Berita Biologi
LIPI
Jurnal ilmu-ilmu hayati

Berita Biologi 23(3): 345–358 (2024)
https://ejournal.brin.go.id/berita_biologi ISSN 2077 7019
DOI: 10.55981/beritabiologi.2024.6267

P-ISSN 0126-1754
E-ISSN 2337-8751

ARTICLE

STUDY OF TB STATUS IN INDONESIA AND ENDOPHYTIC ACTINOMYCETES AS POTENTIAL SOURCE OF NATURAL PRODUCT FOR ANTI-TUBERCULOSIS DRUG RESISTANCE

[*Studi Status Tuberkulosis di Indonesia dan Aktinomiset Endofit Sebagai Sumber Bahan Alam untuk Menanggulangi Resistensi Obat Anti-Tuberkulosis: Studi Kasus Indonesia*]

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ABSRACT

Tuberculosis, caused by *Mycobacterium tuberculosis*, is a significant contributor to global mortality, being responsible for one of the primary causes of death worldwide. The current problem is antibiotic resistance in the treatment of tuberculosis patients, which causes the decreasing effectiveness of drugs for tuberculosis therapy. Therefore, exploration for finding new drugs is still necessary. Actinomycetes represent a group of microbes known for producing bioactive compounds, particularly in the form of antibiotics. This microbe can be found associated with plants as endophytic actinomycetes may have the same or similar secondary metabolites as their host. In certain instances, metabolites generated by endophytic actinomycetes exhibit uniqueness and hold the potential to combat antibiotic-resistant pathogenic microbes effectively. This review focuses on new ideas for exploring the potential of endophytic actinomycetes from medicinal plants, especially in Indonesia, considering existing tuberculosis conditions using reviews from scientific sources such as scientific journals, case reports, official government websites, and tuberculosis drug development. This review was then compiled and created a new idea to explore endophytic actinomycetes from medicinal plants in Indonesia using validated methods and contemporary research.

Keywords: endophytic actinomycetes, medicinal plants, tuberculosis, drug discovery

Submitted: 15 August 2024; **Revision:** 10 September 2024; **Accepted:** 17 October 2024
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ABSTRAK

Tuberkulosis, yang disebabkan oleh *Mycobacterium tuberculosis* merupakan penyumbang kematian global yang signifikan dan merupakan salah satu penyebab utama kematian di seluruh dunia. Permasalahan yang ada saat ini adalah resistensi antibiotik pada pengobatan pasien tuberkulosis yang menyebabkan menurunnya efektivitas obat untuk terapi tuberkulosis. Oleh karena itu, eksplorasi untuk menemukan obat baru masih perlu dilakukan. Aktinomiset merupakan kelompok mikroba yang diketahui mampu menghasilkan senyawa bioaktif khususnya dalam bentuk antibiotik. Mikroba ini dapat ditemukan berasosiasi dengan tumbuhan karena aktinomiset endofit mungkin memiliki metabolit sekunder yang sama atau serupa dengan inangnya. Beberapa kasus menunjukkan bahwa metabolit yang dihasilkan oleh aktinomiset endofit menunjukkan keunikan dan berpotensi menanggulangi mikroba patogen yang resisten terhadap antibiotik secara efektif. Kajian ini fokus pada gagasan-gagasan baru untuk menggali potensi aktinomisetes endofit dari tanaman obat khususnya di Indonesia dengam mempertimbangkan kondisi tuberkulosis yang ada saat ini dengan menggunakan ulasan dari sumber-sumber ilmiah seperti jurnal ilmiah, laporan kasus, website resmi pemerintah, dan pengembangan obat tuberkulosis. Kajian ini kemudian disusun dan memunculkan ide baru untuk mengeksplorasi aktinomiset endofit tanaman obat di Indonesia dengan menggunakan metode tervalidasi dan penelitian kontemporer.

