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REVIEW ARTICLE

Drug-Resistant Pulmonary Tuberculosis: Current Standings in Indonesia

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A B S T R A C T

Tuberculosis (TB) caused by the pathogenic bacteria *Mycobacterium tuberculosis* (MTb) remains a highly prevalent disease, particularly in low and middle-income countries. Due to the bacteria's atypical cell wall structure, ability to form granuloma, and capacity to switch between replicating and non-replicating states in the host lung parenchyma, the fundamental treatment of patients diagnosed with TB involves a 6-month long daily drug administration. With Indonesia ranking among the nations with the highest TB burden worldwide, there has been an alarming increase of drug-resistant MTb (DR-MTb) strains all over the country in recent years. However, there are currently limited studies available that highlight MTb resistance profiles across different regions within Indonesia. The major risk factors contributing to the emergence and spread of TB in Indonesia include health conditions, environmental factors, and socioeconomic status. Furthermore, short-course therapy, natural compounds found in Indonesia, and drug repurposing can be employed to combat the further spread of DR-MTb strains across the country, especially in rural regions. Several studies have studied the potential of natural extracts in treating MTb due to their bioactive components that have anti-inflammatory and antibacterial properties.

K E Y W O R D S

Drug resistance; Mycobacterium Tuberculosis (MTb); Natural compounds; Potential treatment; Risk factors

H I G H L I G H T S

- *Mycobacterium tuberculosis* infection poses a significant disease burden in low and middle-income countries such as Indonesia
- The development of several drug resistant strains of tuberculosis which are unresponsive to both first- and second-line antituberculosis drugs have been observed in multiple regions of Indonesia
- There is a significant and unanswered need for alternative of antituberculosis drugs, which may be answered through the use of natural compounds present in herbal plants endemic to Indonesia, as well as via drug repurposing

INTRODUCTION

Tuberculosis (TB) is an airborne disease that is caused by the bacillus bacteria, *Mycobacterium tuberculosis* (MTb); through the inhalation of nearby aerosol particles. Although it is widely known that TB cases are synonymous with bacterial infections of lung tissues (pulmonary TB), MTb could also infect other non-pulmonary body organs such as the brain, bones, muscles, and pleura, resulting in cases of extra-pulmonary TB (Gopalaswamy et al., 2021). In this review paper, the discussion focuses on pulmonary TB, hence the term TB hereafter refers to pulmonary TB.

Up until this time, TB is still one of the deadliest diseases that holds major health, social, and economic burden around the world, specifically in low and middle-income countries (Delogu et al., 2013). When an individual's immune system can inhibit the growth of MTb after inhalation, this may result in the bacteria turning dormant; causing the condition of latent tuberculosis (Fogel, 2015). Individuals with latent tuberculosis are in a state of being infected with MTb but they do not show any symptoms and do not transmit the disease to others; in other words, they are non-infectious. However, some individuals with latent tuberculosis have the risk of progressing into active tuberculosis (Cruz-Knight & Blake-Gumbs, 2013).

MTb is a successful pathogen that has been causing TB for a long time. It is a rod-like, bacillus obligate aerobic bacteria that requires oxygen to grow and survive. The virulence factor of MTb is due to the presence of an atypical cell wall structure that supports strong impermeable barriers towards harmful drugs and components. According to Delogu et al. (2013), MTb has a cell structure that is similar to gram-negative bacteria by having an asymmetric lipid bilayer containing mycolic acids on the inner layer and glycolipids and waxy components on the outer layer. Moreover, between the inner and outer membrane, there is the presence of thin peptidoglycan that is covalently linked to arabinogalactan and lipoarabinomannan which is also linked to the mycolic acids.

MTb causes infection in the human body by invading the macrophages, modifying the normal progression of phagosomes into acidic, hydrolytically active components; concurrently, inhibiting the activation of immune responses that activate the host cell (Russell, 2001). Following that, the MTb and infected phagosomes migrate to the lung parenchyma and induce the immune system to form the granuloma, a state in which the bacteria is reported to enter the logarithmic growth phase (Maison, 2022). Subsequently, T-helper cells will be activated and give rise to the development of granuloma. The granuloma, which is a bacterial jail comprised of macrophages and lymphocytes that imprisons MTb (Pai et al., 2016), imposes a hypoxic environment that may stimulate angiogenesis to the tuberculoma (Krock et al., 2011).

Up until 2019, MTb remained a common infectious agent that causes death from a single pathogen. It was known that in 2019 alone, 10 million people worldwide are estimated to have developed TB. This has been a major disease burden in which starting in 1977, the World Health Organization (WHO) published a *Global Tuberculosis* report each year. In the report, it was targeted that a reduction in incidence rate by 20% should be achieved from 2015 until 2020; however, it was disclosed that the reduction was only 9%, with an annual reduction of only around 2% (Chakaya et al., 2021). According to WHO (2022), Indonesia ranks second in TB incident cases worldwide in 2021 behind India. Furthermore, Noviyani et al. (2021) mentioned that there was a rising trend of TB prevalence with age in the Indonesian population, with an estimated prevalence value of 759.1 per 100,000 population older than 15 years old. In addition, it was found that a total of around 33,336 cases of TB patients in Indonesia were acquired by children with an incidence rate of 2.52 cases per 1,000 populations by the year 2021 which is similar to the 2019 TB incidence rate in Pekalongan which reaches 2.21 cases per child population (Irnawati et al., 2022; Kementerian Kesehatan Republik Indonesia, 2021). It is also worth mentioning that higher TB prevalence was observed in urban areas compared to rural areas, which may indicate the significance of sociodemographic conditions to TB prevalence.

The disease burden of TB increases due to the presence of drug-resistant TB (DR-TB); furthermore, there are various forms of DR-TB, including MDR-TB and XDR-TB. To differentiate between MDR-TB and XDR-TB, MDR-TB or multidrug-resistant TB is a form of TB that does not respond to isoniazid and rifampicin; while XDR-TB or extensively drug-resistant TB is an extended form of MDR-TB as it is resistant to both isoniazid and rifampicin with an additional resistant to any fluoroquinolone and at least one of three injectable second-line drugs (Sultana et al., 2021). Treating MDR-TB and XDR-TB has a higher complexity compared to normal TB due to its prolonged treatment period, elevated treatment cost, as well as unexpected complications. Thus, the presence of both MDR-TB and XDR-TB increases the threat of TB to human health, especially in

low-income countries (Xi et al., 2022). However, there has not been much study or analysis of DR-TB in Indonesia.

With the increasing presence of DR-TB, there have been multiple approaches that may become prospective treatment options as an alternative to available treatments. One option includes natural extracts obtained from different medicinal plants as there are different biologically active chemicals present in plants that display powerful antibacterial properties. Historically, numerous plants have been used to treat MTb; from several reports, the benefits of plant extracts were due to the presence of phytochemicals that helps prevent bacteria from utilizing multiple drug efflux systems (Mangwani et al., 2020). Nonetheless, there has not been much study on the effects of natural extracts in treating TB. Considering the aforementioned points, this paper seeks to provide an overview of the causes of DR-MTb based on Indonesia's current drug therapies, risk factors, and potential treatment options.

