoms	Better lung capacity in probiotic group vs control (FVC: 61.5 ± 26.8 vs 54.1 ± 15.3; FEV1: 79.4 ± 14 vs 77.6 ± 16.9). Reduced symptoms including cough, wheezing, chest pain, and activity limitation.
Asthmatic patients[43]	Multi-strain probiotic (1 capsule/day): *L. casei*, *L. acidophilus*, *L. rhamnosus*, *L. bulgaricus*, *B. breve*, *B. longum*, *S. thermophilus* + 38.5 mg FOS	Pulmonary function (FEV1, FEV, FEV1/FVC)	Small but significant improvement in FEV1 and FEV (Cohen's d ≈ −0.30). No significant change in FEV1/FVC ratio.
Children with asthma and allergic sensitization[44]	Lactobacillus rhamnosus GG ATCC 53103, 10^{10} CFU	Immunological markers (IgE, eosinophils, ECP)	Significant improvement: lower total IgE (13.6 vs 20.2 IU/mL), reduced eosinophils, and lower ECP levels (15.6 vs 24.4 mg/mL) compared to control.
Children with allergic disease[45]	Fermented milk containing Lactobacillus casei 10^8 CFU	Health status, asthma outcomes	Improvement in general allergic health status, but no significant effect on asthma outcomes.
Paediatric asthma patients[46]	Probiotic capsule containing *L. acidophilus* (37.5%), *B. bifidum* (37.5%), *L. delbrueckii* subsp. *bulgaricus* (25%); total dose 3.2 × 10^9 CFU/day	Immunological markers (CD8/CD45RA$^+$ cells, HLA-DR), clinical outcomes	Decrease in CD8/CD45RA$^+$ cell percentage and increase in HLA-DR receptor expression. Clinically reduced asthma exacerbations and bronchodilator use at end of therapy.
Adult asthma patients	Lactocare (7 strains): *L. casei*, *L. acidophilus*, *L. rhamnosus*, *L. bulgaricus*, *B. breve*, *B. longum*, S. *thermophilus* + FOS — 1 capsule/day for 60 days	FEV1, FVC, FEV1/FVC ratio; ACT & AQLQ scores; plasma IL-4 & IFN-γ levels; miRNA expression (miR-16, -21, -126, -133b, -146a, -155)	Significantly improved FEV1 and FVC within the probiotic group, however the FEV1/FVC ratio showed no significant difference between groups. IL-4 plasma levels were significantly decreased after probiotic administration.

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Table 2. Research Summary of Pharmacodynamic Probiotics in Asthma

Model	Strain	Mechanism	Outcome	Ref
BALB/c mice (OVA-induced allergic airway inflammation)	Short-chain fatty acids (SCFAs: acetate, propionate, butyrate) - microbial metabolites, not live strains.	Dampens Notch signaling in dendritic cells (downregulates Jag1 and DLL4) and induces the sequential expansion of PMN-MDSCs and Regulatory T (Treg) cells.	Alleviates allergen-induced airway inflammation, decreases OVA-specific IgE and IL-5 levels, and lessens airway hyperresponsiveness (AHR).	[11]
BALB/c mice (OVA-sensitized airway allergy)	*Lactobacillus multi-species* preparation (LMP) containing *Lactobacillus plantarum* LP109, *L. plantarum* LP110, and *Pediococcus acidilactici* PA320.	Modulates Th1/Th2 balance by reducing Th2 cytokines (IL-4, IL-5, IL-13) and enhancing Th1 cytokines (IL-12, IFN- γ).	Significantly reduces airway hyperreactivity (AHR), lowers OVA-specific IgE and IgG1 levels, and increases IgG2a levels.	[20]
C57BL/6 mice (OVA-induced asthma)	*Lactobacillus fermentum* CECT5716	Downregulates TLR2 and TLR4 expression and improves intestinal barrier leakage by upregulating tight junction proteins (E-cad, ZO-1, and Occludin)	Relieves inflammatory cell infiltration, decreases pro-inflammatory factors (IL-4, IL-5, IL-13), inhibits pulmonary fibrosis, and lowers IgE production.	[30]
Human clinical trial (Asthmatic patients, randomized, double-blind, placebo-controlled) [4]	*Bifidobacterium lactis* Probio-M8 (co-administered with Symbicort Turbuhaler).	Modulates gut microbiome resilience and alters serum/gut predicted bioactive metabolites (e.g., tryptophan, sphingomyelin, and linoleoyl ethanolamide).	Decreases fractional exhaled nitric oxide (FeNO) and alveolar nitric oxide concentration (CaNO), and significantly improves Asthma Control Test (ACT) scores.	[31]
BALB/c mice (OVA-induced Atopic Dermatitis and late-stage asthma),	*Bacteroides plebeius* , *Bacteroides ovatus* , *Faecalibacterium duncaniae* , *F. taiwanense* , and *F. prausnitzii*	Regulates Th2-driven immune dysregulation.	Lowers serum total IgE and OVA-specific IgE, reduces IL-4 levels in bronchoalveolar lavage fluid, and improves skin scores.	[40]