Kata kunci: aktinomiset endofit, tanaman obat, tuberkulosis, penemuan obat

INTRODUCTION

Tuberculosis (TB) is a transmitted disease that has increased the number of new cases and the number of deaths. This infectious disease is caused by *Mycobacterium tuberculosis* bacteria (Mar'iyah and Zulkarnain 2021). This microbe infected the alveolar macrophage and proliferated in there to make granuloma called ghon focus and make clinical manifestation (Maison 2022). Some tuberculosis risk factors occur due to sociodemographic, environmental, host-related, and comorbidities (Pralambang and Setiawan 2021).

The most effective first-line anti-tuberculosis drugs are rifampicin, isoniazid, ethambutol, and pyrazinamide (Irianti *et al*., 2016). A 4-month regimen including rifapentine, isoniazid, pyrazinamide, and moxifloxacin may be considered case by case. The typical TB treatment plan for drug-susceptible tuberculosis consists of six months of combination therapy with isoniazid, rifampicin, pyrazinamide, and ethambutol (Queensland Health, 2023).

Patient non-compliance in taking anti-tuberculosis drugs can cause drug resistance, which can cause side effects of the tuberculosis drug itself. Tuberculosis patients who experience side effects from treatment or patients who stop treatment unilaterally without permission from health workers are some examples of factors that contribute to anti-tuberculosis drug resistance (Nugrahaeni and Malik 2013). Resistance of *M. tuberculosis* to anti-tuberculosis drugs is a condition when the bacteria cannot be killed with anti-tuberculosis drugs. Inadequate or unsuccessful treatment is not the only factor contributing to resistance to tuberculosis, but *M. tuberculosis* itself can do spontaneous mutation leading to anti-tuberculosis resistance (Siregar 2019).

Drug-resistant tuberculosis treatment has grown fast over the past few years. According to the latest findings, to evaluate and improve the effectiveness of current treatments, management of tuberculosis and drug resistance to tuberculosis will be updated at any time (Soedarsono 2021). Due to the continued misuse of antibiotics and the lack of a new antibiotic industry, the antibiotic resistance crisis remains growing and widespread (Mobarki *et al.,* 2019).

Novel tuberculosis (TB) drugs are essential to shorten treatment duration and replace the anti-tuberculosis that is already resistant, enabling widely spaced intermittent treatment. Implementing such programs can effectively reduce latent tuberculosis infection (LTBI) and enhance the treatment of multidrug-resistant TB (MDR-TB) (O'Brien and Nunn 2001). MDR-TB is a significant challenge for the control of TB in many parts of the world and a threat to TB elimination (Tiberi *et al*., 2018). The development of new drugs treatment of latent TB is one of the efforts to control TB to reach the end of TB 2035 (Soedarsono 2021).

Infectious diseases have long been controlled with antibiotic treatment, but the emergence of resistant bacteria has created new gaps that are currently difficult to close. The limitations of current antibiotic therapy, namely severe side effects and increased incidence of bacteria resistant to

conventional antibiotics, require active countermeasures. The search for new therapeutic alternatives to conventional treatments is gaining increasing interest among scientists, and natural products are the main focus today. The main advantages of these compounds are different mechanisms of action that can overcome bacterial resistance and reduce side effects (Pancu *et al*., 2021).

Microbial natural products are the most varied and interesting due to their distinct structures and functions, making them an essential of drug discovery. Despite the fact that the utilization of microbes as a source of pharmaceuticals is a relatively new discovery, they provide the majority of necessary and commercially available antibiotics as well as many other anti-infectives. Endophytic microbes found a lot of attention in recent studies because they are important sources of new chemical compounds (Abdel-Razek *et al*., 2020).

This review focuses on describing the development of tuberculosis in the world in comparison to conditions in Indonesia, followed by progress in tuberculosis drug research and the generation of new ideas for exploring bioactive compounds as anti-tuberculosis from one of the less explored natural products, endophytic actinomycetes from Indonesian medicinal plants.