CURRENT TREATMENTS FOR TUBERCULOSIS IN INDONESIA

Based on the Indonesian National Guideline for the Treatment of Tuberculosis (*Pedoman Nasional Pelayanan Kedokteran Tatalaksana Tuberkulosis*) (Kementerian Kesehatan Republik Indonesia, 2020), the treatment period for extrapulmonary TB highly differs from that applied in pulmonary TB, at which it has been noted that the duration of antituberculosis drug administration can reach up to a minimum of 20 months. This phenomenon occurs due to the distinct infection site that would give rise to separate clinical symptoms and drug target sites. Thus, as this review focuses on pulmonary TB, this section will strictly elucidate the treatment plan administered for patients suffering from this lung infection.

First-line drug for tuberculosis

Similar to other countries, in Indonesia, the first line of treatment for tuberculosis include commonly utilized drugs, such as isoniazid (INH), rifampicin (RIF), ethambutol (EMB), and pyrazinamide (PZA). In patients infected with drug-susceptible TB strains, two months of treatment using INH, RIF, EMB, and PZA, followed by four and a half months of only INH and RIF can be given (O'Connor & Brady, 2022; Kementerian Kesehatan Republik Indonesia, 2020). As previously mentioned, MTb can switch between replicating and non-replicating states, at which the mycobacteria may become undetectable by antimycobacterial drugs, such as INH and RIF. Thus, it is imperative to fully eliminate the mycobacteria in TB patients via the administration of sterilizing drugs, such as PZA, that are accompanied by antimycobacterial drugs to ensure a thorough elimination and devoid of relapse risk (Getahun et al., 2015). It has been recorded that TB treatment shorter than 4 months has resulted in 40% of patients experiencing relapse (Goletti et al., 2018). Hence, it is quintessential for TB patients not to skip and stop the treatment as it may lead to the development of antibiotic resistance and relapse of MTb infection (Asres et al., 2016).

Isoniazid. Isoniazid (INH) is one of the first-line oral drugs given to TB patients. On its own, INH is prescribed for 2 months as an initial phase drug followed by either 4- or 7-months prescription as a continuation (Blumberg et al., 2003). After being activated by the bacterial catalase-peroxidase enzyme KatG in MTb, INH works by forming isonicotinoyl alcohol (IA). Isonicotinoyl alcohol can form a key chemical adduct with nicotinamide adenine dinucleotide ($INH^{-}NAD^{+}$) which can inhibit mycolic acid biosynthesis of the MTb cell wall resulting in bacterial death, as outlined in Figure 1 (Khan et al., 2019).

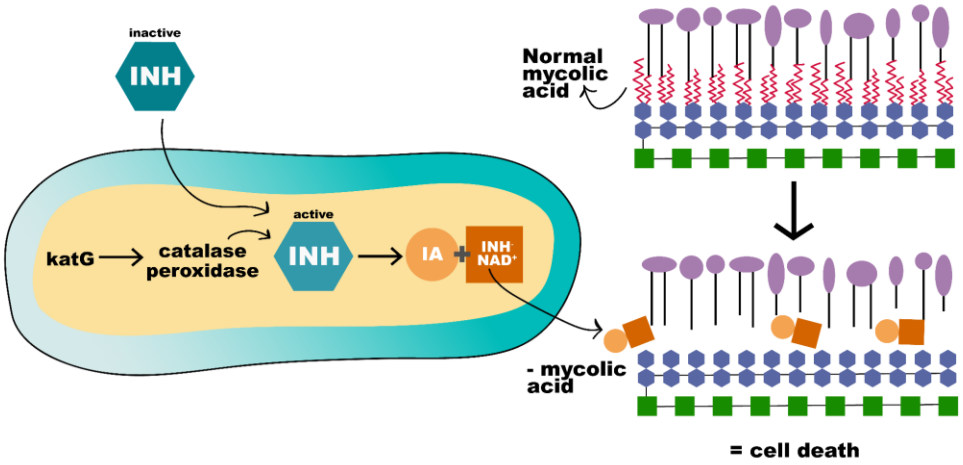

Figure 1. Schematic representation of INH mechanism of action

Rifampicin. Rifampicin (RIF) is a drug commonly used to treat infectious diseases caused by various mycobacterial and Gram-positive bacteria, such as tuberculosis. This drug is semi-synthetically derived from rifamycin B commonly produced by *Amycolatopsis rifamycinica* (Dutta & Karakousis, 2015). Rifampicin acts on tuberculosis by binding to the β-subunit of the RNA polymerase (RNAP) resulting in the inhibition of DNA-dependent RNAP which would prevent RNA chain elongation, as illustrated in Figure 2. However. the mechanism of how RIF causes cell death by transcription interference is still not well understood (Nusrath & Hanna, 2017). For patients with health conditions such as human immunodeficiency virus (HIV) and who are co-infected with TB infections, RIF and INH can also be administered as Campbell et al. (2021) found that these drugs are equally safe and effective in co-infected populations.

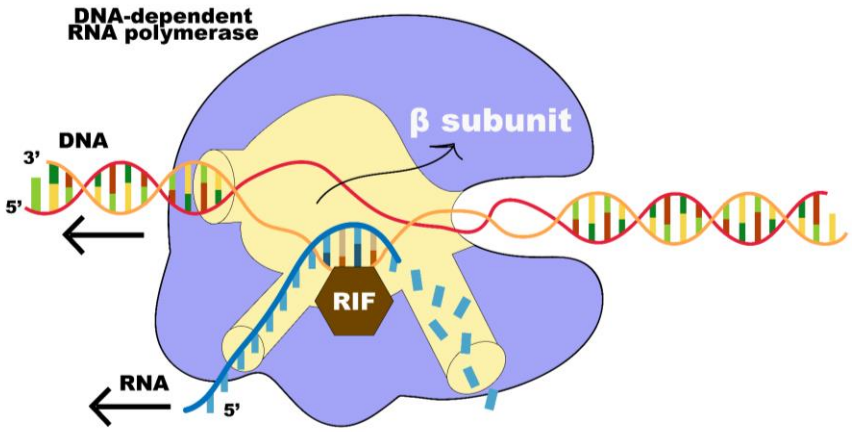

Figure 2. Schematic representation of RIF mechanism of action

Ethambutol. Ethambutol (EMB) is considered a bacteriostatic first-line antituberculosis drug that is not able to be administered by itself due to its capability to induce optic neuropathy in TB patients that could lead to blindness (Tang et al., 2014). It is considered to be a bacteriostatic drug as it inhibits mycobacterial proliferation by disrupting arabinogalactan synthesis and cell wall integrity. This inhibition is possible through the drug targeting arabinosyl transferase that is essential in producing an arabinogalactan intermediate called D-arabinofuranosyl-P-decaprenol and is also vital in the arabinogalactan polymerization, as shown in Figure 3. The drug is synergistically administered along with INH as both drugs target the disruption of the cell wall, at which INH represses the expression of enoyl-acyl carrier protein reductase that is vital in cell wall synthesis and EMB binds to TetR transcriptional enhancer that increases INH sensitivity (Lee & Nguyen, 2021;

Palomino & Martin, 2014; Zhu et al., 2018). Additionally, similar to INH and RIF, it should be noted that EMB is only capable of inhibiting replicating MTb (Jnawali & Ryoo, 2013).

