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Review Article

The Potential of Probiotic Role in Tuberculosis Therapy: A Narrative Review

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Abstract

Antibiotics treatment for tuberculosis reduces pro-inflammatory cytokines, which is one of the reasons for dysbiosis. The proportion of Actinobacteria, Firmicutes, and Bacteroidetes in the gut microbiota differentiates drug-sensitive and drug-resistant tuberculosis. The gut-lung axis theory explains how tuberculosis alters the gut microbiota and the immune response. The gut-lung axis is a two-way system that allows microbial products, endotoxins, metabolites, hormones, and cytokines to enter the bloodstream and affect both the intestines and the lungs. Probiotics, according to the gut-lung axis theory, may influence tuberculosis immune responses. This narrative review encompasses studies conducted in English and Indonesian between 2010 and 2023. The review will use the databases Cochrane Library, Scopus, Medline, PubMed, and grey literature. Studies using specimens from pulmonary tuberculosis patients, healthy volunteers infected with Mycobacterium tuberculosis, volunteers with a history of pulmonary tuberculosis disease, and volunteers who had close contact with pulmonary tuberculosis patients were all considered eligible. The current review highlights the immune modulation induced by probiotics usage in tuberculosis. Accordingly, probiotics have been shown to enhance the immune response against tuberculosis. More studies are needed to understand probiotic's role in different types of tuberculosis, and the influence of different probiotic bacteria on immune modulation.

Keywords: Gut-Lung Axis; Immunity; Lactobacillus; Microbiota; *Mycobacterium tuberculosis*

Potensi Peran Probotik Dalam Terapi Tuberkulosis: *Narrative Review*

Abstrak

Terapi antibiotik untuk tuberkulosis mengurangi sitokin pro-inflamasi, yang merupakan salah satu penyebab disbiosis. Proporsi *Actinobacteria, Firmicutes,* dan *Bacteroidetes* dalam mikrobiota usus membedakan antara tuberkulosis sensitif dan resisten obat. Teori *gut-lung axis* menjelaskan mekanisme tuberkulosis mengubah mikrobiota usus dan respons imun. *Gut-Lung Axis* adalah sistem dua arah yang memungkinkan produk mikroba, endotoksin, metabolit, hormon, dan sitokin mencapai aliran darah serta memberikan efek pada intestinal dan paru. Menurut teori gut-lung axis, probiotik dapat berperan pada respon imun tuberkulosis. Tinjauan ini mencakup penelitian yang dilakukan dalam bahasa Inggris dan Indonesia tahun 2010-2022. Sumber data yang digunakan dalam tinjauan ini adalah *The Cochrane Library, Scopus, Medline, PubMed,* dan *grey literature*. Penelitian ini menggunakan spesimen pasien tuberkulosis paru, relawan sehat yang diinduksi *Mycobacterium tuberculosis*, relawan dengan riwayat penyakit tuberkulosis paru, dan relawan yang memiliki kontak erat dengan pasien tuberkulosis paru. Review ini menyoroti modulasi kekebalan yang disebabkan oleh penggunaan probiotik pada tuberkulosis. Berdasarkan tinjauan ini, probiotik telah terbukti meningkatkan respon imun terhadap tuberkulosis. Penelitian lebih lanjut diperlukan untuk memahami peran probiotik dalam berbagai jenis tuberkulosis, dan pengaruh berbagai bakteri probiotik terhadap modulasi kekebalan tubuh.

Kata Kunci: *Gut-Lung Axis*; Imunitas, Lactobacillus; Mikrobiota; *Mycobacterium tuberculosis*

1. Introduction

Tuberculosis (TB) is an infectious disease that is a leading cause of death globally and the leading cause of death from a single infectious agent [ranking above HIV (Human Immunodeficiency Viruses)/AIDS (Acquired Immune Deficiency Syndrome)]. In 2022, it was estimated 10.6 million people worldwide were infected with TB and estimated deaths form TB among people with HIV were 167.000 people. Drug-resistant TB is a major public health concern. Multi drug- or rifampicin-resistant TB (MDR or RR TB) affects 3.3% of new TB cases and 17% of previously treated TB cases worldwide.[1,2]