MATERIALS AND METHODS

This journal review was arranged by searching various scientific publications, books, validated databases, and global reports, including search terms such as "tuberculosis," "actinomycetes," "endophytic," and "Indonesian medicinal plants." The reviewed literature presents findings on the tuberculosis status in Indonesia compared to worldwide, as well as the latest findings on new anti-tuberculosis drugs and drug sources derived from natural products, especially actinomycetes. Each source studied is combined into a new idea for exploring actinomycetes endophytes in Indonesian medicinal plants.

RESULTS AND DISCUSSION

Indonesia Tuberculosis Status

Tuberculosis is an infectious disease caused by *M. tuberculosis* is a worldwide concern disease that occurs frequently in tropical and subtropical climates. This tropical disease can even spread quickly and become one of the factors in increasing the death rate. Climate change in Indonesia is believed to impact the development of tropical diseases like tuberculosis (Aulia and Fajar Ayu 2017). Among the other tropical diseases, tuberculosis is the deadliest and the most difficult to overcome because of the high prevalence and resistance rates (Ruminem *et al*., 2020).

Tuberculosis is an easily transmitted disease that, in recent years, has seen an increase in the number of new cases and the number of deaths caused by tuberculosis. Based on the Global TB Report 2023, the incidence rate of tuberculosis increased from 5.8 million in 2020 to 6.4 million in 2021 worldwide (WHO 2023). The same pattern happened in Indonesia. Based on the Indonesian tuberculosis dashboard, tuberculosis cases in Indonesia have increased from 2021 to 2022 up to 251,573 cases (Kementerian Kesehatan Republik Indonesia 2024).

The TB burden of drug-resistant TB (DR-TB) continues to be a public health problem, especially for rifampicin resistance. Meanwhile, rifampicin, the most effective first-line drug, is of greatest concern. Globally, the estimated number of people who developed multidrug or rifampicin resistance -TB (MDR/RR -TB) was relatively stable between 2015 and 2020 but grew in 2021. There were an estimated 450,000 incidents in 2021, up 3.1% from 437,000 in 2020. The main explanation for the increasing number of TB incidences between 2020 and 2021 is estimated to have been caused by the impact of the COVID-19 pandemic on TB detection (WHO 2023). On the other hand, based on final data in 2022, RR-TB/MDR TB confirmed cases in Indonesia have reached 12,531 cases (Kementerian Kesehatan Republik Indonesia 2024).

Table 1: Indonesia Tuberculosis Status Past Five Year (*Status tuberkulosis di Indonesia selama lima tahun terakhir*)

Year	Number of Cases (people)	MDR (people)	TB + HIV (%)	Treatment Success Rate (%)
2019	568,987	11,463	51%	82.9%
2020	393,323	7,921	55%	83.1%
2021	443,235	8,268	67%	85.9%
2022	724,309	12,531	52%	86.5 %
2023	821,200	9,134	57%	87%

Source: (Ditjen Pemasyarakatan Kemenkumham 2023; Kementerian Kesehatan Republik Indonesia 2024)

According to this situation (Table 1), reaching global TB commitments, strategies, and targets with a percentage reduction in the TB incidence rate by 95% in 2035 is difficult. Key requirements to reach targets and milestones were defined within the End TB Strategy pillars, such as integrated, patient-centered care and prevention, bold, supportive systems and policies, intensified research, and innovation (WHO 2023). The recovery treatment success rate, which has only increased slightly, and both the number of cases and MDR cases have increased over the last few years, is very worrying for achieving the goals of end-TB 2035. Indonesia itself committed to ending TB by 2030, and to realize the target, Indonesia has developed a National Strategic Plan consisting of 6 main strategies (Kementerian Kesehatan Republik Indonesia 2022).