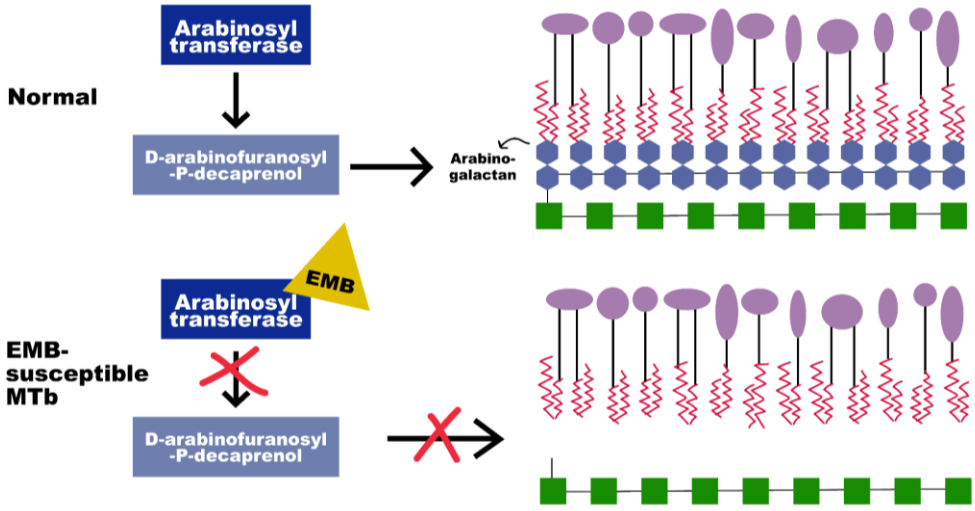

Figure 3. Schematic representation of EMB mechanism of action

Pyrazinamide. Pyrazinamide (PZA) is an anti-tuberculosis drug that shortens the initial 12 months into the current 6-month treatment duration. The mechanism employed by PZA can be considered unique compared to other first-line TB drugs as this drug has a sterilizing capability to eliminate non-replicating persister or dormant variants of the MTb (Gopal et al., 2019; Zhang et al., 2014). However, PZA is solely consumed during the first 2 months of the 6-month treatment duration as it was discovered that the administration of PZA exceeding 2 months did not produce any significant benefits for the patient (Zhang et al., 2014). Moreover, although the drug has been a cornerstone of first-line TB treatment formulation ever since it was discovered to possess the anti-tuberculosis capability, the mechanism of how PZA specifically targets and eliminates MTb remains unclear (Mucugi, 2017; Sun et al., 2020). Nonetheless, several pathways have been postulated to be a part of the PZA mechanism of action. This drug is consumed as a prodrug and is metabolized into its bioactive form, pyrazinoic acid (POA), during an enzymatic reaction involving pyrazinamidase at an acidic pH. Moreover, it was paramount for the prodrug to act in an acidic environment as it was recorded that 99.9% of PZA do not turn into POA in a non-acidic environment, specifically at a pH level over 5.5 (Santucci et al., 2022). Although not exact, it was found that POA targets ribosomal protein S1 (RpsA), a ribosome-sparing protein that is involved in the trans-translation process in the bacteria, at which the elimination of RpsA leads to the disruption of protein translation due to stalled ribosomes, as outlined in Figure 4 (Shi et al., 2011).

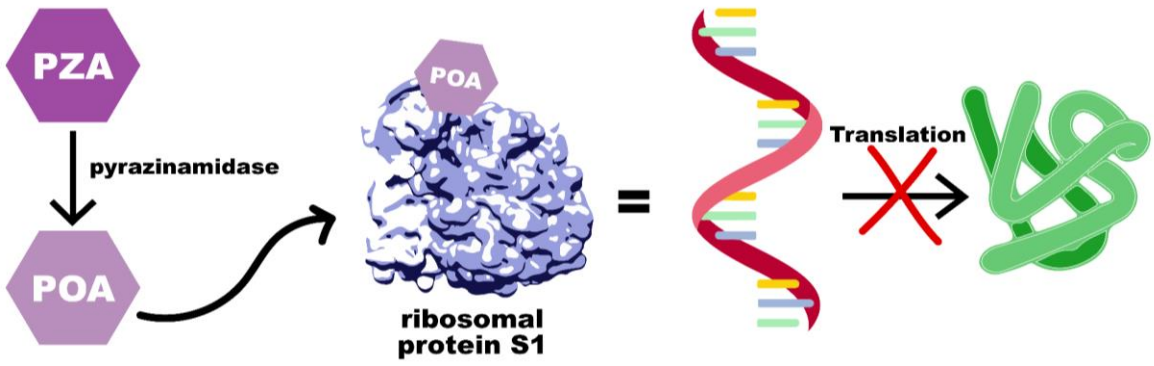

Figure 4. Schematic representation of PZA mechanism of action

Streptomycin. Streptomycin (STM) is an aminocyclitol glycoside antibiotic that kills actively-replicating MTb, but not the non-replicating and intracellular bacteria (Mitchison, 1985). As illustrated in Figure 5, the drug's mechanism is based on its binding to 16S rRNA which disrupts the translation proofreading and protein expression in the bacteria, resulting in cellular death due to the lack of proteins. This drug used to be administered as a first-line drug during TB treatment years after its first usage, although in the last two decades, the drug is relegated as a second-line drug for TB due to the drug's prolonged administration that resulted in the emergence of resistance against it and is currently only administered in limited cases of multidrug-resistance TB (Cohen et al., 2020; Ruiz et al., 2003). The development of acquired antibiotic resistance against STM was recorded to appear 5 years after its introduction as an antituberculosis agent in 1944 (Sotgiu et al., 2015). Nevertheless, the drug remains one of the best drugs administered in the case of unavailability and/or intolerance of INH, EMB, RIF, and PZA supply (Waters & Tadi, 2022).

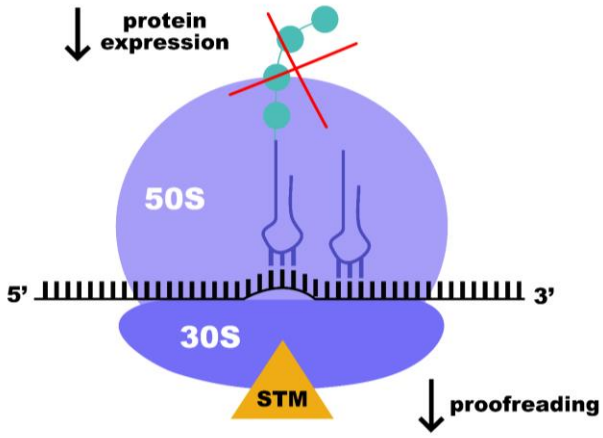

Figure 5. Schematic representation of STM mechanism of action

Second-line drug for tuberculosis

Amikacin. Amikacin (AMK) is a second-line injectable antibiotic drug in the aminoglycosides class. As outlined in Figure 6, the drug mainly disrupts bacterial growth by binding to 16S rRNA composing the 30S small ribosomal subunit and ultimately preventing protein synthesis in the bacterial cytoplasm (Ramirez & Tolmasky, 2017; Sowajassatakul et al., 2014). AMK is mostly strictly utilized for the treatment of multidrug-resistant TB in the case of an inefficacious first-line drug treatment regimen (Modongo et al., 2014). However, AMK is only administered for a short period and is mostly accompanied by other antituberculosis drugs as a longer administration could lead to ototoxicity and nephrotoxicity (Sturkenboom et al., 2018).

