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The potential of several compounds in *Peperomia pellucida* as a solution to rifampicin resistance in tuberculosis disease

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Abstract

Background: Tuberculosis is a lung disease caused by *Mycobacterium tuberculosis*. In 2018, the incidence of tuberculosis in Indonesia was 1,017,290. The number of cases was accompanied by an increase in the number of resistances to first-line antibiotics (rifampicin) used due to patient non-compliance as well as the long duration of treatment. The increase in resistance around the world is always increasing every year by about 2%. Therefore, we need another alternative to existing plants in Indonesia that has the potential to be a solution to the problem and overcome resistance to these treatments.

Objective: This review was conducted to find out the potential of *Peperomia pellucida* as an antituberculosis drug that can be a solution to rifampicin resistance in tuberculosis disease.

Results: The results of the literature review showed that the *Peperomia pellucida* or suruhan plants have antibacterial potential against *Mycobacterium tuberculosis* because it contains a class of alkaloid compounds that function to inhibit deprenyl-phosphoryl-β-D-ribose-2 oxidase (an enzyme responsible for the biosynthesis of arabinogalactan in the cell walls of *Mycobacterium tuberculosis*), a flavonoid that has activity inhibition of fatty acid synthase II (FAS-II) enzymes, tannins that can precipitate proteins in *Mycobacterium tuberculosis,* and triterpenoids that have an activation mechanism of intracellular killing cascades in host cells during tuberculosis bacterial infection.

Conclusion: *Peperomia pellucida* or suruhan plants have the potential to be further investigated as a solution to overcome rifampicin resistance in tuberculosis disease.

Keywords: *Mycobacterium tuberculosis*, rifampicin resistance*, Peperomia pellucida*

1. Introduction

Tuberculosis, which is a lung disease caused by *Mycobacterium tuberculosis,* was reported to have a high incidence rate by RISKESDAS in 2018 (Dheda *et al.*, 2016). The incidence rate reached 0.42%, or a total of 1,017,290 (Tim Riskesdas, 2019). The management of tuberculosis necessitates a relatively extended duration, which is typically accompanied by diverse treatment-related adverse effects, leading to frequent discontinuation of treatment by patients during the recovery phase. This fact is exacerbated by the high incidence of Multi Drug-Resistant Tuberculosis (MDR-TB). MDR-TB, or *Mycobacterium tuberculosis* bacteria has resistance to the first-line anti-tuberculosis drugs such as rifampicin (Falzon *et al.*, 2015). The occurrence of MDR-TB is a result of non-compliance with drug use in patients and causes

patients to have to take second-line drugs, which of course have a longer duration of treatment. Therefore, it is necessary to find alternative compounds or new drugs as a solution to the occurrence of resistance by utilizing the potential of plants in Indonesia.

Peperomia pellucida Kunth. is a shrub-type plant with succulent leaves that have a distinctive aroma and grow in moist soil and wet rock crevices (De Oliveira *et al.*, 2017). *Peperomia pellucida* Kunth., also called suruhan, is a member of the *Piperaceae* family. This plant is an herbaceous plant that is widely found in South America and Asia. This plant species has a history of ethnomedicinal use, which includes the treatment of abdominal pain, abscesses, acne, ulcers, colic, fatigue, gout, headaches, kidney dysfunction, rheumatic pain, and to treat breast cancer, impotence, measles, anxiety disorders, and smallpox (Oloyede & Onocha, 2011). In addition, *Peperomia pellucida* Kunth. also has potential as an antibacterial for several types of pathogenic bacteria, including *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumonia*, *Salmonella typhi*, and *Pseudomonas aeruginosa* (Idris *et al.,* 2016).

Previous research stated that the essential oil of *Peperomia pellucida* Kunth. has an antimicrobial effect. *In vitro* testing using the bacterium *Bacillus subtilis* showed inhibition zones of 11.6 mm and 17.3 mm. This bactericidal ability may be influenced by the presence of various secondary metabolites contained in the *Piperaceae* family, including flavonoids and phytosterols such as acacetin, apigenin, isovitexin, pellucidatin, campesterol, and stigmasterol (Oloyede & Onocha, 2011). Besides that, *Peperomia pellucida* Kunth. also contains alkaloids, flavonoids, saponins, tannins, and triterpenoids, which are reported to have anti-tuberculosis activity (Truong *et al.*, 2011; Radji *et al.,* 2015; Mishra *et al.*, 2017; Okoh *et al.*, 2017; Kaczmarek, 2020; Rabaan *et al.*, 2022). This indicates *Peperomia pellucida* Kunth. has the potential to be utilized in the treatment of MDR-TB.