Drug Discovery of Anti-Tuberculosis Drug

The emergence of antibiotic resistance events raises the need for a new source of antibiotics that can fight resistant M. tuberculosis, especially for *M. tuberculosis* which is resistant to first-line drugs such as rifampicin. Treatment of drug-resistant tuberculosis has advanced rapidly over the past few years. New, shorter MDR-TB regimens and increased availability of new drugs are needed together with the management of tuberculosis and drug-resistant tuberculosis, which will be updated at any time according to the latest findings to evaluate and improve the effectiveness of treatment (Soedarsono 2021). New tuberculosis drug development (Table 2) shows that only three new drug candidates in phase 3 of the clinical trial were added with rifapentine as a derivate compound from rifampicin (*Working Group on New TB Drugs* 2024).

Emphasizing the significance of researching the diversity of bioactive compounds from endophytic microorganisms is crucial due to its promising potential in discovering new antibiotics. This avenue of research holds great promise for addressing antibiotic resistance and advancing the development of effective therapeutic interventions (Silva *et al*., 2022). Exploring the ability of bioactive compounds produced by endophytic microorganisms can be an effective way to overcome the problem of resistance in tuberculosis patients. Utilization and further research on compounds produced by endophytic microorganisms as anti-tuberculosis will also help research related to new drug candidates for tuberculosis.

Table 2. Clinical pipeline of new anti-tuberculosis drugs (*Status alur uji klinis kandidat obat baru terapi tuberkulosis*)

Discovery (*Penemuan*)	**Preclinical Development** (*Pengembangan prakilis*)		**Clinical Development** (*Pengembangan klinis*)			**Regulatory Market Approvals** (*Persetujuan regulator pasar*)
Lead Optimization (*Optimasi lead*)	**Early Stage Development** (*Pengembangan Tahap Awal*)	**GMP/ GLP Tox.**	**Phase 1** (*Fase 1*)	**Phase 2** (*Fase 2*)	**Phase 3** *(Fase 3*)	
Diarylthiazoles	CPZEN-45*	OTB-658	TBI-223	Pyrifazimine (TBI-166) SQ-109*	Sudapyridine (WX-081)	Bedaquiline*
Arylsuflonamides	JSF-3285*	GSK-839*	TBD09 (MK-7762)	TBAJ-876		Delamanid*
DprE1 Inhibitors	CLB-073*		TBAJ-587	TBA-7371*		Pretomanid*
Direct InhA Inhibitors	NTB-3119*		Macozinone*(PBTZ-169)	Sanfetrinem		
DnaE1/Nargenicin analogs	FIM-253		GSK-286*	Ganfeborole (GSK-656*/070)		
Gyrase Inhibitors	TBD10 (MK-3854)			BTZ-043*		
M. tuberculosis energy Metabolism	FNDR-20364*			Telacebec*(Q203)		
Oxazolidinones	SPR720*			Quabodepistat (OPC-167832*)		
Indazole sulfonamides	MPL-447*			Alpibectir (BVL-GSK098)*		
Inhibitors of MmpL3, Translocase-1, ClpC1, ClpP1P2,PKS13, F-ATP synthase, RNAP synthase, RNAP	MBX-4888A (1810)*			Delpazolid, Sutezolid, Tedizolid		

*New chemical class. Source: (Working Group on New TB Drugs, 2024)

Natural Product from Endophytic Actinomycetes for Tuberculosis

Natural products remain an important source of anti-tuberculous chemotherapy drugs. Their exploration and utilization underscore natural compounds' ongoing relevance and potential in developing effective medications for tuberculosis treatment. More recently, researchers have considered them a source of diverse chemical structures with structural compositions that can be used as scaffolds for replication in synthetic chemistry. However, the low success rate of discovering new drugs from natural products requires fundamental changes in innovative drug development strategies. The continued development of sensitive, rapid assays and cost-effective materials has become essential and will encourage scientists worldwide to contribute to developing natural product resources (Davies-Bolorunduro *et al*., 2021).