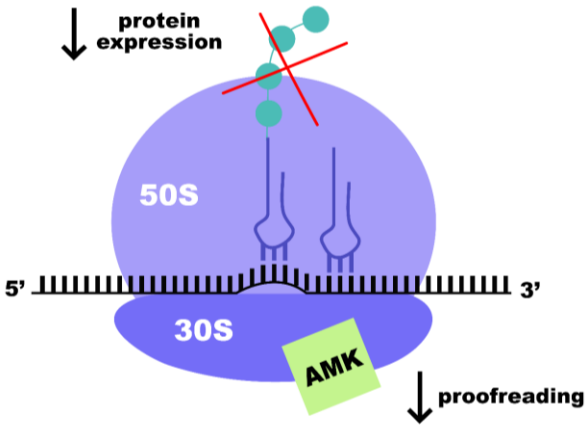

Figure 6. Schematic representation of AMK mechanism of action

Ethionamide. Similar to AMK, ethionamide (ETO) is utilized mainly for the treatment of multidrug-resistant TB to substitute INH particularly due to ETO being a structural analog of INH. ETO is a thionamide prodrug that when activated would inhibit InhA, an NADH-specific enoyl-acyl carrier protein reductase, that is vital in mycolic acid synthesis, as shown in Figure 7 (Ang et al., 2017). This prodrug is activated by a mycobacterial enzyme called EthA, whose function is still unexact, although it has been hypothesized to be an adherence factor to mammalian cells as it is composed mycolic acid wall seen in MTb (Ang et al., 2014).

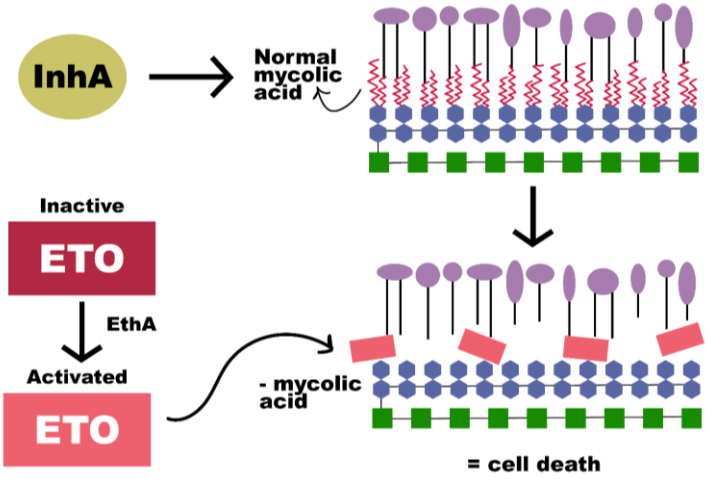

Figure 7. Schematic representation of ETO mechanism of action

RESISTANCE

The fundamental treatment of patients diagnosed with TB involves a 6-month treatment, in which a combined regimen of four first-line drugs can be administered during the first 2 months. These drugs include INH, EMB, RIF, and PZA (Sotgiu et al., 2015; WHO, 2019a). However, the incompleteness or dose insufficiency of these four-drug regimen treatments may result in drug-resistant TB (DR-TB) (Tiberi et al., 2022), further posing a threat to reducing the prevalence of TB patients in Indonesia.

Classifications of drug-resistant MTb

As described by WHO (2019a) and Seung et al. (2015), DR-TB can be categorized into mono-, polydrug-, multidrug- (MDR), rifampicin- (RR), extensive drug- (XDR), and extreme drug-resistant (XXDR) Tuberculosis (Table 1).

Table 1. The different types of DR-TB

Category of drug-resistance	Resistance towards
Monoresistance	One first-line drug
Polydrug resistance	More than one first-line drug (not a combination of INH and RIF), commonly RIF+EMB and INH+EMB
Multidrug resistance (MDR)	Both INH and RIH
Rifampicin resistance (RR)	RIF (along with the absence or presence of first-line drug resistance)

Extensive drug resistance (XDR)	RIF, INH, fluoroquinolone, and one or more second-line drugs (amikacin, kanamycin, or capreomycin)
Extreme drug-resistance (XXDR)	All first- and second-line drugs

Mechanism of resistance associated with gene mutations

The presence of DR-TB further increases the urgent demand to find a rapid molecular diagnostic tool, in order to accurately determine the molecular characteristics of TB drug resistance and its mechanisms. This can be done through several molecular test platforms to sequence the TB genome in patients for the detection of genetic mutations. These automated molecular tests include the Xpert MTB/RIF assay (Sahiratmadja et al., 2020), whole genome sequencing (Maladan et al., 2021), PCR-RFLP (Vera et al., 2018), multiplex ligation-dependent probe amplification assay (Chaidir et al., 2015), and Genotype MTBDRplus assay (Choerunisa et al., 2021). The findings of mutations in these studies in Indonesia are similar to the mutation catalog published by WHO (2021), which summarized the results of whole genome sequencing data on the collection of multinational *M. tuberculosis* associated with genetic variants contributing to first- and second-line drug resistance (Table 2). Understanding mutations and their mechanism contributing to the virulence of MTb will aid in the accuracy of DR-TB diagnosis, hence facilitating the proper treatment of TB patients.

Table 2. Gene mutations associated with drug resistance in Indonesian TB patients

Drug	Gene (WT)	Normal gene function	Mutations	Reference	Mechanism of resistance
Rifampicin (RIF)	rpoB	Encodes for the β subunit of RNA polymerase, being the target of RIF (André et al., 2017)	S450L (Ser450Leu)	Chaidir et al. (2019); Maladan et al. (2021); Umar et al. (2020)	Mutated *Mycobacterium tuberculosis* RNA polymerase (MTb-RNAP) reduces the binding affinity of RIF through the disruption of intermolecular forces and key hydrogen bonds, as well as conformational flipping (Zhang et al., 2019).
			L430P (Leu430Pro)		
			H445Y (His445Tyr)/ H445D (His445Asp)		
			Q432K (Glu432Lys)/ Q432P (Glu432Pro)		
			D435Y (Asp435Tyr)/ D435V (Asp435Val)		
			I491F (Ile491Phe)		

	rpsL	Encodes for the S12 ribosomal protein (Wang et al., 2011)	K43R (Lys43Arg)	Chaidir et al. (2019); Maladan et al. (2021); Tania et al. (2020)	Mutated S12 ribosomal protein may result in the instability of the 16s rRNA structure, subsequently decreasing STM affinity (Musser, 1995).
Streptomycin (STM)	rrs	Encodes for the 16s rRNA gene (Cuevas-Córdoba et al., 2013)	c-492t	Chaidir et al. (2019); Tania et al. (2020)	Mutations in streptomycin binding site on 16S rRNA may cause structural alterations, abolishing the interaction between STM and 16s rRNA (Sreevatsan et al., 1996)
			c-462t		
			a-514t/ a-514c		
			g-878a	Umar et al. (2020)	
			S514R		
Isoniazid (INH)	katG	Encodes for the catalase-peroxidase enzyme to activate INH (Rawat et al., 2003)	S315T (Ser315Thr)	Chaidir et al. (2019); Umar et al. (2020)	Influence the interaction between INH and the drug binding site through the alteration of pi interaction or the introduction of steric clashes (Phelan et al., 2016)
			S315N (Ser315Asn)		
			G279R (Gly279Arg)		
			E340Q (Glu340Gln)		
			R373G (Arg373Gly)		
			W191R (Trp191Ar)g		
	inhA	Encodes for the NADH-dependent enoyl-ACP reductase enzyme for the synthesis of mycolic acids. Activation of INH inhibits inhA (Rawat et al., 2003).	I21V (Ile21Val)	Maladan et al. (2021); Tania et al. (2020)	Mutations in this gene may greatly reduce the catalase-peroxidase enzymatic activity, hence reducing the toxicity of INH (Heym et al., 1995; Tseng et al., 2015).