Several types of secondary metabolites can be used in the treatment of MDR-TB. The first is the piperine alkaloids found in plant extracts, which are known to induce the proliferation of T and B cells, increase Th-1 cytokines (IFN-γ and IL-2), and increase macrophage activation (Okoh *et al.*, 2017). Second, flavonoid compounds are known to help fight tuberculosis by removing hydroxyl radicals and superoxide anion radicals. This is because the increasing free radicals is related to the severity of the disease. Flavonoids also produce inhibitors of the fatty acid synthase II (FAS) enzyme (Idris *et al.*, 2016). Third, tannin compounds as anti-tuberculosis agent work by damaging bacterial cell membranes and can

induce the formation of tannin complexes with metal ions that can increase the toxicity of tannins. Moreover, tannins can create crenation of cell walls and membranes, which can interfere with cell permeability so that their growth can be inhibited and induce death (Chung *et al.*, 1998). The fourth component is triterpenoid, which also has anti-tuberculosis activity by activating intracellular killing cascades in host cells during infection with tuberculosis bacteria or by increasing the main pre-inflammatory cytokines, namely INF-γ and TNF-α (Wei *et al.*, 2011). The four secondary metabolites above indicated *Peperomia pellucida* Kunth. can be used as a potential anti-tuberculosis agent for the treatment of MDR-TB in the future.

2. TB drug resistance

Mycobacterium tuberculosis is a bacterium that causes the infectious disease tuberculosis. Most of these bacteria attack the lungs, but they can also attack other organs of the body. This disease can be transmitted through the air, but the bacteria that cause it can die in the presence of direct sunlight and can survive for several hours in a dark and humid place (Kemenkes RI, 2014). The government's efforts to overcome this disease include providing free treatment. In order to help people affected by the disease, the drugs are rifampin, ethambutol, pyrazinamide, streptomycin injection, and INH (Kemenkes RI, 2014). The structure of the anti-tuberculosis drug can be seen in Figure 1.

WHO updated the therapy standard for adult patients and stated that those who have drug-susceptibility pulmonary TB may have a 4-month regimen of isoniazid, rifapentine, moxifloxacin, and pyrazinamide (2HPMZ/2HPM) (WHO, 2022). Resistance is a condition when bacteria change while they resist antibiotics. Resistance has been reported to antibiotics against tuberculosis. This is a global crisis that poses the greatest threat to the health of the population. This problem occurs due to several factors, namely the use of antibiotics that are not appropriate, patients are not compliant, drugs are not available at health care facilities, patients cannot tolerate side effects, the treatment period is so long, and the patient feels he is already healthy. This can lead to antibiotic resistance, leading to increased morbidity, mortality, and treatment costs (Harris *et al.*, 2014; Mason *et al.*, 2018).

Updated information from WHO (2022) stated that there were cases named XDR-TB, which means patients resistant to any fluoroquinolone and at least one additional group A drug (such as levofloxacin or moxifloxacin, bedaquiline, and linezolid). Meanwhile, antituberculosis

drug resistance is one of the antibiotic resistances that is always increasing, with an average increase of 2% per year worldwide. Indonesia is included in the 27 countries with the highest levels of antituberculosis drug resistance in the world (World Health Organization, 2013). There were 442,000 TB cases in 2017, and an estimated 8,600-15,000 of them suffered from antituberculosis drug resistance, but the coverage that was treated only reached 27.36% (Kemenkes RI, 2021). Anti-TB drugs with poor quality DOTS (Directly Observed Treatment Short-course), patient non-adherence to treatment, patient age 40-60 years, poverty, disease duration of more than a year, previous treatment, and smoking have a close relationship with the incidence of tuberculosis resistance (Zhao *et al.*, 2012).

