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Activity of Antimycobacterial Candidate from Bacteriocins and Lactic Acid Isolated from *Lactobacillus bulgaricus* Against *Mycobacterium tuberculosis*

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Abstract

Mycobacterium tuberculosis (Mtb) is a bacterium that causes a respiratory infectious disease known as tuberculosis. Tuberculosis (TB) is a global infectious disease that causes death. The current TB treatment method has a weakness, namely the tendency of patients to disobey the rules in taking drugs because they have to take several tablets of medicine for a long time. As a result, some strains of *M.tuberculosis* can strengthen themselves and become resistant to antimycobacterial drugs used during therapy. Based on these tuberculosis control problems, the WHO declared a global TB emergency. The low effectiveness of currently used antitubercular drugs encourages the development of new antimycobacterial drugs with low side effects, fast-acting, broadly targeted, and can damage the virulence properties of *M.tuberculosis* so that the immune system can phagocytose *M.tuberculosis*. A recent solution from some researchers is to induce immunomodulatory effects that help during the tuberculosis infection process, including from lactic acid bacteria (LAB). This encourages researchers to reveal the interaction of probiotic *L.bulgaricus* on reducing the growth of *M.tuberculosis* by finding the main substance with antitubercular activity to obtain optimal results. This study used sensitive *M.tuberculosis* strain H37Rv to get complete preliminary data. This study tested lactic acid and bacteriocin of *Lactobacillus bulgaricus* at concentrations of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% and 100%. *M.tuberculosis* bacteria were inoculated on media containing lactic acid and *L. bulgaricus* ATCC 11842 bacteriocin, then incubated at 37°C and observed every week from the fourth to the eighth week. Of the five concentrations of lactic acid and bacteriocin tested, only the 60-100% concentration could inhibit the growth of *M.tuberculosis*. In conclusion, lactic acid and bacteriocin of *L. bulgaricus* can hinder the growth of *M.tuberculosis* and can be developed into antimycobacterial drug candidates.

Keywords: Antimycobacterial; Immunomodulator; Lactobacillus bulgaricus, Mycobacterium tuberculosis; Tuberculosis.

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by the bacterium *M. tuberculosis* (Mtb) that infects the lung organ, specifically indicated by the formation of granulomas that result in tissue necrosis. This chronic disease can be transmitted through droplets (Simmons et al., 2018; Alsahafi et al., 2019). In 2022, the Indonesian Ministry of Health detected 717,941 people with TB, an increase of 61.98% compared to 2021, when 443,235 people were infected (Ministry of Health Republic of Indonesia, 2022). TB is one of the important health problems in Indonesia because Indonesia is among the top five countries with the highest number of TB patients in the world (Rothchild et al., 2017). Mtb belongs to a group of slow-growing bacteria that take 24 hours to divide, making TB a chronic disease and contributing to the length of treatment time (Zolnikova et al., 2019).

Currently, the Directly Observe Treatment Course (DOTS) is the WHO-recommended TB treatment strategy, which began in 1995. One of the DOTS strategies is TB treatment therapy with antitubercular drugs for approximately six months using four types of antibacterials. This method of treatment has the disadvantage that patients tend to disobey the rules in taking drugs because they are required to take several tablets of medicine in a sufficient time. As a result, it increases the possibility of resistance, namely Multidrug-Resistant (MDR) and Extensively Drug-Resistant (XDR) TB (Horyath et al., 2016; McAleer et al., 2018).

Mtb is an intracellular pathogen that induces adaptive immune responses, especially cell-mediated immunity (CIM). CIM immune response is an *immune response that uses activated macrophages and CD4 cells to kill bacteria. Mtb phagocytosed by macrophages* will be enveloped by vesicles called phagosomes. These phagosomes will then fuse with lysosomes and form a

phagolysosomal structure so that the *Mtb* can be eliminated. Another component of the CIM immune response is that CD4 T cells will induce the production of cytokines that can activate macrophages so that the elimination process can run more effectively (Smith, 2003; Nurkanto et al., 2024). From this information, it is known that macrophages play an important role in the host immune response and pathogen elimination. Thus, most *Mtb* virulence factors lead to macrophage inactivation.