Secondary metabolites are paramount as they are primarily utilized in the pharmaceutical industry (Twaij and Hasan 2022). Many specialized metabolites are thought to be produced specifically in response to biotic and abiotic ecological demands. This requires careful assessment of the environment and, in the case of symbionts and pathogens, complex interspecific communication between hosts and actinobacteria. It is increasingly recognized that understanding these interactions may open entirely new biological and chemical spaces for drug development (Meij 2020). In 1928, when Sir Alexander Fleming discovered penicillin, access to discovering new compounds useful for fighting bacterial infections (antibiotics) opened widely. Since then, several studies have been conducted to find new molecules with the same activity (De Simeis and Serra 2021). Antibiotics essentially target bacterial structures or functions (Lo Grasso *et al*., 2016). Microorganisms like a group of actinomycetes can produce antibiotics. Rifamycin is produced by *Streptomyces*

mediterranei to treat tuberculosis, with the mode of action of inhibiting protein synthesis (Najafpour 2007).

Actinomycetes, as a group of microorganisms, are the most important source of antibiotics. The world urgently needs to mitigate the risks associated with antibiotic resistance. Immediate actions must be taken, including discovering new antibiotics and a paradigm shift in their usage. This imperative underscores the importance of robust research, responsible antibiotic prescribing practices, and the development of innovative strategies to address and combat antibiotic resistance, especially tuberculosis, on a global scale. Actinomycetes, with their compounds produced by endophytic microorganisms, can be an effective way to overcome the problem of resistance in tuberculosis patients. Utilization and further research on compounds produced by endophytic microorganisms as anti-tuberculosis will also help research related to new drug candidates for tuberculosis (De Simeis and Serra 2021). Endophytes are rich sources of novel natural compounds with a wide spectrum of biological activities and a high structural diversity (Pimentel *et al*., 2011).

Actinobacteria are Gram-positive bacteria with high GC DNA content, constituting one of the largest bacterial phyla (Barka *et al*., 2016). As a potential source of antibiotics, actinomycetes can be found in various places such as soil, water, and plants (van der Meij *et al*., 2017). Studies show that endophytic microbes, especially from medicinal plants, synthesize these compounds in association with plants. Microbes inside the plant tissues produce an array of these compounds and can be a promising resource of valuable bioactive compounds (Singh *et al*., 2017).

Research results indicate that there are types of endophytic microbes that can be a source of natural antimicrobial and antioxidant agents for drug discovery programs (Ezeobiora *et al*., 2021). Endophytic bacteria can regulate the synthesis of secondary metabolites with significant medicinal components and produce various biological effects (Wu *et al*., 2021). Endophytic bacteria have a huge potential in bioprospecting. In the future, endophytic bacteria are going to be one of the potential sources of novel antibiotics (Christina *et al*., 2013).

Based on actinomycetes metabolites information from New TB Drugs, ecumicin mentioned in Table 3 is a promising compound to be the candidate for antituberculosis drugs. The research of ecumicin informs that over 7,000 actinomycetes screened against *M. tuberculosis* for growth inhibition. The active extracts were profiled for potency and selectivity, and 20 were scaled up for primary fractionation, indicating that cumin had demonstrated an excellent result (*Working Group on New TB Drugs* 2024). Ecumicin shows effective and selective in vitro bactericide activity against M. tuberculosis, suppresses *M. tuberculosi*s growth in mouse lungs, and inhibits ClpC1, a legitimate and specific therapeutic target in *M. tuberculosis*. Ecumicin may be used as a lead bioactive compound in the development of anti-tuberculosis drugs (Gao *et al*., 2015).

Previous research has shown that *Streptomyces* sp. is a good source of anti-tuberculosis compounds based on those activities against *M. tuberculosis* (H37Rv). Chrysomycin A as a bioactive compound isolated from Streptomyces from coastal, showed anti-tuberculosis activity at an MIC of 3.13 µg/mL(Muralikrishnan *et al*., 2017) . Actinomycin D produced by Streptomyces from rhizosphere soil (mud) showed anti-tuberculosis activity at a MIC of 0.78 µg/mL (Rakhmawatie *et al*., 2021). Other research mentions that *Amycolatopsis* sp. MST-108494 produces some bioactive compounds called amycolatropis 1 and amycolatropis 2 and tested for *M. tuberculosis* (H37Rv). Amycolatropis 1 has an IC_{50} value of 4.4 µM, and amycolatropis 3 has an IC_{50} value of 5.7 µM (Khalil *et al*., 2017).