Research on the impact of antituberculosis treatment on the lung microbiome indicate that antibiotic therapy has an impact on the human microbiota in the form of alterations in lung microbiota diversity.[3] The microbiota discrepancies between tuberculosis patients' different conditions suggest a dysbiosis caused by TB infection and possibly TB treatment.[4] Changes in microbial communities in the respiratory and intestinal tracts have been linked to immune responses and the development of diseases in the lungs, including tuberculosis, while the immune response to *Mycobacterium tuberculosis* (*Mtb*) infection has also been linked to decreased commensal bacteria in the intestine, a two-way condition explained by the Gut-Lung Axis.[5] Dysbiosis lowers the immune system's ability to resist *Mtb* invasion by lowering the counts of bacterial species that regulate the normal immune system's function.[6] The role of immune response and microbiota alterations in drug-resistant TB paves the way for probiotics to play a role in drug-resistant tuberculosis therapy. Probiotics are living microorganisms that provide a health benefit to the host when administered in sufficient quantities. Probiotics benefit health by integrating into the gut microbiota (both short and long term) and affecting microbial community components through direct effects on immune cells or the release of health-promoting metabolites.[7]

Mtb development can be slowed by targeting granuloma structure, causing autophagy, regulating the inflammatory response, regulating the cell-mediated immune response, and using anti-*Mtb* monoclonal antibodies, according to recent research.[8] This knowledge could be crucial in developing treatments to aid patients with drug-resistant TB in their recovery.

2. Method

The authors collected research data to examine the use of several types of probiotic bacteria to influence the TB immune response using research conducted from 2010-2023. The inclusion criteria for articles included in this review were RCT and non-RCT research that used any types of probiotics, with or without other antibiotics or supplements, also samples containing *Mtb*, whether isolated bacteria or human specimens. Review article, meta analysis and systematics review research were excluded from this review. Article research were carried out using PubMed, Cochrane Library, Science direct, and grey literature with keywords (Tuberculosis OR Mycobacterium tuberculosis) AND (Probiotics OR Probiotic OR "lactic acid bacteria" OR Lactobacillus OR Bifidobacterium) AND (Healthy OR Placebo OR Control) AND (Immune Systems OR Immune OR T-Cells OR CD OR Cytokine OR Cytokines). The procedure flow diagram is shown in Figure 1.

3. Result and Discussion

3.1. Tuberculosis And Immune System

Mtb-host interactions cause a complex immune response that can result in latent infection, TB, or complete pathogen clearance. Macrophages, $CD4^+$ T lymphocytes, and granuloma development have long been thought of as pillars of immune protection against *Mtb*, and their significance cannot be overstated. Innate immunity to *Mtb* is composed of macrophages, neutrophils, dendritic cells, NK cells, mast cells, and complement. Meanwhile, humoral immunity, granuloma, and $CD4^+$ and $CD8^+$ T lymphocytes are the main components of adaptive immune response.[9] T cells, which release cytokines to enable antimicrobial macrophage activity, are needed for acquired mycobacterial resistance.