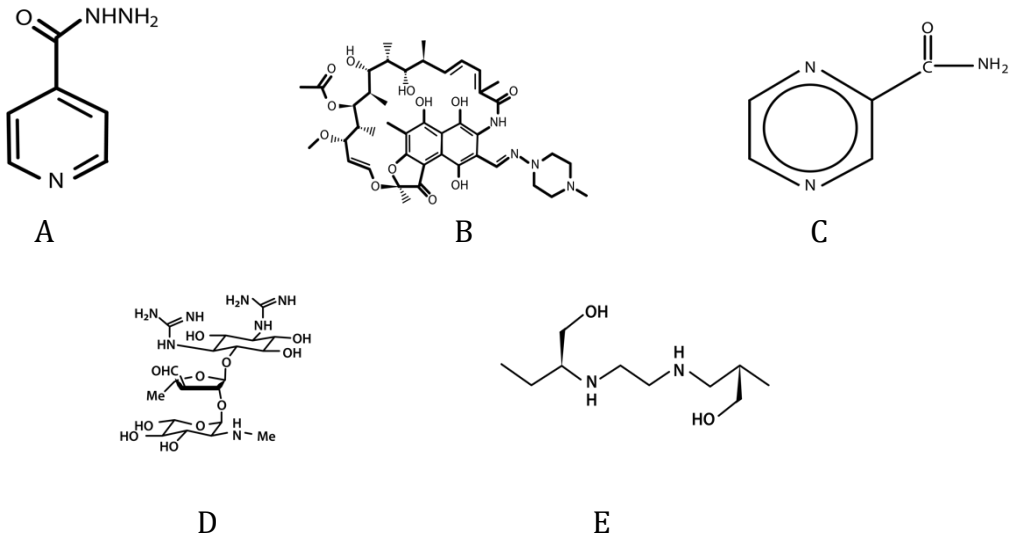


Figure 1. The structure of the antituberculosis drug
A. Isoniazid, B. Rifampicin, C. Pyrazinamide, D. Ethambutol, E. Streptomycin

According to the research to date, it shows resistance to antituberculosis drugs such as rifampicin (RIF), isoniazid (INH), ethambutol (ETB), pyrazinamide, and streptomycin (STR), as shown in Figure 2. These data show that rifampicin resistance is the highest compared to other anti-TB drugs, with a resistance percentage of 80%, while other antituberculosis drugs were 66.7% resistant to isoniazid, 78.7% resistant to pyrazinamide, 65.9% resistant to streptomycin, and 65.9% resistant to ethambutol (Asif *et al.*, 2014; Hu *et al.*, 2017; Tam *et al.*, 2017; Shrestha *et al.*, 2020). Rifampicin, the drug with the greatest resistance, is a serious problem at the global

level because there are about 558,000 new cases of rifampin-resistant TB worldwide (WHO, 2013).

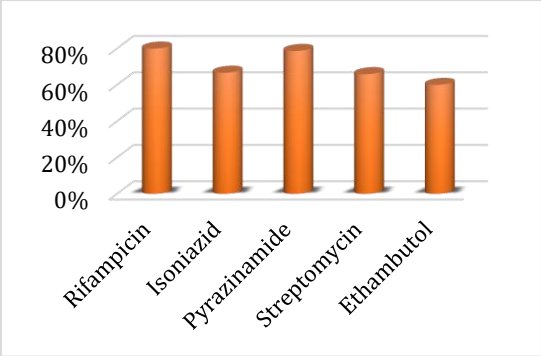


Figure 2. Percentage of resistance to anti-tuberculosis drugs

Resistance is also reported when antituberculosis drugs are given in combination, also known as MDR. The combination of antituberculosis drugs that are most potentially resistant when taken together are rifampicin and isoniazid, but resistance has also been reported with other combinations of first-line antituberculosis drugs (Figure 3) (Kemenkes RI, 2021). Among cases of RR TB (rifampicin resistance) worldwide, as many as 82% are cases of MDR TB. WHO estimates that there are 23,000 MDR/RR cases in Indonesia (WHO, 2013; Kemenkes RI, 2021).

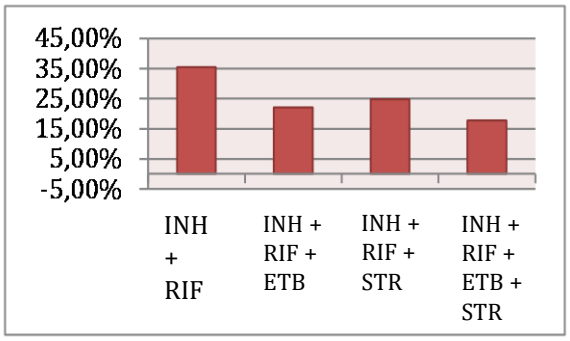


Figure 3. Percentage of MDR-TB against *Mycobacterium tuberculosis*

MDR-TB resistance data using 70 samples was reported by Nikmawati *et al*. (2018). The data shows that the percentage of INH and rifampicin is higher than that of other MDR-TB. This shows that treatment of MDR-TB cases needs to be considered, especially with rifampicin and isoniazid, so that there is no failure in therapy that can cause death (Nikmawati *et al.*, 2018). So far, no effective procedure for dealing with this resistance has been found. Clinicians still have difficulty determining therapeutic regimens for patients in the absence of antibiotics that can