	fabG1 (mabA)	Encodes for the 3-oxoacyl-AcpM reductase for the biosynthesis of mycolic acids (Gurvitz, 2009)	c-15t		mabA and its adjacent region is altered into inhA promoter, causing the overexpression of inhA (Ando et al., 2014)
	kasA	Encodes for the β-ketoacyl synthases involved in mycolic acid synthesis (Slayden & Barry, 2002)	G312S (Gly312Ser)		Decrease the production of mycolic acid precursors and decrease the catalytic efficiency (Slayden & Barry, 2002)
Ethambutol (EMB)	embB	Encodes for the arabinosyl transferases essential for the biosynthesis of arabinogalactan, a mycobacterial cell wall core component (Amin et al., 2008)	M306V (Met306Val)/ M306I (Met306Ile)/ M306L (Met306Leu)	Chaidir et al. (2019); Maladan et al. (2021)	May be due to changes in the cell wall permeability (Safi et al., 2008) or increase in intracellular DPA precursor production which competes for the ethambutol binding sites, maintaining the emb gene function after ethambutol administration (Safi et al., 2013)
			D1024N (Asp1024Asn)		
			G406C (Gly406Cys)/ G406D (Gly406Asp)/ G406A (Gly406Ala)	Chaidir et al. (2019); Tania et al. (2020)	
			D354A (Asp354Ala)		
	embA		c-12t	Tania et al. (2020)	Still unclear and needs further studies, since mutations in embA appears only alongside other emb gene mutations (Plinke et al., 2010)
Pyrazinamide (PZA)	pncA	Encodes for the mycobacterial pyrazinamidase (PZase) required	V139A (Val139Ala)	Tania et al. (2020)	Reduction or abolishment of PZase activity , hindering the
			Y103H (Tyr103His)		

		for the activation of PZA into pyrazinoic acid (Zhang et al., 2014)	T100P (Thr100Pro)		activation of (Tam et al., 2019)
			H82R (His82Arg)		
			D12A (Asp12Ala)		
			L4S (Leu4Ser)		
			W119R (Trp119Arg)	Maladan et al. (2021)	
Amikacin (AMK)	eis	Encodes for an aminoglycoside transferase to acetylate AMK containing a hydroxyl group in 2', important for AMK metabolism (Sanz-García et al., 2019)	c-10t	Chaidir et al. (2019); Maladan et al. (2021); Tania et al. (2020)	Increases leaderless eis mRNA transcript, thus increasing the expression of aminoglycoside transferase and inactivating AMK (Gikalo et al., 2012; Zaunbrecher et al., 2009)
			g-14a		
	rrs	Encodes for the 16s rRNA (Kim et al., 2021)	a-514c		Causes methylations in the A-site of 16s rRNA due to the activation of 16s rRNA methylase, hence hindering the binding of AMK to the 30S ribosomal subunits and avoiding protein synthesis inhibition (Zhang et al., 2022)
Ethionamide (ETO)	fabG1	Encodes for the 3-ketoacyl reductase (Parish et al., 2007) for mycolic acid synthesis	c-15t	Tania et al. (2020)	Still unclear, but may induce conformational changes in the ORF1 gene of inhA locus, impairing drug binding (Abraham et al., 2020)

Mapping MTb drug resistance profiles in Indonesia

A cross-sectional study performed by Dewi (2020) found a total percentage of 8.13% DR-TB in patients treated in North Maluku. In Bandung, West Java, the whole-genome sequencing done by Chaidir et al. (2019) detected monoresistance-conferring mutations towards PZA (4.7%), INH (3.1%), STM (0.9%), and RIF (0.3%). Another study performed in Tangerang, Banten with diverse socioeconomic backgrounds in 2011-

2014 identified 4.4-8.1% isolates with resistance towards isoniazid, 0-10% towards RIF, 0-10.8% towards EMB, and 0-2.7% towards STM (Wiwing et al., 2015). In line with these studies, Tania et al. (2020) found that 93.3% of the isolates had at least one anti-TB drug resistance. It is also interesting that the prevalence of MDR and pre-XDR was as high as 52.5% in previously treated patients at 7 Indonesian hospitals, higher than the recently diagnosed TB patients in a recent study (Burhan et al., 2022). However, the MDR-TB isolates in Bandung and Palembang, South Sumatra themselves were only found to be 2.5% (Chaidir et al., 2019) and 1.4% (Tjekyan et al., 2018), respectively. Moreover, Majdawati et al. (2019) demonstrated an MDR-TB occurrence of only 2.04% in TB-positive patients. The prevalence of polyresistance was also reported to be low, being only 3.1% in Bandung (Chaidir et al., 2019) and 1.6% in Tangerang (Wiwing et al., 2015). From the ethnicity perspective, MDR-TB is found to be the most common in East Asian (Beijing) lineage isolates (63.3%) in Java (Tania et al., 2020) due to the high amounts of mutations correlated with anti-TB drug resistance, but the correlation between ethnicity and drug resistance is still yet to be determined.

Furthermore, a large retrospective cohort study in West Java found many patients conferring anti-TB resistance which either remained undiagnosed or encountered treatment delays, in which 10.5% of presumptive RR-TB were then diagnosed accordingly, 66% were diagnosed with MDR-TB, and 20% were diagnosed with XDR-TB (Soeroto et al., 2019). As this study highlighted the fact that DR-TB patients did not receive their drug-susceptibility testing results and had delays in resistance diagnosis, there might be unreported resistance cases in Indonesia, contributing to the relatively low percentage of DR-TB prevalence in the aforementioned studies. Additionally, delayed treatments in DR-TB patients may result in impaired treatment outcomes.

RISK FACTORS CONTRIBUTING TO THE DEVELOPMENT OF PULMONARY TB, DRUG RESISTANCE, AND IMPAIRED TREATMENT OUTCOME IN INDONESIA

Generally, the emergence of drug-resistant MTb strains in Indonesia is attributed to improper drug regimen and dose, low drug quality, and limited drug availability. Most TB patients in Indonesia did not receive adequate information regarding proper drug consumption, and long treatment times led to non-adherence to TB treatment (Aderita et al., 2016; Nawas, 2010). Furthermore, several risk factors have been noted to also play a role in exacerbating pulmonary TB infection. The major risk factors can further be categorized into health conditions, environmental factors, and socioeconomic status.

Health conditions

A retrospective cohort study by Soeroto et al. (2021) assessed the factors affecting successful treatment outcomes in MDR-TB patients in West Java, Indonesia. A majority of the patients are in their productive age (18-50), and only 50% of MDR-TB patients experienced successful treatment. Male sex, normal body mass index (BMI), and no prior tuberculosis treatment were all independently linked to improved treatment outcomes. In contrast, patients who were suffering from HIV infection, chronic kidney disease (CKD), and cavitary lesions were found to have an increased risk of developing a severe MDR-TB infection. Indeed, it has been previously reported that HIV/AIDS patients were ten times more likely to develop TB infection. Both conditions promote immunological impairment and may result in death (Liberato et al., 2004; Pawlowski et al., 2012). In Papua, there has been an increasing number of cases of HIV/AIDS with TB co-infection, reaching 61.1% in Nabire District and 21% in Timika (Kridaningsih, 2021; Pontororing et al., 2010). Whereas in Banyuwangi and Gresik, East Java, the prevalence of co-infection cases reached 16.93% and 13.79%, respectively (Fatimatuzzuhro et al., 2020; Gumilang et al., 2022). Additionally, other underlying immune conditions such as primary immunodeficiency disorders are also key risk factors for pulmonary TB in children, although this correlation has yet to be recorded in Indonesia (Boisson-Dupuis et al., 2015).