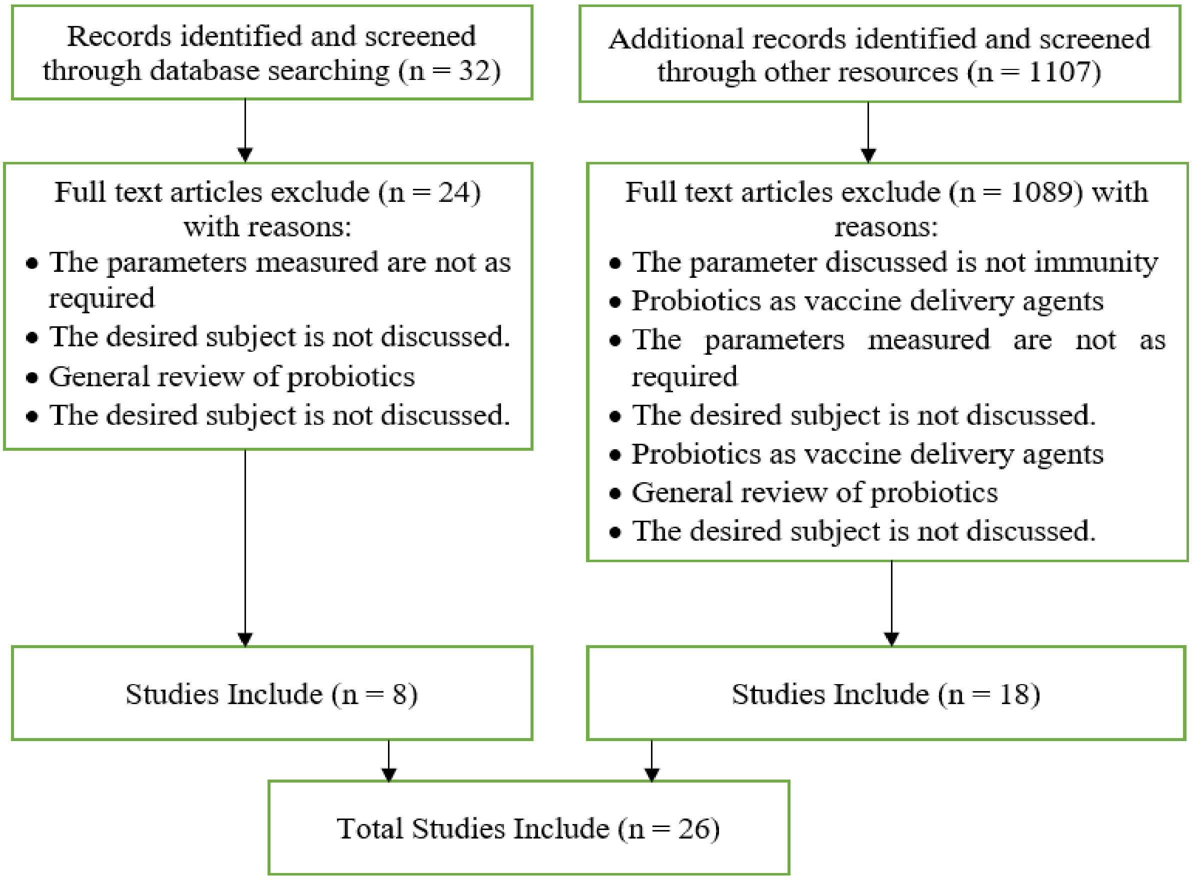

Figure 1. Narrative Review Flow Chart For Probiotics And Tuberculosis Section

In tuberculosis , the released cytokines may have both beneficial and harmful effects.[10] After the immune system is activated, TNF-α is released. TNF-α controls granuloma function and stimulates phagocytes in tuberculosis, but too much TNF-α can cause tissue damage and increase transmission.[10] The key mediator of macrophage activation and protection against intracellular pathogens is IFN-γ. Increased phagocytosis, phagolysosomal fusion, oxidative burst, and other unexplained non-oxidative mechanisms are all positive effects of IFN-γ processing,[10,11] but potentially pathogenic too.[12] IL-2 is a growth factor that promotes the proliferation of mycobacteria-specific antigens on T cells. It aids in the prevention of tuberculosis.[13]

Interleukin-6 is essential in the acute phase of inflammation and the transition from acute to chronic inflammation. Since IL-6 dysregulation is a major contributor to the pathogenesis of chronic inflammation and autoimmune diseases, it can be used as a biomarker in disease diagnosis and prognostic monitoring, including tuberculosis care.[14] IL-6 appears to be associated with early expression of effective immunity in the lungs through a combination of regulated mononuclear inflammation and rapid accumulation of lymphocytes.[10]

Interleukin-10 is a key anti-inflammatory cytokines that has been shown to supress $CD4^+$ T cell responses by inhibiting the APC role of mycobacteria-infected cells. IFN-γ, APC-infected *Mtb*, BCG, Mannosylated lipoarabinomannan (Man-LAM), and Mtb itself can all induce IL-10 development. The primary function of IL-10 is to minimize immune response and tissue injury. On the other hand, overproduction of these cytokines inhibits $CD4^+$ T cell response, resulting in infection control failure.[14,15] In *Mtb*-infected mice, IL-12 was expressed in tuberculous lungs, and IL-12 administration decreased bacterial counts, while IL-12 reduction by antibodies increased bacterial counts.[10]

3.2. Tuberculosis And Microbiota

The presence of certain bacterial species in the gut can cause dysbiosis and subsequent immune dysregulation that can ultimately affect the immune system's capacity to defend the body against TB.[6] Tuberculosis therapy using TB antibiotics has been shown to cause significant changes in the diversity and structure of the community and the composition of gut microbiota, and these changes have occurred since 1 week of using tuberculosis antibiotics. This diversity was mainly associated with alterations in Bacteroides relative abundance.[16] Khan et al. prove that there is a decrease in IFN-γ and TNF-α expression in mice infected with Mtb and received antibiotics, compared to mice that are only infected with Mtb. IFN-γ and TNF-α secretion increases again in mice that have received fecal transplantation.[17]