overcome the problem of resistance (Bhatia & Narain, 2010). To be able to overcome antibiotic resistance, other solutions are needed that can be effective as alternatives to using plants that have the potential to treat tuberculosis.

3. Compounds that have potential as anti-tuberculosis

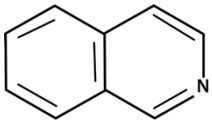
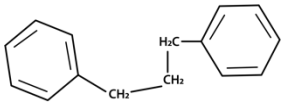
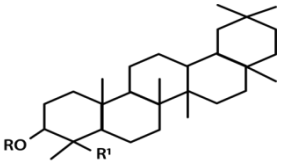
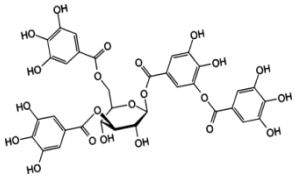
There are some mechanisms that are exposed as newly developed anti-tuberculosis drugs, including targeting DNA replication and protein synthesis, cell wall biosynthesis, energy metabolism, and proteolysis (Mittal *et al.*, 2023). Sutezolid, as one example of a drug that acts as a DNA replication and protein synthesis inhibitor, is now in phase II drug development (Tenero *et al.*, 2019). Meanwhile, some drugs are still in preclinical development, such as Capuramycin (SQ641), which acts as a peptidoglycan biosynthesis inhibitor, and TBAJ-587 (2nd generation diaryquinoline), which can inhibit ATP synthase (Tran *et al.*, 2017; TB Alliance, 2023). Some of the newly developed drugs are isolated from natural products; one example is cyclomarin A, which acts as a proteolysis inhibitor (Li *et al.*, 2010). Besides that, several compounds have also been reported to have anti-tuberculosis activity and can be seen in Table 1.

Alkaloids are natural chemical compounds that contain nitrogen atoms. Alkaloids are produced by a wide variety of organisms, including fungi, bacteria, plants, and animals, and are part of a group of natural products also called secondary metabolites (Khakia, 2012). Alkaloids stop deprenyl phosphoryl-β-D-ribose-2 oxidase from doing its job. This enzyme makes the cell wall of arabinogalactan *Mycobacterium tuberculosis* (Tiwari *et al.*, 2013). Alkaloids also have a role in inhibiting the mycolic acid cyclopropane synthase enzyme and the ketoacyl-ACP KasA synthase enzyme, which can cause death in *Mycobacterium tuberculosis* (Rollando, 2017). In addition, alkaloids can inhibit the cleavage of 32-single-stranded DNA in *Mycobacterium tuberculosis* (García *et al.*, 2018). Plants that contain alkaloids include suruhan (*Peperomia pellucida*), Javanese chili (*Piper chaba*), and *Ziziphus mauritiana* (Panseeta *et al.*, 2011; Mishra *et al.*, 2017).

Flavonoids consist of a large group of polyphenolic compounds that have a benzo-*γ*-pyron structure and are present in plants (Kumar & Pandey, 2007). The enzyme fatty acid synthase II (FAS II) is released by flavonoids, which stops the growth of *Mycobacterium tuberculosis* (Idris *et al.*, 2016). There are several plants and also microbiologists that contain

flavonoid compounds, including Suruhan plants (*Peperomia pellucida*), *Erythrina schliebenii*, and *Cnidoscolus chayamansa* (Angelina *et al.*, 2015; Nyandoro *et al.*, 2017; Pérez-González *et al.*, 2017).