Based on the problems of TB control, WHO declared a global TB emergency. Not only that, the low effectiveness of currently used antimycobacterial drugs encourages the development of new antimycobacterial drugs that have low side effects, work quickly, target widely, and can damage the virulence properties of *Mtb* so that *Mtb* can be phagocytosed by the immune system (Ma et al., 2020).

Probiotics or lactic acid bacteria (LAB) are live microorganisms that provide health benefits to the host when administered in adequate amounts. Probiotics can activate the body's immune system and fight pathogenic bacteria and viruses by increasing the activity of natural killer cells. That way, various diseases can be prevented. Antibacterial agents such as lactic acid and bacteriocins possessed by LAB bacteria also have a very important effect on inhibiting the adhesion of pathogenic bacteria. The inhibition of adhesion of pathogenic bacteria is due to antimicrobial agents being able to reduce the pH to a low level, making it difficult for pathogenic bacteria to survive (Fauziah et al., 2014; Herawati et al., 2014). One of the most commonly used probiotic bacteria is the genus Lactobacillus. Generally, Lactobacillus is a bacterium that is included in the normal microflora of the intestine and is known to be a normal microflora of the upper respiratory tract that is anaerobic, including *L. bulgaricus*. *L. bulgaricus* is one of the probiotic bacteria of the Lactobacillus genus that has passed clinical trials and can secrete enzymes that can overcome lactose intolerance, normalize the composition of digestive tract bacteria killed by antibiotic consumption, and produce antibacterial agents that can boost the immune system. *L. bulgaricus* has high lipolytic activity compared to other lactic acid bacteria, so it has a strong flavor and nutritional value when made into a product (Fauziah et al., 2018; Vioretti et al., 2018; Joshi et al., 2024).

Therefore, this study aimsed to determine the main substances that have antimycobacterial activity to optimize the search for natural antimycobacterial drug candidates. Probiotics are known to activate GM-CSF (Granulocyte Macrophage-Colony Stimulating Factor). GM-CSF plays a role in controlling intracellular Mtb production, inflammation in granulomas, and lung tissue repair (Mishra et al., 2020). However, the exact mechanism of probiotic interaction with immune cells in the gut and lungs remains unexplored. This prompted the researchers to reveal the interaction of probiotics, namely the main metabolite compounds of *L. bulgaricus* in the form of lactic acid and bacteriocins, on the reduction of Mtb growth through inhibition of Mtb growth.

MATERIALS AND METHODS

This research used an experimental method with a solid dilution technique in the Microbiology Laboratory of Mohammad Husni Thamrin University, Jakarta in June-September 2024. This research consists of 5 stages of research, including:

Bacteria Preparation of M.tuberculosis

In this study, the test bacteria used were Mycobacterium tuberculosis H37Rv, which is a pure or sensitive strain. Bacteria were grown using Lowenstein-Jensen (LJ) media on slanted agar tubes and observed for growth in the fourth to eighth week (Gupta et al., 2017; Nkot et al., 2017; Irianti et al., 2022).

Bacteria Preparation of L.bulgaricus ATCC 11842

A pure culture of *L. bulgaricus* ATCC 11842 bacteria was taken from as much as one bacterial colony and then planted into 5 mL of deMan Rogosa Sharpe (MRS) liquid media. Then, the media was incubated for 24 hours at 37°C. Bacteria that have grown on the liquid media are then taken as much as one colony and scratched on MRS Agar media in a tube and then incubated for 24 hours at 37°C (Gupta et al., 2017; Nkot et al., 2017; Irianti et al., 2022).

Lactic Acid Production of L. bulgaricus ATCC 11842

The bacterial filtrate was obtained by centrifuging the activated bacteria in MRS liquid medium at four °C at 6000 rpm for 15 minutes to separate the cells from the filtrate. The supernatant was sterilized with a 0.22 µm Millipore filter. Then, the filtrate in the tube was exposed to UV light at a distance of 40 cm for 40 minutes (Fauziah et al., 2014; Herawati et al., 2014). The research used lactic acid concentrations of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, and 100%.