Table 3. Promising Actinomycetes Bioactive Compound Product as Anti-Tuberculosis (*Senyawa bioaktif menjanjikan dari aktinomiset sebagai anti-tuberkulosis*)

Taxa of Actinomycetes (*Taksa aktinomisetes*)	**Compound** (*Senyawa*)	**Activity Data** (*Data aktivitas*)	**References** (*Referensi*)
Actinoplanes deccanensis	Lipiarmycin	0.3 μM[1]	(Sergio *et al*., 1975; Kurabachew *et al*., 2008; Quan *et al*., 2017)
Nonomuraea sp. MJM5123	Ecumicin	1.5 μM[1]	(Gao *et al*., 2015; Jin *et al*., 2016)
Streptomyces antibioticus	Phenazines	12.5–50 μM[2]	(Laursen and Nielsen 2004; Yang *et al*., 2017)
Streptomyces griseolutein	Phenazines	12.5–50 μM[2]	(Laursen and Nielsen 2004; Yang *et al*., 2017)
Streptomyces griseus	Capuramycin	0.2 – 14 μM[3]	(Yamaguchi *et al*., 1986)
Streptomyces luteogriseus	Phenazines	12.5–50 μM[2]	(Laursen and Nielsen 2004; Yang *et al*., 2017)
Streptomyces prunicolor	Phenazines	12.5–50 μM[2]	(Laursen and Nielsen 2004; Yang *et al*., 2017)
Streptomyces sp., isolate CNB-382	Cyclomarin A	0.09 μM[3]	(Renner *et al*., 1999; Choules *et al*., 2019)

*List of all potential actinomycetes name (Renner *et al*., 1999); [1] Minimum Bactericidal Concentration; [2] Minimum Inhibitory Concentration of halogenated phenazine; [3] Minimum Inhibitory Concentration.

Surprisingly, the main drugs to treat tuberculosis, rifampicin produced from actinomycetes also. *Amycolatopsis rifamycinica* (formerly known as *Streptomyces mediterranei* and *Nocardia mediterranei*), a Gram-positive bacterium, was cultured in French soil in 1957 and the compounds it produced were extracted. Rifampicin is only used to treat bacterial infections, including mycobacterial diseases and a few others with specified indications. It is bactericidal and targets both intracellular and extracellular microorganisms. It is the first-line treatment for *Mycobacterium tuberculosis*, *M. avium* complex, and *M. leprae*, as well as *Legionella pneumophila* (Hardie and Fenn 2022). It is promising to prospect for anti-TB drugs from actinomycetes, considering the considerable evidence indicating that actinomycetes remain underexplored. Previous research has tested their activity against Mycobacterium tuberculosis, yielding impressive data and demonstrating significant potential.

Endophytic bacteria have indeed received comparatively less attention in research when compared to endophytic fungi (Tsipinana *et al*., 2023). While endophytic fungi have been extensively studied for their potential applications in various fields, including agriculture and medicine, the exploration of endophytic bacteria is an area that offers substantial untapped potential. Further research into endophytic bacteria can provide valuable insights into their ecological roles, interactions with host plants, and their potential applications in various biotechnological and medical contexts. Actinomycetes sourced from plants are still rarely reported, especially medicinal plants, which are a potential source for finding actinomycetes that contain the same compounds as these plants called endophytic actinomycetes. As an endophytic bacterium, endophytic actinomycetes exist in various tissue types within numerous plant species (Lodewyckx *et al*., 2002). Actinomycetes have been proven for their ability to produce various bioactive secondary metabolites, which is an important reason for the discovery of antibiotics (Chaudhary *et al*., 2013). Actinomycetes, with their extraordinary metabolism, can assist in providing bioactive compounds that chemists can modify to obtain other beneficial compounds (De Simeis and Serra 2021).