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first responders. Dendritic cells are activated through TLR2/4 signaling, leading to IL-12 upregulation and suppression of Notch signaling (Jag1/DLL4), which redirects antigen presentation toward a Th1-promoting direction. Macrophages similarly respond to TLR activation by producing IL-12, which in turn recruits and activates Natural Killer (NK) cells to secrete IFN-γ. Concurrently, the epithelial barrier is reinforced through upregulation of tight junction proteins ZO-1 and Occludin, reducing antigen leakage and subsequent immune sensitization. These innate signals converge on the T cell axis of adaptive immunity. Th1 cells are expanded, producing IFN-γ and TNF-α via Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)-driven differentiation directly countering the Th2 axis. SCFAs facilitate Treg (FOXP3+ CD4+) induction through Histone Deacetylase (HDAC) inhibition, establishing immune tolerance. Th2 cells are actively suppressed, with IL-4, IL-5, and IL-13 markedly reduced alongside inhibition of IgE class switching. Th17 activity is also modulated as a consequence of improved gut dysbiosis.[4–8]

The downstream consequences are evident across multiple effector cell populations. B cells shift their antibody profile IgE production falls while IgG2a rises, driven by the IFN-γ-mediated suppression of class switching facilitated by miR-146a downregulation. Eosinophil recruitment is curtailed through IL-5 reduction, reflected in lower ECP levels (15.6 vs. 24.4 mg/mL). Mast cell degranulation is diminished as a result of falling IgE levels, reducing histamine and leukotriene release. In bronchial smooth muscle cells, probiotic-induced upregulation of miR-133b suppresses RhoA expression, directly attenuating airway hyperresponsiveness (AHR) and bronchospasm. CD8+/CD45RA+ cell percentages decrease while Human Leukocyte Antigen DR isotype (HLA-DR) expression increases, reflecting a broader shift in immune activation status. The central concept underlying this entire immunomodulatory mechanism is the correction of gut dysbiosis and the restoration of Th1/Th2 balance shifting the immune landscape from a Th2-dominated, pro-asthmatic state toward a restored equilibrium in which Th1 cells and Tregs