Table 1. The mechanism for several compounds

No	Compound group	Mechanism	Basic structure	Reference
1	Alkaloid	Inhibits decaprenylphosphoryl-β-D-ribose 2' oxidase Inhibits mycolic acid cyclopropane synthase and -ketoacyl-ACP KasA synthase enzymes Inhibits cleavage of 32-single-stranded DNA		(Tiwari *et al.*, 2013; Rollando, 2017; García *et al.*, 2018)
2.	Flavonoid	Inhibits mycobacterial fatty acid synthase II (FAS-II)		(Idris *et al.*, 2016)
3.	Triterpenoid	Penetrates the cell membrane and changes its composition, thereby affecting the fluidity or plasticity of the membrane and affecting the signaling by many ligands. Activation of intracellular killing cascades in host cells during tuberculosis bacterial infection. In addition, the anti-tuberculosis effect also appears with an increase in the main pre-inflammatory cytokines, namely INF-γ and TNFα.		(López-García *et al.*, 2015; Netala *et al.*, 2015)
4	Tannin	Inhibits the DNA-topoisomerase enzyme, resulting in the inhibition of the replication process of *Mycobacterium tuberculosis* bacteria Makes imperfect formation of cell walls by targeting cell wall polypeptides so that this causes bacterial cells to become lysed due to osmotic or physical pressure so that bacterial cells will die		(Chung *et al.*, 1998)

Tannins are phenolic compounds that can react, and agglomerate proteins or other compounds containing amino acids and alkaloids and give a bitter and astringent taste. Tannins, which are divided into two groups, namely hydrolyzed and condensed tannins, can act as an antibacterial by precipitating proteins in *Mycobacterium tuberculosis* bacteria. Tannins are found in many types of plants. This compound has the function of protecting plants from predation by pests and herbivores (Julianto, 2019). Plants that contain tannins include starfruit leaves (*Averrhoa bilimbi* L.), which are known to have a Flavan-3,6,7,4',5'-pentaol structure, and

suruhan plants (*Peperomia pellucida* L.) with the ellagitannin group of tannins, which are known to have potential as anti-tuberculosis (Fri & Rantelino, 2018; Hidjrawan, 2018).

4. Conclusion

According to the previous description, it is proven that the suruhan plants contain four compounds that play a role in the inhibition of *Mycobacterium tuberculosis,* which include alkaloids, flavonoids, tannins, and triterpenoids. Therefore, suruhan plants have enormous potential as an alternative to MDR TB, although not much research has been done in this field. It is very promising for further research as an alternative to MDR-TB.

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References

Angelina M., Amelia P., Irsyad M., Meilawati L., & Hanafi M. (2015). Karakterisasi Ekstrak Etanol Herba Katumpangan Air (*Peperomia pellucida L . Kunth*) (Characterization of Ethanol Extract from Katumpangan Air Herbs (Peperomia). *Universitas Islam Negeri Jakarta*, 6(2), 53–61.

Asif S. A. Bin, Khan S. B., & Asiri A. M. (2014). Efficient Solar Photocatalyst Based On Cobalt Oxide/Iron Oxide Composite Nanofibers For The Detoxification of Organic Pollutants. *Nanoscale Research Letters*, 9(1), 1–9. https://doi.org/10.1186/1556-276X-9-510

Bhatia R. & Narain J. P. (2010). The Growing Challenge of Antimicrobial Resistance In The South-East Asia Region - Are We Losing The Battle?. *Indian Journal of Medical Research*, 132(11), 482–486. https://doi.org/10.4103/0971-5916.73313.

Chung KT, Wong TY, Wei CI, Huang YW, & Lin Y. (1998). Tannins and Human Health: A Review. *Critical Reviews in Food Science and Nutrition*, 38(6), 421–464. https://doi.org/10.1080/10408699891274273.

Dheda K., Barry C. E. & Maartens G. (2016). Tuberculosis. *The Lancet*, 387(10024), 1211–1226. https://doi.org/10.1016/S0140-6736(15)00151-8.

Falzon D, Mirzayev F, Wares F, Baena IG, Zignol M, Linh N, Weyer K, Jaramillo E, Floyd K, & Raviglione M. (2015). Multidrug-Resistant Tuberculosis Around The World: What Progress Has Been Made?. *European Respiratory Journal*, 45(1), 150–160. https://doi.org/10.1183/09031936.00101814.

Fri R. & Rantelino V. (2018). Bunga Rampai Saintika. *Fk Uki*, 7, 51–52.

García MT, Carreño D, Tirado-Vélez JM, Ferrándiz MJ, Rodrigues L, Gracia B, Amblar M, Ainsa JA, & de la Campa AG. (2018). Boldine-derived Alkaloids Inhibit The Activity of DNA Topoisomerase I and Growth of *Mycobacterium tuberculosis*. *Frontiers in Microbiology*, 9, 1–9. https://doi.org/10.3389/fmicb.2018.01659.