Bacteriocin Production of L.bulgaricus ATCC 11842

The bacterial filtrate was obtained by centrifuging the activated bacteria in MRS liquid medium at four °C at 6000 for 15 minutes to separate the cells from the filtrate. Neutralized with NaOH. Then, the supernatant was sterilized with a Millipore filter (0.22 µm) (Fauziah et al., 2014; Herawati et al., 2014). This study used bacteriocin concentrations of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, and 100%.

Antimycobacterial Activity Testing of Bacteriocin and Lactic Acid of L.bulgaricus ATCC 11842 against M.tuberculosis H37Rv

The concentration of bacteriocins and lactic acid from *L. bulgaricus* used was 10-100%. Inoculation was

performed on one strain of *M.tuberculosis*, namely strain H37Rv. Then, *M.tuberculosis* was put into 0.9% NaCl to obtain a turbidity of 10-3 and 10-5 McFarland. A total of 0.1 mL of bacterial suspension was inoculated on the surface of LJ media that had been given various concentrations of lactic acid or L. bulgaricus bacteriocin. It was then incubated at 37°C. The growth of bacterial colonies was observed every week from the fourth week to the eighth week (Gupta et al., 2017; Irianti et al., 2022).

RESULTS AND DISCUSSION

The antimycobacterial activity test results showed that the lactic acid filtrate of *L. bulgaricus* ATCC 11842 at a 50% concentration inhibited the growth of *M.tuberculosis* H37Rv (Table 1). This situation can be seen by the absence of *M.tuberculosis* H37Rv bacterial growth on LJ media after 8 weeks of incubation.

Table 1. Results of Antimycobacterial Test from Lactic Acid of *Lactobacillus bulgaricus.*

Observation Time	Groups													
	Repetition	Negative Control	Solvent Control (MRS *Broth*)	Possitive Control (Isoniazid)	Concentrations of Lactic Acid of *Lactobacillus bulgaricus*									
					10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
Week I	(1x)	-	-	-	-	-	-	-	-	-	-	-	-	-
	(2x)	-	-	-	-	-	-	-	-	-	-	-	-	-
Week II	(1x)	-	-	-	-	-	-	-	-	-	-	-	-	-
	(2x)	-	-	-	-	-	-	-	-	-	-	-	-	-
Week III	(1x)	-	-	-	+	+	+	-	-	-	-	-	-	-
	(2x)	-	-	-	+	+	+	-	-	-	-	-	-	-
Week IV	(1x)	+	-	-	+	+	+	-	-	-	-	-	-	-
	(2x)	+	-	-	+	+	+	+	-	-	-	-	-	-
Week V	(1x)	+	-	-	+	+	+	+	-	-	-	-	-	-
	(2x)	+	-	-	+	+	+	+	-	-	-	-	-	-
Week VI	(1x)	+	-	-	+	+	+	+	-	-	-	-	-	-
	(2x)	+	-	-	+	+	+	+	-	-	-	-	-	-
Week VII	(1x)	+	-	-	+	+	+	+	-	-	-	-	-	-
	(2x)	+	-	-	+	+	+	+	-	-	-	-	-	-
Week VIII	(1x)	+	-	-	+	+	+	+	-	-	-	-	-	-
	(2x)	+	-	-	+	+	+	+	-	-	-	-	-	-

Notes: +: *M.tuberculosis* Growth; -: No Growth of *M.tuberculosis*

The antimycobacterial activity test results showed that the bacteriocin filtrate of *L. bulgaricus* ATCC 11842, at a concentration of 40%, could inhibit *M.tuberculosis* H37Rv growth (Table 2). This situation can be seen by the absence of *M.tuberculosis* H37Rv bacterial growth on LJ media after 8 weeks of incubation.