Furthermore, end-stage CKD patients are also more likely to acquire TB infection through the disruption of normal immune responses (Ruzangi et al., 2020). This condition leads to defective phagocytic activity, impaired antigen presentation capability, decreased B-cell and antibodies production, increased apoptotic rates, and compromised cell-mediated immunity (Cohen & Hörl, 2012). CKD and TB co-infections have been reported in Bandung and Manado, North Sulawesi, with a prevalence of 39.2% and 2.34%, respectively (Bandiara et al. 2022; Putranto et al., 2018). Moreover, drug resistance and treatment failure have also been linked with TB pulmonary cavitation, which is formed when the center of granuloma undergoes necrosis resulting in the destruction of lung parenchyma (Gadkowski & Stout, 2008; Kim et al., 2010; Stek et al., 2018). Pulmonary cavitation allows exponential growth of MTb, leading to the increased likelihood of disease transmission and the formation of drug-resistant strains (Kaplan et al., 2013; Urbanowski et al., 2020). It has been recorded that Ghaesani et al. (2021) examined the characteristics of TB infection in children aged 1 to 18 years old at dr. Hasan Sadikin General Hospital Bandung, from which the study found that 7.6% of the subjects had pulmonary cavities through X-ray examination. Comparably, MDR-TB patients in Persahabatan Hospital, Jakarta were found to have larger chest X-ray lesions and pulmonary cavities in comparison to drug-susceptible TB (DS-TB) patients (Icksan et al., 2018). A cross-sectional study by Taslim (2016) found a strong correlation between bacterial load and the occurrence of pulmonary cavities in TB patients admitted at Persahabatan Hospital, Jakarta. Similarly, cavitary pulmonary had the highest odds ratio of emerging in MDR-TB patients in West Sumatra (Nindrea et al., 2020). Fortunately, Pradana et al. (2018) discovered that the development of pulmonary cavities could/can be suppressed through the implementation of a standardized drug regimen for drug-resistant TB by the Ministry of Health of the Republic of Indonesia.

In addition, several other risk factors for developing MDR-TB in Indonesia include nutritional status and diabetes mellitus (Aderita et al., 2016; Kadri et al., 2022; Nindrea et al., 2020). TB is bi-directionally linked to malnutrition, at which the condition increases the risk of acquiring active TB, while concurrently, TB also predisposes the patient to malnutrition (Cegielski & McMurray, 2004). Malnutrition causes a decrease in appetite, nutritional and micronutrient malabsorption, and altered metabolism in TB patients, all of which consequently lead to secondary immunodeficiency and delayed TB treatment outcomes (Kant et al., 2015). Moreover, it has been noted that there was a significantly higher prevalence of anemia and decreased retinol and zinc titers in the plasma collected from TB patients in Jakarta (Karyadi et al., 2000). Additionally, a 16.7-fold greater risk of acquiring TB was found in TB patients whose body mass index (BMI) was below the normal range (Tobing et al., 2021). Furthermore, a case study in Medan, North Sumatra revealed that malnutrition accounts for 31.25% and 36.3% of TB patients suffering from HIV co-infection and those experiencing treatment failure, respectively (Ritonga, 2020). Among children suffering from TB in Lombok, West Nusa Tenggara, 63.1% have poor nutritional status and 29.2% experienced malnutrition (Apsari et al., 2020). Similarly, around 50% and 71.2% of TB and MDR-TB patients in Malang, East Java had malnutrition status (Cahyani et al., 2021; Kurnia et al., 2020). Another study by Isa et al. (2022) revealed that more than half of TB patients expressing RIF resistance were undernourished (58.3%), all were anemic (100%), and half (50%) suffer from hypoalbuminemia. Thus, in order to combat this issue, vitamins and nutrient supplementations (e.g., *Channa striata*) have been utilized in Indonesia. This extract-containing supplementation was discovered to induce an improvement in BMI levels and accelerate recovery in TB patients (Ma'rufi et al., 2019; Ma'rufi et al., 2020). In Medan, vitamin A and C supplementations in TB patients were also discovered to improve sputum conversion, meaning that the previously TB-positive sputum has been converted to a TB-negative smear result (Safitri et al., 2022; Sari et al., 2019).

For TB patients suffering from diabetes mellitus (DM), it is believed that impaired immunity plays a role in the progression of TB reactivation. Patients with DM respond to TB treatment less effectively than those without DM, putting them at an increased risk of treatment failure, death, and disease relapse (Baker et al., 2011; Lönnroth et al., 2014). Out of a total of ten countries with the highest number of DM patients

worldwide, six countries, including Indonesia, are categorized as high burden for TB, accounting for 80% of the TB cases worldwide (Restrepo, 2016). In North Semarang, the prevalence of TB and DM reached 16,7% (Saraswati, 2014). A strong association between TB and DM was also found in two urban clinics in Jakarta and Bandung, where almost 15% of relatively young, lean TB patients presented with DM (Alisjahbana et al., 2006). A mathematical modeling analysis study by Awad et al. (2022) found that in 2020, one in five TB cases and one in four TB-related deaths were attributed to DM. By 2050, it is expected that the proportions will rise to one in four and one in three, respectively.

Environmental factors

Development of drug-resistant TB has been closely linked with several environmental risk factors, namely housing conditions, alcohol consumption, and tobacco smoking. Being the fourth most populous country in the world, the increasing population growth in Indonesia has consequently raised the demand for housing. This then results in an increase in social problems and a housing environment that does not meet health requirements, facilitating faster disease transmission. A healthy household should follow the criteria provided in KEPMENKES RI No.829/Menkes/SK/VII/1999, involving proper floors, walls, ceilings, windows, ventilation, lighting, kitchen chimneys, basic sanitation facilities, and occupants' density. A case-control research in Pamekasan Regency found that a healthy housing condition can reduce the incidence of pulmonary TB up to 35 times (Wahyudi et al., 2018). Other researches have also assessed the relationship between the occupants' density, ventilation, air temperature, humidity, and the incidence of pulmonary TB disease (Marbun, 2022; Musfirah et al., 2022; Siregar et al., 2022; Syamsuddin et al., 2020). Sutomo (2013) found that dense residential areas, inadequate ventilation, inappropriate air temperature, and the absence of natural lighting in Banjarmasin, South Kalimantan housing increase the risk of developing pulmonary TB up to 2.2 times, 14.44 times, 13.14 times, and 17.54 times, respectively. As MTb is an airborne pathogen, dense housing conditions facilitate MTb transmission in indoor congregate settings (Deol et al., 2022), whereas improper ventilation increases the accumulation of infectious aerosol due to the lack of air circulation, which is supposed to reduce the concentration of infectious particles (Du et al., 2020; Escombe et al., 2019). In addition, milder temperatures generally aid in the growth of MTb and correlate with a higher incidence of infections, although the range of temperatures differs between countries (Fernandes et al., 2017). Concurrently, these temperatures are closely related to humidity, in which infectious droplets are able to evaporate and remain in the air for a relatively long time, easing their entry into susceptible hosts (Xu et al., 2020). Moreover, low natural light exposure in the form of UV-B relates to vitamin D deficiency, which in turn interferes with the development of innate immunity (Boere et al., 2017).