Harris AD, Pineles L, Belton B, Johnson JK, Shardell M, Loeb M, Newhouse R, Dembry L, Braun

B, Perencevich EN, Hall KK, Morgan DJ; Benefits of Universal Glove and Gown (BUGG) Investigators; Shahryar SK, Price CS, Gadbaw JJ, Drees M, Kett DH, Muñoz-Price LS, Jacob JT, Herwaldt LA, Sulis CA, Yokoe DS, Maragakis L, Lissauer ME, Zervos MJ, Warren DK, Carver RL, Anderson DJ, Calfee DP, Bowling JE, & Safdar N. (2014). Universal Glove and Gown Use and Acquisition of Antibiotic-Resistant Bacteria in the ICU', *Survey of Anesthesiology*, 58(4), 158–159. https://doi.org/10.1001/jama.2013.277815.

Hidjrawan, Yusi. (2018). Identifikasi Senyawa Tanin Pada Daun Belimbing Wuluh (*Averrhoa bilimbi L.*). *Jurusan Teknik Industri*, 4(2), 78–82.

Hu Y, Wu X, Luo J, Fu Y, Zhao L, Ma Y, Li Y, Liang Q, Shang Y, & Huang H. (2017). Detection of Pyrazinamide Resistance of *Mycobacterium tuberculosis* Using Nicotinamide As A Surrogate. *Clinical Microbiology and Infection*, 23(11), 835–838. https://doi.org/10.1016/j.cmi.2017.03.028.

Idris O., Olatunji B. & Madufor P. (2016). In vitro Antibacterial Activity of the Extracts of *Peperomia pellucida* (L). *British Microbiology Research Journal*, 11(4), 1–7. https://doi.org/10.9734/bmrj/2016/21421.

Julianto T. S. (2019). *Fitokimia Tinjauan Metabolit Sekunder dan Skrining Fitokimia*, *Journal of Chemical Information and Modeling*.

Kaczmarek B. (2020). Tannic Acid With Antiviral and antibacterial Activity As A Promising Component of Biomaterials-A Minireview. *Materials*, 13(14). https://doi.org/10.3390/ma13143224.

Kemenkes RI. (2014). Pedoman Nasional Pengendalian Tuberkulosis-Keputusan Menteri Kesehatan Republik Indonesia Nomor 364. *Kementerian Kesehatan Republik Indonesia*, (Pengendalian Tuberkulosis), 200.

Kemenkes RI. (2021). *TB MDR*. diakses di https://tbindonesia.or.id/pustaka-tbc/informasi/teknis/tb-mdr/ (pada: 17 February 2022).

Khakia T. I. (2012). *Alkaloids and Alkaloids Plants*. Turkey: Adana University Industry Joint Research Center.

Kumar S. & Pandey A. K. (2007). Chemistry and Biological Activities of Flavonoids: An Overview. *Farmacevtski Vestnik*, 58(4), 145–148. https://doi.org/10.2307/j.ctt1w0ddx8.35.

Li DH, Chung YS, Gloyd M, Joseph E, Ghirlando R, Wright GD, Cheng YQ, Maurizi MR, Guarné A, & Ortega J. (2010). Acyldepsipeptide Antibiotics Induce The Formation of A Structured Axial Channel In ClpP: A Model For The ClpX/ClpA-bound State of ClpP. *Chemistry and Biology*, 17(9), 959–969. https://doi.org/10.1016/j.chembiol.2010.07.008.

López-García S, Castañeda-Sanchez JI, Jiménez-Arellanes A, Domínguez-López L, Castro-Mussot ME, Hernández-Sanchéz J, & Luna-Herrera J. (2015). Macrophage Activation By Ursolic and Oleanolic Acids During Mycobacterial Infection. *Molecules*, 20(8), 14348–14364. https://doi.org/10.3390/molecules200814348.

Mason T, Trochez C, Thomas R, Babar M, Hesso I, & Kayyali R. (2018). Knowledge and Awareness of The General Public and Perception of Pharmacists About Antibiotic Resistance. *BMC Public Health*, 18(1), 1–10. https://doi.org/10.1186/s12889-018-5614-3.

Mishra SK, Tripathi G, Kishore N, Singh RK, Singh A, & Tiwari VK. (2017). Drug Development Against Tuberculosis: Impact of Alkaloids. *European Journal of Medicinal Chemistry*, 137, 504–544. https://doi.org/10.1016/j.ejmech.2017.06.005.