Several studies observed dramatic changes in gut microbiota in TB patients as reflected by significant decreases in species number and microbial diversity.[18,19] Healthy and TB patients discriminate based on the abundance of *Haemophillus parainfluenzae, Roseburia inulinivorans,* and *Roseburia hominis,* and also by SNPs in the species of *B.vulgatus*.[18] These findings are consistent with Wang et al.'s following research. The Bifidobacterium, Balutia, Butyricimonas, Ruminococcus. Roseburia and Dorea show downregulation of abundance in the PTB samples. These genera have been shown to influence SCFAs production, particularly acetic, propionic, and butyric acids, which can exacerbate inflammation.[19]

A meta-analysis on microbiota of the lower respiratory tract in TB patients and healthy controls identified *Tumebacillus ginsengisoli, Propionibacterium acnes,* and *Haemophilus parahaemolyticus* were found to be differentially abundant species signatures in healthy controls, while *Caulobacter henricii, Actinomyces graevenitzii, Rothia mucilaginosa,* and *Mycobacterium tuberculosis* were found to be differentially abundant species signatures in TB patients. The anchoring species in a network of bacteria co-occurring with Mtb infection is *R. mucilaginosa*.[20] This species is known to opportunistically cause bacteraemia and pneumonia in immunocompromised patients, which may aid Mtb establishment in lungs or vice versa.[6] Understanding the composition of microbiota in the respiratory and gastrointestinal tracts, as well as the factors that influence them, can lead to new therapeutic options, both primary and adjuvant, that may benefit TB patients.

3.3. Gut-Lung Axis In Tuberculosis

Various studies have shown that gut microbiota can provide immune-regulating effects on the immunity of other organs, including brai and lungs, and its effect on lung immunity is known as gut-lung axis. This theory is proved by a research in which the decreased gut microbiota causes a more severe pulmonary infection in mice induced by pneumonia *Eschericia coli*. The gut-lung axis is a phenomenon that has been discovered in some research to modulate immunity in various organs, including the brain and lungs. The Gut-lung axis system allows microbial products, endotoxins, metabolites, hormones, and cytokines to enter the bloodstream connecting the intestines and lungs. When the lungs are inflamed, this mechanism works in both directions, altering blood and gut microbiota parameters. In this case, blood flow serves as a conduit for metabolites, immune signals, bacteria, and bacterial products to travel from and to the lungs and intestines. This pathway can also pass through the liver, which can activate immune cells like neutrophils and macrophages. The lymphatic system helps immune signals travel from intestines to lungs.[5]

Mycobacterium tuberculosis infection in the lung requires long-term antibiotic therapy in its treatment. Long-term use of antibiotics leads to dysbiosis in the intestine. Based on changes in the gut and lung microbiota as well as gut-lung axis principle, it is suspected that Mtb infection can harm the balance of microbiota in intestine and vice versa, and the effects of modulation of the immune system by gut microbiota have a positive effect on TB.[16,17,21,22] The ingested microorganism can enter the intestine and activate immune cells, such as naïve T-cells and B-cells. These activated cells then migrate out of GALT and into peripheral mucosal and non-mucosal tissues, including the bronchial epithelium, then modify the immune response based on the induced cell profile (becoming Th1, Th2, and other cells), boosting the immune response to pulmonary pathogens. Furthermore, bacterial products generated by bacterial fermentation in the body will enter the lungs through systemic circulation, activating dendritic cells and macrophages, as well as priming and differentiation of T cells.[23] Bacterial products, such as Short Chain Fatty Acids (SCFA), modulate the immune system in the intestine in several ways, including modulating T lymphocyte activation and effector cell response.[24] The immune response to pathogens in the lungs is thought to strengthen as immune cell components migrate through lymphatic flow and systemic circulation pathways.[6,23] This hypothesis suggests that probiotics may be used in TB treatment to improve dysbiosis and strengthen the immune system.

3.4. Probiotics And Immune Response

Probiotics is live microorganisms which, when administered in adequate amounts, confer a health benefit on the host.[25] Probiotics are dietary factors that can improve the gut microbiota and stimulate host cells, resulting in physiological effects on the host. Probiotics can modulate the host immune system by stimulating host immunoglobulins and antibacterial compounds, as well as enhancing the innate and adaptive immune response.[26]