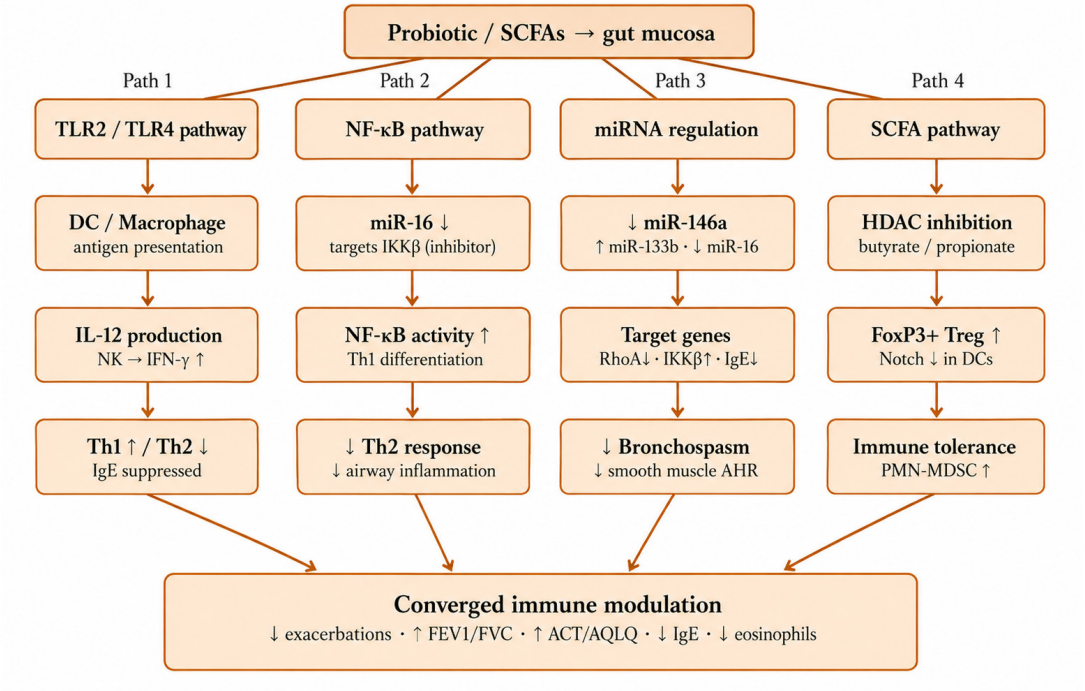


Figure 3. Signal pathways of probiotics activation target

Table 3. Targeting the Immune System with Probiotics

Cell Type / Pathway	Immunity Category	Probiotic Effect	Molecular Mechanism / Cytokines	Clinical / Functional Outcome
Dendritic Cells (DCs)	Innate Immunity	Increase (↑)	TLR2/4 -> IL-12↑, Notch ↓ (Jag1/DLL4)	Enhanced antigen presentation to Th1 cells
Th1 Cells	Adaptive Immunity	Increase (↑)	IFN-γ↑, TNF-α !, NF-κB activation	Restoration of Th1/Th2 balance
Th2 Cells	Adaptive Immunity	Decrease (↓)	IL-4↓, IL-5↓, IL-13↓, miR-146a ↓	Reduced IgE class switching
Treg Cells	Immune Regulation	Increase (↑)	FoxP3+ CD4+, SCFAs -> HDAC inhibition	Increased immune tolerance to allergens
Airway Inflammation	Respiratory Pathophysiology	Decrease (↓)	Reduced inflammatory cell infiltration	Reduced pulmonary fibrosis and improved FEV1/FVC
Bronchial Smooth Muscle	Molecular Regulation / miRNA	Decreased contraction (↓)	miR-133b ↑ -> RhoA ↓	Reduced airway hyperresponsiveness (AHR) and bronchospasm
Macrophages	Innate Immunity	Increase (↑)	TLR activation -> IL-12↑ IFN-γ production ↑	Increased NK cell recruitment
NK Cells	Innate Immunity	Increase (↑)	IL-12 -> IFN-γ↑	Inhibition of Th2 differentiation
B Cells / Antibodies	Adaptive Immunity	IgE(↓), IgG2a (↑)	miR-146a ↓reduced IgE class switching	Increased Th1 response markers (animal models)
Eosinophils	Adaptive / Effector	Decrease (↓)	IL-5↓, ECP reduction (15.6 vs 24.4 ng/mL)	Reduced eosinophil recruitment
Mast Cells	Airway Effector Cells	Decrease (↓)	IgE ↓ reduced degranulation	Reduced histamine and leukotriene release

govern immune tolerance, ultimately translating into reduced asthma exacerbations, improved lung function, and enhanced quality of life (**Figure 2** and **Table 3**).[9]

Probiotics have a broad potential role as adjuvant therapy in asthma. They target several key points in asthma pathogenesis, including downregulation of gene expression, correction of immune system dysregulation, enhancement of immune tolerance within the respiratory tract, and improvement of pulmonary function capacity. Existing studies have generally not demonstrated significant differences based on the specific probiotic strains used, with Lactobacillus and Bifidobacterium

being the most commonly employed, despite varying colony-forming unit (CFU) concentrations. While the majority of studies have indicated clinical improvement, these findings have often lacked statistical significance. This may be attributed to insufficient sample sizes, which limit the ability to detect a meaningful effect size. Moreover, heterogeneity in dosing regimens, frequency of administration, and duration of intervention may further contribute to the inconsistency observed in clinical trial outcomes. Probiotics have potential side effects on the gastrointestinal system, such as diarrhea, vomiting, nausea, abdominal discomfort, a burning sensation in the stomach, and an unpleasant taste in the mouth. However, in the clinical trials reviewed, no significant differences in the incidence of adverse events were reported between the intervention group (probiotics) and the control group, and no undesired side effects were identified.[13,42,45–47]

Critical Appraisal and Future Research Directions

This scoping review highlights the complex interplay between probiotics and immune mechanisms involved in asthma, particularly through the gut–lung axis. The included studies demonstrate a wide range of pharmacological and immunological effects of probiotics, suggesting their potential role in modulating inflammatory responses. However, the findings remain heterogeneous, which may be attributed to variations in probiotic strains, dosages, duration of intervention, study populations, and outcome measures. In comparison with previous systematic reviews and meta-analyses, the findings of this review are generally consistent in demonstrating the immunomodulatory potential of probiotics. Nevertheless, inconsistencies in clinical effectiveness have been reported across studies.

This scoping review extends existing evidence by mapping a broader spectrum of mechanisms and study designs, rather than focusing solely on quantitative outcomes. Several limitations should be acknowledged. As a scoping review, this study does not include a formal assessment of methodological quality or risk of bias of the included studies. Additionally, the heterogeneity of the included literature limits direct comparison and generalization of findings. The search strategy was also limited to selected databases and English-language publications, which may have resulted in the exclusion of relevant studies. Future research should focus on well-designed clinical trials with standardized probiotic strains, dosages, and outcome measures to improve comparability across studies. Further investigation is also needed to clarify strain-specific effects and to better understand the role of probiotics in the prevention and management of asthma and other allergic diseases

Conclusion

Based on preclinical and clinical study that had been held, probiotic treatment in asthmatic patients shows large variety of outcomes. There are no consistency clinical outcomes shown in previous study. In biomedical perspective, probiotic shows a good candidate for therapeutic agent in asthmatic patients. But it needs well controlled, dose ranging, and selective strain for future study.

Authors' Contribution

AYR and AG were involved in concepting and planning the research, AYR drafted the manuscript and designed the figures, AG aided in interpreting the results. All authors took parts in giving critical revision of the manuscript.

Conflict of Interest

The authors declare that there is no conflict of interest associated with this publication.

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