Mittal G, Bisht M, Pai VS, & Handu S. (2023). The Cost-Effectiveness of and Adherence to Disease-Modifying Antirheumatic Drug (DMARD) Therapy in Rheumatoid Arthritis

Patients in a Tertiary Care Teaching Hospital in Uttarakhand, India. *Cureus*, 15(2). https://doi.org/10.7759/cureus.34664.

Netala, V. R., Ghosh, S. B., Bobbu, P., Anitha, D., Tartte, V. (2015). Triterpenoid Saponins: A Review On Biosynthesis, Applications and Mechanism of Their Action. *International Journal of Pharmacy and Pharmaceutical Sciences*, 7(1), 24–28.

Nikmawati A., Windarwati W. & Hardjoeno, H. (2018). Resistensi *Mycobacterium tuberculosis* Terhadap Obat Anti Tuberkulosis. *Indonesian Journal of Clinical Pathology and Medical Laboratory*, 12(2), 58. https://doi.org/10.24293/ijcpml.v12i2.843.

Nyandoro SS, Munissi JJ, Kombo M, Mgina CA, Pan F, Gruhonjic A, Fitzpatrick P, Lu Y, Wang B, Rissanen K, & Erdélyi M. (2017). Flavonoids from *Erythrina schliebenii*. *Journal of Natural Products*, 80(2), 377–383. https://doi.org/10.1021/acs.jnatprod.6b00839.

Okoh SO, Iweriebor BC, Okoh OO, & Okoh AI. (2017). Bioactive Constituents, Radical Scavenging, and Antibacterial Properties of the Leaves and Stem Essential Oils from *Peperomia pellucida* (L.) *Kunth. Pharmacognosy Magazine*, 13(3), 392–400. https://doi.org/10.4103/pm.pm_106_17.

De Oliveira, J. C. S., da Camara, C. A. G., Neves, R. C. S., Botelho, P. S. (2017). Chemical Composition and Acaricidal Activity of Essential Oils From *Peperomia pellucida kunth*. Against Tetranychus Urticae. *Revista Virtual de Quimica*, 9(6), 2204–2213. https://doi.org/10.21577/1984-6835.20170130.

Oloyede G. & Onocha P. (2011). Phytochemical, Toxicity, Antimicrobial and Antioxidant Screening of Leaf Extracts of *Peperomia pellucida* from Nigeria', *Advances in Environmental Biology*, 5(12), 3700–3709.

Panseeta P, Lomchoey K, Prabpai S, Kongsaeree P, Suksamrarn A, Ruchirawat S, & Suksamrarn S. (2011). Antiplasmodial and Antimycobacterial Cyclopeptide Alkaloids From The Root of *Ziziphus mauritiana*, *Phytochemistry*, 72(9), 909–915. https://doi.org/10.1016/j.phytochem.2011.03.003.

Pérez-González MZ, Gutiérrez-Rebolledo GA, Yépez-Mulia L, Rojas-Tomé IS, Luna-Herrera J, Jiménez-Arellanes MA. (2017). Antiprotozoal, Antimycobacterial, and Anti-Inflammatory Evaluation of *Cnidoscolus chayamansa* (Mc Vaugh) Extract and The Isolated Compounds. *Biomedicine and Pharmacotherapy*, 89, 89–97. https://doi.org/10.1016/j.biopha.2017.02.021.

Rabaan AA, Alhumaid S, Albayat H, Alsaeed M, Alofi FS, Al-Howaidi MH, Turkistani SA, Alhajri SM, Alahmed HE, Alzahrani AB, Mashraqi MM, Alwarthan S, Alhajri M, Alshahrani FS, Almuthree SA, Alsubki RA, Abuzaid AA, Alfaresi M, Al Fares MA, & Mutair AA. (2022). Promising Antimycobacterial Activities of Flavonoids against *Mycobacterium* sp. Drug Targets: A Comprehensive Review. *Molecules*, 27(16), 1–15. https://doi.org/10.3390/molecules27165335.

Radji M., Kurniati M. & Kiranasari A. (2015). Comparative Antimycobacterial Activity of Some Indonesian Medicinal Plants Against Multi-Drug Resistant *Mycobacterium tuberculosis*, *Journal of Applied Pharmaceutical Science*, 5(1), 019–022. https://doi.org/10.7324/JAPS.2015.50104.