Additionally, alcohol consumption has been correlated to an increased TB disease burden due to disruption in the activity of alveolar macrophages and neutrophils, epithelial barrier dysfunction, and surfactant secretion (Molina et al., 2010; Rehm et al., 2010; Simet & Sisson, 2015). Sinaga et al. (2018) discovered that the habitual consumption of alcoholic beverage *tuak* by people of Batak ethnicity raises their risk of developing TB. Correspondingly, in Makassar, South Sulawesi, MDR-TB cases were more likely to have a history of excessive alcohol (Massi et al., 2011). Drinking history also has been proven to have a significant correlation with TB infection in DM patients (Anwar, 2015). In Minahasa, North Sulawesi, severe alcoholism increases the risk of developing TB up to 1,133 times (Makalew, 2010).

Indonesia is considered one of the countries with a high tobacco smoking rate, reaching a prevalence rate of 29% in the population aged 15 years and above (Nurhayati-Wolff, 2022). Although some studies in Indonesia did not find the significance of tobacco smoking in the prevalence of MDR-TB and DR-TB (Soeroto et al., 2021; Widiastuti et al., 2017; Windiyaningsih & Badaruddin, 2021), increased amount and duration of tobacco smoking have been linked to reduced lung macrophages and lymphocytes activity, along with an increased the likelihood of poor treatment outcome (Burusie et al., 2020; Nijenbandring de Boer et al., 2014). A study by Cahyani et al. (2021) found that 46.2% of MDR-TB patients fall into the category of active smokers.

Similarly, Bam et al. (2015) also found a high percentage of TB patients (77.6%) were smokers and 5.3% were ex-smokers. Furthermore, people with smoking habits are more at risk of developing pulmonary TB and MDR-TB up to 6 and 7.63 times, respectively (Aristiana & Wartono, 2018; Sianturi, 2014). The proportion of TB deaths attributed to smoking in Indonesia reached 25.8%, making Indonesia one of the top three countries with the highest smoking-attributable TB deaths (Amere et al., 2018).

Socioeconomic determinants

TB infection is also associated with poverty; people from low-income households are more likely to acquire TB infection and are incapable of complying with the high cost of diagnosis and long-term treatment (Oxlade & Murray, 2012; Siroka et al., 2016). Additionally, poverty contributes to poor living conditions, thereby increasing the risk of exposure to various TB risk factors, namely HIV, smoking, malnutrition, air pollution, and alcohol abuse (WHO, 2022). A study by Fuady et al. (2018) revealed that Indonesian households in urban, suburban, and rural areas affected by TB continue to be at risk for catastrophic costs and greater poverty. The incidences of total catastrophic costs in all TB-affected households and MDR-TB-affected households were 36% and 83%, respectively, all of which were affected by poor households, being a provider for the family, and exposure to previous TB treatment. Working status and level of education have also been previously attributed to developing TB. Unemployed TB patients had a 1.286 times higher chance of being undernourished due to difficulties in acquiring nutrient-rich food, which exacerbated their TB infection (Kurnia et al., 2020). This is evident by the case-control study performed by Wardani (2018) in Bandar Lampung, Lampung in which household food insecurity represented by decreased food budget and diversity resulted in a significant increase in TB spread.

In association with working status, occupational exposure to dust and other particulate matter is associated with a higher risk of developing respiratory disorders and higher pulmonary TB mortality rates (Muaz, 2014). A case-control study in Asahan Regency, North Sumatra by Gultom et al. (2022) revealed that construction workers who work more than eight hours and without face masks were 3.1 and seven times more likely to get pulmonary TB, respectively. In another case-control study examining gold miners in Lebong District, Bengkulu, drilling mine activity increases the risk of developing pulmonary TB up to 26.3 times, as the bacteria possesses the ability to survive and remains virulent in soil (Darmawansyah, 2017; Ghodbane et al., 2014). Another well-studied risk factor for pulmonary TB is pneumoconiosis, which is also one of the most common occupational lung diseases (Hung et al., 2016; Yang et al., 2022). Ikhsan (2019) discovered that 16.7% of industrial and mining workers suffered from pneumoconiosis, where 0.9% of them had pulmonary TB infiltrates when examined through The International Labor Organization (ILO) chest x-ray readings.

POTENTIAL TREATMENT FOR TB IN INDONESIA

As aforementioned, the current treatment of MTb is given for 6 months which increases the development of drug-resistance MTb. Similar to other bacterial infections, the introduction and administration of a new therapeutic agent are most likely to cause a resistant strain toward that drug (Gupta et al., 2017). In 2014, approximately 480 thousand cases with 190 thousand mortalities were recorded for MDR MTb and hence, alternative treatment should be considered. One of the alternatives is short-course therapy through the utilization of adjunct treatment to improve the efficacy of the primary treatments in a shorter time period, in which its effectiveness has been proven through clinical trials (Spellberg & Rice, 2019). Other possible treatments could also be done, such as the use of natural extracts (Mourya & Mourya, 2017) and inhalation therapy via drug repurposing (Mehta et al., 2018). As of today, these treatments have been extensively studied as a potential cure for MTb patients through *in vitro* and *in vivo* studies. Regardless, there

are limited to no studies mentioning the efficacy of these treatments in clinical trials. Therefore, these could be used as a future consideration to reduce the risk of MDR MTb in Indonesia.

Short-course therapy

The current treatment utilized worldwide has been noted to significantly decrease efficacy due to the lack of compliance with drug consumption. This disobedience may stem from the long duration of potentially-toxic drug administration and in the case of developing countries, the costly drug pricing also immensely impedes patients' capability to continuously supply the required drugs (Prasad & Gupta, 2015). Thus, a shorter drug regimen is established by WHO by replacing RIF with fluoroquinolone drugs, such as gatifloxacin and clofazimine, and adding kanamycin and prothionamide along with the conventional INH, PZA, and EMB. As this drug regimen employs fluoroquinolones and injectable second-line anti-tuberculosis drugs, the implementation of this regimen requires prerequisite antibiotic susceptibility tests to detect whether the bacteria possess genetic mutations that may hinder the drug from producing therapeutic effects. Through this short-course regimen, the conventional treatment that can reach up to 2 years can be immensely shortened to 9-12 months (WHO, 2019b). The effectiveness of this regimen has been proven to be highly successful in trials in developing countries, namely Bangladesh and Niger, with >80% cure rates (van Deun et al., 2010; Trébucq et al., 2014).

Natural extract

Medicinal plants have been widely used since ancient times and possess anti-inflammatory and antimicrobial properties. Specifically, the secondary metabolites produced by the plants, called phenolics, have been investigated to inhibit drug-resistant MTb as summarized in Table 3 (Mourya & Mourya, 2017).