Lactobacillus rhamnosus and *Lactobacillus acidophilus* can promote IFN-γ and IL-12 production. *Lactobacillus plantarum* can cause proinflammatory IFN-γ, IL-6, and IL-1 to be produced. *Lactobacillus paracasei* promotes the production of IL-12. *Lactobacillus delbrueckii* and *L.plantarum*, on the other hand, reduces IL-12 and IFN- γ production while increasing IL-1 production.27,28 In an in vitro study, 6 probiotic strains (*L.casei* Shirota, *L.rhamnosus* GG, *L.plantarum* NCIMB 8826, *L.reuteri* NCIMB 11951, *B.longum* Sp07/3, and *B. bifidum* MF20/5) were compared to controls, and Lipopolysacchrida (LPS) showed that different probiotic strains affected cytokine production differently. *Lactobacillus casei* Shirota and *L.plantarum* NCIMB 8826 ($p<0.001$) were more effective at inducing IL-12 than other *Lactobacillus* strains, whereas Bifidobacterium strains were better inducers of IL-10 ($p<0$ 0.01), IL-6 ($p<0.001$), and Monocyte chemotactic protein-1 (MCP-1) ($p<0.01$ for B.bifidum MF20/5; $p<0.05$ for B.longum S07/3).

Probiotic strains with a high TNF-α /IL-10 ratio that is more likely to activate Th1 cells are *L.casei* Shirota, *L.plantarum* NCIMB8826, *L.rhamnosus* GG, and *L.reuteri* NCIMB11951, while those with a high IL-10/TNF-α ratio are B.bifidum MF20/5 and B.longum SP07/3 (respectively).29 Lactobacillus acidophilus AD300 and L.paracasei BRAP01 ($p<0.001$) were probiotics with the largest IFN-/IL-10 ratio, so that they were most effective in activating Th1 cells, according to PBMC stimulated by 6 probiotic strains (*L.paracasei* BRAP01, *B.longum* BA100, *Enterococcus faecium* BR0085, *L.acidophilus* AD300, *L.reuteri* BR101, *L.rhamnosus* AD500).[30] The magnitude of the effect may vary depending on the population's native microbiota, the strain utilized, the amount used, and the incubation time.

3.5. Probiotics And Tuberculosis

Increased production of proinflammatory cytokines can also cause excessive lung inflammation and tissue damage during MTB infection.[8] Therefore, a therapy that can stimulate Th1 cells is needed to help control tuberculosis infection, and one that has the potential to do this is probiotics. Lactobacillus strain is effective in increasing the activity of Th1 cells, therefore, it has the potential to be an immunomodulator in TB.[27,28,29,30]

Microbiological studies on the effect of probiotic bacteria on Mycobacterium B5 have revealed that probiotic bacteria strains can suppress Mycobacterium B5 growth,[31] adapted to low pH exposure, and are stable when exposed to several antibiotics used in TB treatment.[32] These research results support the opportunity for further research on the use of probiotics in complex TB therapy.

A database search yielded 1108 studies, 30 of which met the review's inclusion criteria, where eighteen of the studies were duplicates, resulting in 12 articles which were continued as sample (Table 1). Two study used RCTs design,[33,58] five case-controlled studies,[34,35,36,37,38] one quasi-experimental study39, and four in-vitro studies.[40,41,42,59] An RCTs study was conducted in Spain to examine the side effects and immunogenic response of probiotics in latent tuberculosis infection (LTBI) patients by comparing low and high dosages of probiotics.[33] Another RCTs study was conducted in China to fills in the clinical data gap about probiotic's effect on TB patients, even though observational studes have shown that they can alter inflammatory cytokines and metabolites.[58] The patients and probiotic types employed in all five case-controlled studies were the same.

This study looked at the levels of cytokines in drug-sensitive tuberculosis patients who were administered probiotics.[34,35,36,37,38] A quasi-experimental study investigated the immune response of pulmonary tuberculosis patients before and after administration of probiotics and zinc.[39] Four in-vitro experiments were carried out to see if probiotics could act as immunomodulatory agents in adult tuberculosis patient's peripheral blood mononuclear cells (PBMCs),[42] children's PBMCs,[41] and Mtb antigen-stimulated PBMCs.[40] Table 2 provides information about the studies discovered.

In healthy donor PBMCs with PPD-negative who are also given Mtb antigen, administration of *L.rhamnosus* GG and

Table 1. The Database's Search Results

Database	Identified Studies	Inclusion Studies	Exclusion Studies	Exclusion Reasons
PUBMED	8	3	5	• The parameters measured are not as required
The Cochrane Library	13	8	5	• The desired subject is not discussed. • General review of probiotics
Science Direct	10	1	9	• The desired subject is not discussed.
DOAJ	1	0	1	• The parameter discussed is not immunity
PMC	931	0	931	• The desired subject is not discussed. • General review of probiotics • Probiotics as vaccine delivery agents
Clinical Trials. gov	2	2	0	-
Proquest Dissertation and Theses	17	0	17	• The desired subject is not discussed.
Oxford Academics	111	0	111	• The desired subject is not discussed.
Google Scholar	25	9	16	• The parameters measured are not as required • Probiotics as vaccine delivery agents
CENTRAL	8	6	2	• The desired subject is not discussed.
Research Gate	12	1	11	• General review of probiotics • The parameters measured are not as required • Probiotics as vaccine delivery agents
Total	1138	30	1108	