As a potential new source of novel microorganisms, endophytic actinomycetes present in plant roots significantly differ from those found in soil environments (Matsumoto and Takahashi 2017). Comprehensive characterization and identification of diverse populations of endophytic actinomycetes associated with medicinal plants may also provide greater insight into the evolution of plant-endophyte interactions and symbiosis (Golinska *et al*., 2015).

Most of the known antibiotics today were originally isolated from actinomycetes (Mast and Stegmann 2019). The actinomycetes group produces active compounds that are useful in medicine like their several antibiotic products such as tetracycline, amphotericin, chloramphenicol, neomycin,

vancomycin, novobiocin, gentamicin, nystatin, and erythromycin. The potential of actinomycetes in discovering new compounds with activity against microorganisms has been realized and hence opens exciting avenues in the fields of biotechnology and biomedical research (Sharma *et al*., 2014).

Endophytic Actinomycetes from Indonesia Medicinal Plants Have Potential as Anti-Tuberculosis Drugs

Plants have been used as medicines throughout history (Radio and Pack 2020). Many secondary metabolites have been isolated from Indonesian medicinal plants. Some have potential biological activities that can be further developed for the pharmaceutical industry and modern medicine. To develop Indonesian medicinal plants as national products that are competitive in multinational markets, research on the safety, efficacy, and standardization of these medicinal plants is needed (Sholikhah 2016). Microbial symbionts produce many of plants' bioactive compounds. The study of endophytes of these medicinal plants will help isolate and produce their active ingredients (Alvin *et al*., 2014).

Previous studies have shown medicinal plants treat tuberculosis in Indonesia (Table 4); most can potentially kill *M. tuberculosis* bacteria in small amounts of concentration. The active compounds of those Indonesian medicinal plants' target proteins can treat tuberculosis diseases through immune stability in the patient's body caused by involvement in the immune system (Aristyani *et al*., 2018). *Curcuma domestica* (*Curcuma longa* L) and *Zingiber officinallis* are two of nine medi The Indonesian Food and Drug Authority/BPOM priority for focusing research on drug development (Sholikhah 2016).

Exploring the potential of synergistic botanical medicines and other herbal products that can reduce the side effects of standard drugs can improve overall patient treatment outcomes (Gautam *et al*., 2023). Combining the targeting properties of anti-tuberculosis drugs with the diverse health benefits of medicinal plants may lead to positive advances in the treatment of tuberculosis and its associated side effects (Mangwani *et al*., 2020). Plants with medicinal history have yielded novel drugs and are preferred for endophyte isolations (Nalini and Prakash 2017).

Indonesian herbal plants, as anti-tuberculosis, have the potential to have endophytic actinomycetes, which have the same content as the secondary metabolites produced by these plants. Several studies have stated that some of these plants have been studied as possessing endophytic actinomycetes (Table 4). Besides, it can be an opportunity for further research to explore five medicinal plants that are predicted to fight tuberculosis. Some researchers approved that Indonesian medicinal plants have potential activity against *M. tuberculosis* multidrug resistance (MDR) strains, such as *Pluchea indic*a and *Rhoeo spathacea* (Radji *et al*., 2015).

Table 4. Indonesian Medicinal Plants Used for Tuberculosis Treatment (*Tanaman Obat Indonesia Digunakan untuk Pengobatan Tuberkulosis*)