Table 3. Potential natural extracts against MTb

Plant	Extract	Mechanism	MBC	Reference
C. longa	Curcumin	Regulate the inflammatory response	175 ppm	Pakadang et al. (2021)
A. cordifolia	Ursolic acid and Oleanolic acid	Penetrate the MTb cell wall	250 µg/mL	Pitaloka & Sukandar (2018)
K. galanga	Ethyl p-methoxycinnamate	Inhibit MTb growth	500 µg/mL	Fauziyah et al. (2017)
P. granatum	Epigallocatechin-3-gallate	Control vital cellular mechanism	100 ppm	Rauf et al. (2019)
H. sabdariffa	Anthocyanins	Regulate the inflammatory response	10 mg/mL	Djide et al. (2019)

Curcuma longa. *Curcuma longa*, also commonly known as turmeric, is a herbal flowering plant which is commonly grown in tropical climates, including Indonesia. The steam of turmeric has been widely used for medicinal purposes due to the presence of curcumin, a natural lipophilic polyphenol (Kocaadam & Şanlıer, 2017). In Indonesia, curcumin is one of the main ingredients for *jamu*, a traditional herbal drink, that could act as an immune booster and immunomodulator, as well as a potential antibacterial substance (Harmayani

et al., 2019). Being an immunomodulator, curcumin plays a major role in regulating the immune response, such as the regulation of T-cells and macrophages, during MTb infection. In T-cell regulation, curcumin allows the production of IFN-γ and other pro-inflammatory cytokines to fight the MTb. Concurrently, it prevents the overproduction of pro-inflammatory cytokines to avoid a cytokine storm which may result in tissue damage. Furthermore, curcumin promotes the apoptosis of macrophage cells that have phagocytosed MTb, in which a significant decrease of MTb colonies was observed by the addition of 30 µM of curcumin to the culture compared to the control (Faisal et al., 2022). Another study conducted by Pakadang et al. (2021) stated that the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of curcumin towards Mtb H37RV were 50 ppm and 175 ppm, respectively.

***Anredera cordifolia*.** *Anredera cordifolia*, also known locally as binahong, is a miracle plant that has been commonly used and trusted for treating chronic infectious diseases like MTb, especially in Indonesia. A yellow-colored saponin is concentrated on the leaves and stems of this plant, in which the saponin is made up of triterpenoid and steroids that had been studied to possess anti-inflammatory and analgesic properties (Astuti et al., 2011). Another study by Pitaloka and Sukandar (2018) mentioned that the binahong leaves contain ursolic acid (UA) and oleanolic acid (OA) which acts as pentacyclic triterpenes. Based on the result of their study, the MBCs of n-hexane extract binahong leaves were 250 and 500 µg/mL in Ethambutol-isoniazid (HE) and rifampicin-streptomycin (RS) resistant MTb strains. The characteristic of the pentacyclic triterpenes being highly lipophilic is the major possible factor of binahong to be a bactericidal agent. Due to its lipophilicity properties, this extract could penetrate through the mycobacterium cell wall which has been mentioned to be a non-toxic approach to killing the bacteria. Furthermore, a synergistic effect of binahong when combined with other first-line drugs, including INH, RIF, and EMB, has been proven in treating drug-resistant MTb.

Kaempferia galanga. *Kaempferia galanga*, commonly known as aromatic ginger or *kencur*, is an aromatic plant that has been used for anti-inflammatory treatment in folk medicine, particularly the rhizome of *K. galanga* (Yao et al., 2018). The main biological active compound of this plant is ethyl p-methoxycinnamate (EPMC) which possesses antimycobacterial activity even towards MDR strains of MTb (Umar et al., 2014). According to Fauziyah et al. (2017), the MBCs of *K. galanga* were 500 and 750 µg/mL towards RS and HE-resistant MTb strains, respectively. Also, it has a synergistic effect when combined with RIF to have a lower drug dosage. However, a decrease in the efficacy of *K. galanga* of around 50% was shown when synergized with INH and EMB. Another study by Lakshmanan et al. (2011) also found that the MTb H37Rv strain was inhibited by EPMC extract of *K. galanga* at a concentration of 0.485 mM. This study also suggested that the macrophage cells had an IC50 value of 3.8mM towards EPMC and hence the concentration of EPMC to inhibit DR-MTb was not toxic towards the macrophage cell that acts as a first-line defense during infection.

Punica granatum. *Punica granatum*, also known as pomegranate, is a nutritious fruit that possesses medicinal value for parasitic diseases and diarrhea in Ayurvedic medicine. Several studies have reported the antioxidant, anti-inflammatory, and antimicrobial properties of pomegranate for treatment, especially in its juice, peel, and leaves (Dey et al., 2015a). The pomegranate contains polyphenolic compounds, called epigallocatechin-3-gallate (EGCG), which is known for its anti-inflammatory activity. Pomegranate juice and peel crude extract exhibited a MIC of 128 and 64 µg/mL towards DR-MTb. Meanwhile, a pure EGCG extract from pomegranate showed a higher potency of inhibiting DR-MTb with an MIC value of 32 µg/mL (Dey et al., 2015b). In addition, Rauf et al. (2019) examined that the flavonoid contents of pomegranate leaves inhibited the growth of MTb H37Rv at 100 ppm, in which yellow-colored cords were absent in the Middlebrook 7H9 culture medium. The cord factor is one of the cell wall components that are unique to mycobacterium and thus, it could be used as an indication of MTb growth.

***Hibiscus sabdariffa*.** *Hibiscus sabdariffa*, also known as roselle, is a flowering plant that is commonly found in Indonesia for traditional medicine. The petals of the roselle flower have been investigated to have

antispasmodic, anthelmintic, and antibacterial properties due to their phenolic content. The main active phenolic content of this plant is called anthocyanins which include the delphinidin-3-glucoside, sambubioside, and cyanidin-3-sambubioside (Brown et al., 2019). Furthermore, it has been studied that rosella calyx extracts showed bactericidal activity towards MTb. It was proven by the study of Djide et al. (2019) which stated that the MBCs of ethanol-extract roselle petals against MTb was 10 mg/mL. They also mentioned that 1 mg/mL of the extract could reduce the growth of HE-resistant strains up to 86%. Moreover, the MIC of the roselle calyx extract was found to be 10 mg/mL against MDR MTb, where water extract of roselle calyx has higher anthocyanins concentration compared to ethanol extract (Lena et al., 2019; Sartini et al., 2020).

Inhalation therapy

Drug repurposing is a technique to re-formulate well-established drugs for different delivery routes of administration. In the case of MTb treatment, the approved oral drug treatment would be designed for the delivery through pulmonary route (Mehta et al., 2018). One of the advantages of the utilization of inhalation therapy for managing MTb includes the efficiency to deliver a high concentration of the drugs towards the alveolar macrophages in the lungs which is the main site of the MTb cells. As such, this could reduce the frequency of dosing which, in turn, lowers the risk of systemic toxicity (Wei et al., 2020). A study conducted by Boisson et al. (2014) showed that a higher antimicrobial efficacy was observed using inhaled therapy through aerosol delivery compared to the normal drug administration route with lower dosage forms, particularly for those suffering from pulmonary infections. Furthermore, they examined that a lower systemic drug absorption level with a higher level of drug distribution in the lungs would have reduced the drug toxicity. Hence, from this evidence, inhalation therapy might be a potential alternative treatment for treating MTb, as well as reducing the risk of MDR- and XDR-MTbs.

CONCLUSION

With the still-increasing prevalence of TB in Indonesia, particularly due to the emergence of resistance, this burden remains moderately studied. Numerous resistance towards both first- and second-line antituberculosis drugs were observed and reported to occur in multiple regions of Indonesia through both genetic and environmental factors. The major risk factors contributing to the emergence and spread of TB in Indonesia include health conditions, environmental conditions, and socioeconomic status. Furthermore, one of the potential treatments, which are particularly feasible and plausible treatments that can be deployed in Indonesia, could be done by implementing short-course therapy to reduce the treatment period with the addition of fluoroquinolones in the primary treatment. There are also other alternative treatments for MTb treatments, namely the utilization of natural compounds found epidemically in or near Indonesia and the repurposing of existing drugs for the treatment of TB. These measures could be applied to diminish the risk of spreading DR-TB throughout Indonesia, as well as to prevent the current misuse of drug consumption in Indonesia that could lead to multiple drug resistance.

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