Table 2. Studies Regarding The Role of Probiotics in Tuberculosis

Type of Study	Sample	Probiotic used, concentration, species/strain	Outcome	Findngs
Randomized Controlled Trials	30 LTBI-negative and 21 LTBI-positive. Each group was divided into 3 subgroups: • Placebo • *Nyaditum resae®* (NR) low dose • *Nyaditum resae®* (NR) high dose	Heat-killed *M. manresensis* The number of bacteria administered : 104 per dose and 105 per dose	Parameters : $CD25^{+}CD39^{-}$ $CD25^{+}CD39^{+}$ $CD25^{-}CD39^{-}$ $CD25^{-}CD39^{+}$ Specimen : PBMC Method : Flowcytometry	Essentially, Treg response has increased for both LTBI-negative and LTBI-positive participants. In the LTBI-positive groups treated with NR 105, the effector Tregs levels were higher (p 0.0469).[33]
	Case : 16 patients in the low-dose *L. casei* group 16 patients in the high-dose *L. casei* group Control : 15 patients in the control group (without *L. casei* intervention).	*Laactobacillus casei* from commercial probiotic drink • 1x1010 CFU daily (low dose) • 2x1010 CFU daily (low dose)	Parametes : IFN-γ TNF-α IL-6 IL-10 IL-12 Specimen : Plasma Method : ELISA	The high-dose probiotic group had significantly reduced quantities of tumor necrosis factor-α (TNF-α) (p<0,01), interleukin-6 (IL-6) (p<0,05), interleukin-10 (IL-10) (p<0,01), and interleukin-12 (IL-12) (p<0,001) when compared to the control and low-dose groups. The control and low-dose probiotic groups had comparable levels of these cytokines.[66]
In Vitro Study	Case : Healthy PPD(-) donor PBMC, BCG immunizations, and stimulation with Mtb antigen (1), Mtb antigen and LAB combinations (2) Control : PBMC of healthy PPD(-) donor, BCG vaccination and medium added.	*Lactobacillus rhamnosus* GG 2x107 CFU/mL Bifidobacterium bifidum MF20/5 2x107 CFU/mL Stimulation for 48 hours	Parameters: IL-4 IL-13 IFN-γ Specimen : PBMC Method : ELISA	Two types of LABs added to the PBMCs with Mtb antigen causes: • Increased IFN-γ (p < 0,05) (VS Mtb antigen only) • Inhibition of IL-4 and IL-13 secretion (p < 0,05) (VS Mtb antigen only) • Increase in IFN-γ / IL-4 + IL-13 ratio (p < 0.05) (VS medium only).[40]

Type of Study	Sample	Probiotic used, concentration, species/strain	Outcome	Findngs
	Case : 19 PBMCs of tuberculosis patients who received various kefir concentrations (1/20, 1/50, 1/100, 1/200)*last* Control : 19 PBMCs of tuberculosis patients who did not received kefir.	Kefir (*Lactobacillus kefiri*) Concentration : 1/20. 1/50, 1/100, 1/200 (v/v; kefir supernatant/medium comparison) Incubated for 4 days at 37°C and 5% CO_2	Parameters : CD4+ CD8+ IFN-γ IL-2 IL-10 Specimen : PBMC Method : Flowcytometry ELISA	• There was no significant difference in CD4+ and CD8+ populations when Kefir Supernatant was added. • In comparison to negative controls, the addition of Kefir supernatant tends to induce IL-2 production (p=0,162) • Compared to negative controls, the addition of Kefir surnatant increased IL-10, in particular at a kefir concentration of 1/200 (p=0,002) • IFN-γ synthesis tended to be lower in the Kefir group compaed to the negative control group (statistically insignificant) • IL-4 levels tended to be higher after stimulation with Kefir at 1/20 and 1/50 concentrations (statistically insignificant).[42]
In Vitro Study	PBMC of Tuberculosis patients aged 2–14 years who were taking medication. The PBMC were cultured in 4 groups : (1) without treatment, (2)	Multiculture of Lactic acid bacteria (*Lactobacillus acidophilus, Lactobacillus bulgaricus, Lactobacillus casei, Bifidobacterium bifidum,*	Parameter : IFN-γ Specimen : PBMC Method : ELISA	The IFN-γ level increased by 15.79% compared to control group (p 0.04).[41]