Plants (*Tumbuhan*)	**Local Name** (*Nama lokal*)	**Location** (*Lokasi*)	**MIC (µg/mL)**	**Method** (Metode)	**Reference** (*Referensi*)
Annona muricata L.	Soursoup leaf	South Sulawesi / East Nusa Tenggara	50	Lowenstein Jensen	(Pakadang *et al*., 2021)
Anredera cordifolia (Ten.) v Steenis	Binahong	West Java	500	Lowenstein Jensen	(Pitaloka and Sukandar 2018)
Citrus aurantifolia (Christa) Swingle	Lime leaves	South Sulawesi / East Nusa Tenggara	50	Lowenstein Jensen	(Pakadang *et al*., 2021)
Coleus scutellarioides (L.) Benth	Miana leaf	South Sulawesi / East Nusa Tenggara	50	Lowenstein Jensen	(Pakadang *et al*., 2021)
Curcuma longa L.	Turmeric rhizome	South Sulawesi / East Nusa Tenggara	50	Lowenstein Jensen	(Pakadang *et al*., 2021)
Curcuma mangga Val		North Sumatera	500	Microscopic Observation Drug Susceptibility (MODS)	(Pratiwi *et al*., 2020)
Hibiscus sabdariffa L.	Rosella flower	South Sulawesi / East Nusa Tenggara	50	Lowenstein Jensen	(Pakadang *et al*., 2021)
Merremia mammosa Hall.	Bidara upas tuber	East Java	100	Solid agar media (Middlebrook 7H10)	(Mangestuti Agil, Herra Studiawan 2021)
Morinda citrifolia	Mengkudu	South Sulawesi	1.500	Lowenstein Jensen	(Nurdin and Bahar 2020)
Musa paradisiaca L.	Ambon banana skins	South Sulawesi / East Nusa Tenggara	50	Lowenstein Jensen	(Pakadang *et al*., 2021)
Ocimum citriodorum Vis.	Basil leave	South Sulawesi / East Nusa Tenggara	50	Lowenstein Jensen	(Pakadang *et al*., 2021)
Phyllanthus urinaria L.	Meniran leaves	South Sulawesi / East Nusa Tenggara	50	Lowenstein Jensen	(Pakadang *et al*., 2021)
Syzygium aromaticum	Cengkeh	North Maluku	0.8	Microplate Alamar Blue Assay (MABA)	(Kaur and Kaur 2015)
Zingiber casumounar Roxb.	Rhizome bangle	South Sulawesi / East Nusa Tenggara	50	Lowenstein Jensen	(Pakadang *et al*., 2021)

Research has confirmed that the bioactive compounds in medicinal plants are a habitat for specific endophytic bacteria associated with medicinal plant tissues (Mamangkey *et al*., 2022). There is evidence that actinomycetes are found in Indonesian medicinal plants. For example, actinomycetes isolated from the rhizosphere of sambiloto (*Andrographis paniculata*) medicinal plants such as *Streptomyces griseorubiginosus*, *S. phaeopurpureus* and *S. purfeofuscus* (Rante *et al*., 2020).

CONCLUSION

Achieving the goal of eliminating the global TB epidemic by 2035 requires further innovation and development in drug discovery, particularly to address resistance to TB drugs. Consequently, anti-tuberculosis drugs are often less effective against *Mycobacterium tuberculosis* due to resistance. Natural products have proven to be a valuable source of new bioactive compounds for combating tuberculosis. Unfortunately, the exploration of new compounds derived from actinomycetes endophytes remains limited. Both technically and beneficially, endophytic microbes can be more effective than their plant hosts. Indonesia boasts a rich diversity of medicinal plants, and there have been reports of such plants containing bioactive compounds against tuberculosis. This presents an opportunity to explore their actinomycetes endophytes and conduct further research on the secondary metabolites of these endophytes to combat *M. tuberculosis*. There is substantial evidence that actinomycetes produce antibiotics and possess bioactive compounds effective against *Mycobacterium tuberculosis*. Furthermore, many Indonesian medicinal plants show promise for tuberculosis treatment. Rather than focusing solely on these plants, this review emphasizes endophytic bacteria, specifically actinomycetes, which are believed to offer comparable potential while presenting additional advantages.

ACKNOWLEDGMENT

This research was carried out with research grant funds from Hibah BIMA Kemendikbud RI.

AUTHOR CONTRIBUTIONS

MFE: collecting research data and drafting the article; A: revise manuscripts and final revision of manuscript; AN: create research concepts and revise manuscripts.

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