Table 2. Results of Antimycobacterial Test from Bacteriocins of *Lactobacillus bulgaricus.*

Observation Time	Groups													
	Repetition	Negative Control	Solvent Control (MRS *Broth*)	Possitive Control (Isoniazid)	Concentrations of bakteriosin of *Lactobacillus bulgaricus*									
					10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
Week I	(1x)	-	-	-	-	-	-	-	-	-	-	-	-	-
	(2x)	-	-	-	-	-	-	-	-	-	-	-	-	-
Week II	(1x)	-	-	-	-	-	-	-	-	-	-	-	-	-
	(2x)	-	-	-	-	-	-	-	-	-	-	-	-	-
Week III	(1x)	-	-	-	+	+	+	-	-	-	-	-	-	-
	(2x)	-	-	-	+	+	+	-	-	-	-	-	-	-
Week IV	(1x)	+	-	-	+	+	+	-	-	-	-	-	-	-
	(2x)	+	-	-	+	+	+	-	-	-	-	-	-	-
Week V	(1x)	+	-	-	+	+	+	-	-	-	-	-	-	-
	(2x)	+	-	-	+	+	+	-	-	-	-	-	-	-
Week VI	(1x)	+	-	-	+	+	+	-	-	-	-	-	-	-
	(2x)	+	-	-	+	+	+	-	-	-	-	-	-	-
Week VII	(1x)	+	-	-	+	+	+	-	-	-	-	-	-	-
	(2x)	+	-	-	+	+	+	-	-	-	-	-	-	-
Week VIII	(1x)	+	-	-	+	+	+	-	-	-	-	-	-	-
	(2x)	+	-	-	+	+	+	-	-	-	-	-	-	-

Notes: +: *M.tuberculosis* Growth; -: No Growth of *M.tuberculosis.*

Lactic acid filtrate from *L.bulgaricus* was lethal or bactericidal at concentrations of 50-100% and inhibitory or bacteriostatic at concentrations of 10-40% against *M.tuberculosis* H37Rv bacteria. All concentrations of lactic acid filtrate affected the growth of *M.tuberculosis*. The treatment of various concentrations of *L. bulgaricus* lactic acid filtrate (50-100%) influenced the death of *M.tuberculosis* after being observed until the eighth week. The greater the concentration of the lactic acid filtrate, the greater the inhibition of *L.bulgaricus* growth until *M.tuberculosis* died, which was characterized by no growth of *M.tuberculosis* on LJ media that had been treated with the lactic acid filtrate.

Discussion

Probiotics are lactic acid bacteria *L.bulgaricus, which* can generally break down glucose to produce lactic acid. This causes the pH of the pathogenic bacteria media to be low (<4.5) so that it can inhibit pathogenic bacteria growth. Lactic acid produced by probiotic or LAB bacteria will diffuse into pathogenic microbial cells, and then the pathogenic bacterial cells will dissociate, which will disrupt the nutrient transportation system. The dissociation of pathogenic bacterial cells causes the cells to form protons and anions, so the presence of protons disrupts the balance of nutrient transportation of pathogenic bacterial cells. Therefore, the bacteria will try to remove the protons from the cell. The process of removing these protons requires high energy and causes the pathogenic bacteria to die because they run out of energy. In addition, lactic acid produced in the fermentation process can reduce pH, and this situation will interfere with enzyme activity so that pathogenic bacterial cells are unable to carry out metabolic activities (Fauziah et al., 2014; Herawati et al., 2014; Joshi et al., 2024).

The composition of the biochemical from lactic acid produced by probiotics has different abilities to provide antagonistic effects on pathogenic bacteria. The results of the study by Fauziah et al. [11] showed that lactic acid filtrate at a concentration of 30% was able to inhibit *Klebsiella pneumoniae* bacteria growth, while in this study, the concentration of lactic acid filtrate was 50%, which could inhibit *M.tuberculosis growth*. This is because *M.tuberculosis* is an acid-resistant bacterium, so its ability to adapt to an acidic environment is stronger; so it is only at a lactic acid filtrate concentration of 50% that its growth is inhibited (Nurkanto et al., 2024).