Type of Study	Sample	Probiotic used, concentration, species/strain	Outcome	Findngs
	incubation with Mtb, (3) incubation with LAB, (4) incubation with Mtb and LAB	*Bifidobacterium animalis, Lactobacillus plantarum, Streptococcus thermophilus*) Dosage : 2x108 CFU/mL Incubation for 48 hours		
	PBMC of adult TB drug-sensitive patients with category-1 therapy regimens.	*Bacillus subtilis* and *Bacillus wiedmannii* from red passion fruit	Parameter : IFN-γ Specimen : PBMC Method : ELISA	The IFN-γ levels rose from 0,82% to 23,71%.[67]
Quasi-experimental Study	Case : 21 patients with pulmonary tuberculosis were given a combination of antituberculosis drugs, probiotics, and zinc. Control : 15 Pulmonary tuberculosis patients received anti-tuberculosis drug therapy.	Oral Probiotics for 4 weeks	Parameters : Lymphocyte level Neutrophil – Lymphocyte Ratio (NLR) Monocyte level Specimen : Whole blood Method : Flowcytometry	Lymphocyte Level • In the case group, the post-therapy levels were increased (p 0.002) • NLR • In the case group, the post-therapy level were decrease (P 0.008) • In the control group, the post-therapy level tended to decreased (p 0.097) • The differences in post-therapy NLR levels between groups were statistically insignificant (p 0.239) • Monocyte Level • In the case group, the post-therapy levels were decreased (P 0.026) • In the control group, the post-therapy levels tended to decreased (p 0.303)

Type of Study	Sample	Probiotic used, concentration, species/strain	Outcome	Findngs
				• The differences in post therapy monocyte levels between groups were statistically significant (p 0.040).[39]
Case Control	Case : 11 drug-sensitive tuberculosis patients who received anti-tuberculosis drug therapy, probiotics and vitamin B6 Control : 11 drug-senstitive tuberculosis patients who received anti-tuberculosis drug therapy and vitamin B6	*Lactobacillus acidophilus, L.casei, L.rhamnosus, L. bulgaricus, Bifidobacterium breve, B.longum, Streptococcus thermophilus* Probiotics are administered over 2 months	Parameters : IFN-γ IL-12 Specimen : Whole blood Method : ELISA	After 1 month of therapy • The IFN-γ and IL-12 levels in the case group tended to be higher than the control group (p 0.178 and p 0.559; sequentially) • 1st to 2nd month of therapy • When compared to the control group, IFN-γ and IL-12 levels in the case group tended to decrease (p 0.004 and p 0.207 sequentially). After 2 months of therapy Levels of IFN-γ and IL-12 in the case group tended to decrease compared to its levels prior therapy, when compared to control group (p 0.017 and p 0.468; sequentially).[37]
Case Control	Case : 11 drug-sensitive tuberculosis patients who received anti-tuberculosis drug therapy, probiotics and vitamin B6	*Lactobacillus acidophilus, L.casei, L.rhamnosus, L. bulgaricus, Bifidobacterium breve, B.longum, Streptococcus thermophilus*	TNF-α	The TNF-α in the case group tended to decrease and then increase at second month (p 0,777 and p 0,366; 0,366; sequentially).[38]

Type of Study	Sample	Probiotic used, concentration, species/strain	Outcome	Findngs
	Control : 11 drug-senstitive tuberculosis patients who received anti-tuberculosis drug therapy and vitamin B6	Probiotics are administered over 2 months	IL-10	The probiotic group had increased levels of IL-10 after 1 month (p> 0.594) and decreased after 2 months compared to pre-supplementation levels (p>0.594) and the control group (p<0.026).[36]
			IL-17	The IL-17 levels tend to decrease in the first (p=0.05) and second months (p=0.423).[34]
			IgG	Plasma IgG levels tend to increase in the first month (p=0.229) and tend to decrease after two months (p=0.489 vs p=0.249) in the supplementation and control group.[35]

Notes :
- **PPD : Purified Protein Derivative of Mycobacterium**
- **LAB : Lactic Acid Bacteria**
- **BCG : Bacilli Calmette–Guerin**