Rollando. (2017). Pendekatan Struktur Aktivitas dan Penambatan Molekul Senyawa 2-iminoethyl 2-(2-(1-hydroxypentan-2-yl) phenyl) acetate Hasil Isolasi Fungi Endofit Genus *Fusarium sp* pada Enzim β-ketoasil-ACP KasA Sintase. *Pharmaceutical Journal of Indonesia*, 3(2), 45–51.

Shrestha D, Maharjan B, Thida Oo NA, Isoda N, Nakajima C, & Suzuki Y. (2020). Molecular

Analysis of Streptomycin-Resistance Associating Genes in *Mycobacterium tuberculosis* Isolates from Nepal. *Tuberculosis*, 125, 101985. https://doi.org/10.1016/j.tube.2020.101985.

Tam KK, Leung KS, To SW, Siu GK, Lau TC, Shek VC, Tse CW, Wong SS, Ho PL, & Yam WC. (2017). Direct detection of Mycobacterium tuberculosis and drug resistance in respiratory specimen using Abbott Realtime MTB detection and RIF/INH resistance assay. *Diagnostic Microbiology and Infectious Disease*, 89(2), 118-124. https://doi.org/10.1016/j.diagmicrobio.2017.06.018.

TB Alliance. (2023). *Clinical Development and Marketed Products*. diakses di https://www.tballiance.org/portfolio (pada: 8 December 2023).

Tenero D, Derimanov G, Carlton A, Tonkyn J, Davies M, Cozens S, Gresham S, Gaudion A, Puri A, Muliaditan M, Rullas-Trincado J, Mendoza-Losana A, Skingsley A, & Barros-Aguirre D. (2019). First-Time-in-Human Study and Prediction of Early Bactericidal Activity for GSK3036656, a Potent Leucyl-tRNA Synthetase Inhibitor for Tuberculosis Treatment. *Antimicrobial Agents and Chemotherapy*, 63(8). https://doi.org/10.1128/AAC.00240-19.

Tim Riskesdas. (2019). *Laporan Di Provinsi Yogyakarta Riskesdas 2018*. Jakarta: Lembaga Penerbit Badan Penelitian dan Pengembangan Kesehatan (LPB).

Tiwari R, Moraski GC, Krchňák V, Miller PA, Colon-Martinez M, Herrero E, Oliver AG, & Miller MJ. (2013). Thiolates Chemically Induce Redox Activation of BTZ043 and Related Potent Nitroaromatic Anti-Tuberculosis Agents. *Journal of the American Chemical Society*, 135(9), 3539–3549. https://doi.org/10.1021/ja311058q.

Tran AT, Watson EE, Pujari V, Conroy T, Dowman LJ, Giltrap AM, Pang A, Wong WR, Linington RG, Mahapatra S, Saunders J, Charman SA, West NP, Bugg TD, Tod J, Dowson CG, Roper DI, Crick DC, Britton WJ, & Payne RJ. (2017). Sansanmycin Natural Product Analogues As Potent and selective Anti-Mycobacterials That Inhibit Lipid I Biosynthesis. *Nature Communications*, 8, 1–9. https://doi.org/10.1038/ncomms14414.

Truong NB, Pham CV, Doan HT, Nguyen HV, Nguyen CM, Nguyen HT, Zhang HJ, Fong HH, Franzblau SG, Soejarto DD, & Chau MV. (2011). Antituberculosis Cycloartane Triterpenoids From *Radermachera boniana*. *Journal of Natural Products*, 74(5), 1318–1322. https://doi.org/10.1021/np200022b.

Wei LS, Wee W, Fu Siong JY, & Syamsumir DF. (2011). Characterization of Anticancer, Antimicrobial, Antioxidant Properties and Chemical Compositions of *Peperomia pellucida* Leaf Extract. *Acta Medica Iranica*, 49(10), 670–674.

WHO. (2022). *WHO consolidated guidelines on tuberculosis.*, *WHO Press*.

WHO. (2013). *Global Tuberculosis Report*. France: World Health Organization.

Zhao P, Li XJ, Zhang SF, Wang XS, & Liu CY. (2012). Social Behaviour Risk Factors For Drug Resistant Tuberculosis In Mainland China: A Meta-Analysis. *Journal of International Medical Research*, 40(2), 436–445. https://doi.org/10.1177/147323001204000205.