Bacteriocin filtrate from *L.bulgaricus* was lethal or bactericidal at concentrations of 40-100% and inhibitory or bacteriostatic at concentrations of 10-30% against *M.tuberculosis* H37Rv bacteria. All concentrations of bacteriocin filtrate affected the growth of *M.tuberculosis*. Treatment of various concentrations of *L. bulgaricus* bacteriocin filtrate (40-100%) influenced the death of *M.tuberculosis* after being observed until the eighth week. The greater the concentration of bacteriocin filtrate, the greater the inhibition of *L.bulgaricus* growth until *M.tuberculosis* died, which was characterized by no growth of *M.tuberculosis* on LJ media that had been treated with lactic acid filtrate.

Bacteriocins are protein compounds secreted from probiotic or LAB bacteria that are antibacterial and can hinder pathogenic bacteria. The difference in each bacterium's growth is due to differences in the activity of inhibitors, which is influenced by the bacterial cell wall type that is inhibited (Fauziah et al., 2014; Herawati et al., 2014; Joshi et al., 2024).

This affects the resistance of a bacterium to antibacterial substances due to differences in cell wall structure. The activity of bacteriocin production from probiotic or LAB bacteria will be influenced by carbon source, temperature, growth phase, and pH. The source of carbon and nitrogen type used in the production medium affects the growth rate of probiotic or LAB bacteria cells, which in turn affects the bacteriocin production metabolism. In addition, the salinity level of the production medium, such as the salt content in the medium, will also affect the bacteriocin production metabolism. The application of bacteriocins as preservatives in food does not change the flavor and texture but inhibits the growth of pathogenic microbes (Cheruvari et al., 2025).

The main target of bacteriocins is the pathogenic microbial cytoplasmic membrane of cells. This is because the initial reaction of bacteriocins can damage membrane permeability and eliminate the PMF (Proton Motive Force), thus inhibiting energy production and protein biosynthesis. The mechanism of bacteriocins' bactericidal activity involves direct contact with the pathogenic bacterial cell membrane. This process can disrupt the membrane potential, resulting in cytoplasmic membrane instability, which makes the cell unstable. Membrane instability can lead to the formation of holes or pores in the cell membrane of pathogenic bacteria through the disruption of the PMF. The leakage that occurs due to hole formation in the cytoplasmic membrane is indicated by the activity of the entry and exit of cellular molecules. This leakage results in a decrease in cellular pH. The cytoplasmic effect of hole formation is a bacteriocin impact, which can change the membrane potential gradient and cause the release of intercellular molecules, as well as the entry of extracellular substances. These events inhibit the growth of pathogenic bacterial cells and can cause the death of bacterial cells that are sensitive to bacteriocins (Thuy et al., 2024; Cheruvari et al., 2025).

The bacteriocin is synthesized during the exponential growth phase. Extended incubation time after the stationary phase can cause bacteriocin activity to decrease because proteases are liberated from cells when cells enter the death phase. Bacteriocins are protein compounds that have bactericidal properties against Gram-negative and Gram-positive pathogenic bacteria

with a broad spectrum of target bacteria that have specific binding sites (Fauziah et al., 2014; Herawati et al., 2014; Thuy et al., 2024; Cheruvari et al., 2025).

Probiotics are known to activate the granulocyte-macrophage-colony Stimulating Factor (GM-CSF), which plays a role in controlling intracellular *M.tuberculosis* production, inflammation in granulomas, and lung tissue repair (Mishra et al., 2020). However, the exact mechanism of probiotic interactions with immune cells in the gut and lungs remains unrevealed.

Many probiotic bacteria are potentially useful in the treatment of tuberculosis disease, but their antimycobacterial properties have not been investigated due to the lack of appropriate material and scientific facilities. This study is the first report of antimycobacterial activity of bacteriocins and lactic acid filtrate from *L. bulgaricus* against *M.tuberculosis*.

CONCLUSIONS

Bacteriocin and lactic acid filtrate of *L. bulgaricus* gave different antimycobacterial powers at each concentration against the inhibition of colony growth of *M.tuberculosis*. The administration of bacteriocin and lactic acid filtrate of *L.bulgaricus* is expected to be beneficial for health because live probiotic bacteria are carried into the body, so that it is expected to inhibit *M.tuberculosis* bacteria growth and can overcome the outbreak of tuberculosis infection in the future.

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