B.bifidum induces a synergistic increase in IFN-γ when compared to PBMCs stimulated with *Mtb* antigen alone ($p<0.05$). Probiotics administration in Mtb antigen-stimulated PBMCs or PBMCs alone induces decrease in IL-4 and IL-13 levels ($p<0.05$). The ratio of IFN-γ to IL-4 and IL-13 secretion in lactic acid bacteria (LAB)-treated PBMCs is higher ($p<0.05$) than in unstimulated PBMCs, indicating a reaction that favors T-helper-1 (Th1) cytokine profiles. Increased IFN-γ, IL-12, and NO levels, combined with decreased IL-4, IL-13, and CCL-18 levels, induce autophagy, which destroys intracellular bacteria and mononuclear phagocyte survival.40 The cytokines IL-4 and IL-13 are associated with the Th2 response, which inhibits the Th1 response, which is essential for tuberculosis immunity. IL-4 can transform *Mtb*-induced granuloma from mononuclear to granulocytic characteristics in tuberculosis, but its effect on disease is limited. Autophagy is an essential intracellular degrading homeostatic mechanism with a protective function during mycobacterial infection, and IL-13 can modulate it.[10]

Kefir containing Lactobacillus spp., yeast, and fungi was assessed at four different concentrations: 1/10, 1/20, 1/50, 1/100, and 1/200 (v/v; Kefir supernatant/medium). It was incubated for four days with PBMC at 37°C and 5% CO_2. The result revealed a trend of negligible increase in the proportion of $CD4^+$ and $CD8^+$ population in PBMCs of kefir-stimulated tuberculosis patients compared to negative control (without kefir).42 The increase in $CD4^+$ and $CD8^+$ indicates an increased immune response to TB infection.[39,43,44,45,46] Suppression of $CD4^+$ and $CD8^+$ T cell counts has been associated with tuberculosis infection.45 The main role of $CD4^+$ lymphocyte helper is to activate other immune cells, including $CD8^+$ cells, which then eliminate Mtb bacteria.[42] $CD8^+$

also plays a role in the protective immunity to mycobacteria, controls Mtb replication and appears to accumulate at the sites of mycobacterial infection, forming shackles on the periphery of epithelioid cell granuloma.[44,45]

According to research on the use of multi-strain probiotics and zinc in tuberculosis patients, the immune system improves after four weeks of use, as evidenced by increased lymphocyte levels (p 0.002), decreased NLR levels (Δ-0.2±2.40, p 0.008) and decreased monocyte levels (Δ-0.12±0.3, p 0.026). After 4 weeks of supplementation, there was an increase in lymphocyte levels (Δ0.2±0.35 VS Δ-0.06±0.41, p 0.013), a tendency for decreased NLR levels (Δ0.2±2.40 VS Δ-0.72±2.26, p 0.239), and decreased monocytes (Δ-0.12±0.37 VS Δ-0.03±0.03, p 0.040) in the multi-strain probiotic group.[39] *Mycobacterium tuberculosis* has been thought to target monocytes, and lymphocytes are the major effector cells in TB immunity. Since monocytes and lymphocytes are essential immune cells, their levels can represent an individual's immunity to tuberculosis infection. Monocytes and macrophages will phagocytose and restrict mycobacteria in the early stages of tuberculosis infection, attracting them to form granulomas.[47] Lymphocytes, especially the T-lymphocyte subset, are important immune cells against TB infection.[48]

4. Conclusion

Tuberculosis has a low success rate when it comes to therapy. Based on the gut-lung axis theory, disturbances in the balance of microbiota that occur in the lungs, one of which is detected in sputum, can also disrupt the balance of microbiota in the intestine. Therefore, long-term use of antibiotics is thought to be one of the causes of dysbiosis in TB. Th1 cell-mediated immunity is essential for controlling *Mtb* replication in APC and eradicating *Mtb* bacteria. Therefore, therapies to balance dysbiosis and modulate the immune system of TB patients are possible. Probiotics can affect the composition and function of the intestinal flora, as well as the immune system, by interacting directly with the mucosal immune system. Probiotics' benefits in preserving and controlling lung health have been demonstrated in several studies, which are clarified by the gut-lung axis theory. Lactobacillus strains show their ability to modulate the immune system by stimulating Th1 cells. This stimulation will improve the activity of alveolar macrophages in the lungs, enhancing the immune system's ability to counter *Mtb*. This improvement in immunity is followed by the delivery of anti-tuberculosis drugs, which are expected to minimize *Mtb* infection and increase TB patient cure rates.

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Conflict of interests

The authors declare that they have no conflict of interest.

Ethical approval

Not required

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