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Potential of Herbal Plants Against Mycobacterium Tuberculosis Infection

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ABSTRACT

Introduction: Tuberculosis is an infectious disease caused by Mycobacterium tuberculosis. The leading cause of death worldwide is responsible for 1.5 million deaths each year. The cause of tuberculosis infection is the tubercle bacillus discovered by Robert Koch in 1882. The organism causing it is Mycobacterium tuberculosis.The spread of new cases is divided in several regions including Southeast Asia and Africa, which are the regions that have the biggest contribution to the prevalence of tuberculosis. So it takes pillars and components of TB control that cover all lines.

Method: This study aims to discuss the potential of herbal plants spread in Indonesia as herbal medicines that have the potential to treat tuberculosis infection. This study uses a literature study method which prepares the same as other research, but the sources and methods of data collection are by taking data from the library, reading, taking notes, and processing research materials.

Result: One of the components that are currently being developed in TB infection intervention methods is the development of herbal medicines for tuberculosis control. The herbal medicines used come from garlic (Allium sativum), Centellaasiatica, beluntas leaves, Hibiscus rosasinensis L., Boechmeria virgate (Forst) Guill, tobacco leaves, Morindacitrifolia L., Javanese wood bark, Spondiaspinnata (Lf)Kurz.

Conclusion: The herbal medicinal ingredients contain major chemicals such as alicin, ajoene, asiaticoside, asiatic acid, madecassic acid, and madecassoside, alkaloids, flavonoids, tannins, saponins, phenolic, and triterpenoids which have the ability to have a bactericidal effect to kill the Mycobacterium tuberculosis bacteria.

Keywords: *Herbal Plants; Mycobacterium Tuberculosis*

Introduction

Tuberculosis is a disease that causes high morbidity and mortality in the world. Although the number of deaths due to tuberculosis decreased by 22% between 2000–2015 according to WHO, tuberculosis was still ranked as the 10th highest cause of death in the world in 2016. Therefore, until now TB is still the top priority in the world and one of the goals in the SDGs (Kemenkes, 2018).

Tuberculosis is an infectious disease caused by Mycobacterium tuberculosis. The leading cause of death worldwide is responsible for 1.5 million deaths each year. The cause of tuberculosis infection is the tubercle bacillus discovered by Robert Koch in 1882. The organism causing it is Mycobacterium tuberculosis. The spread of new cases is divided in several regions including Southeast Asia and Africa, which are the regions that have the biggest contribution to the prevalence of tuberculosis. TB disease is also an infectious disease that can develop rapidly in people living in poverty, marginalized groups, and other vulnerable populations and is affected by population density. Indonesia is one of the most densely populated countries. The population density in Indonesia is 136.9 per 2km with the number of poor people in September 2017 at 10.12%. In 2017, the number of TB cases in Indonesia was 254 per 100,000 or 25.40 per 1 million population. Meanwhile, in the Minister of Health Regulation Number 67 of 2016 concerning Tuberculosis Control, the target of a national TB control program is elimination in 2035 and a TB-free Indonesia in 2050. Elimination of TB is the achievement of the number of TB cases 1 per 1,000,000 population (Pusdatin Kemenkes, 2018).

So it takes pillars and components of TB control that cover all lines. Both patient-centered TB integrated services and TB prevention efforts, clear policies and support systems as well as intensification of research and innovation such as the discovery, development, and rapid application of new TB control tools, intervention methods and strategies. One of the components that are currently being developed in TB infection intervention methods is the development of herbal medicines for tuberculosis control. Medically giving anti-tuberculosis (OAT) drugs is one of the therapies in curing TB disease. Tuberculosis treatment is divided into 2 phases, namely the intensive phase (2-3 months) and the follow-up phase of 4 or 7 months. The drug guide used consists of a combination of the main and additional drugs. The main types of drugs (line 1) used are

rifampin, isoniazid, pyrazinamide, streptomycin and ethambutol. This fixed dose combination consists of: 1). four anti-tuberculosis drugs in one tablet, namely rifampin 150 mg, isoniazid 75 mg, pyrazinamide 400 mg and ethambutol 275 mg, 2). three antituberculosis drugs in one tablet, namely rifampin 150 mg, isoniazid 75 mg and pyrazinamide 400 mg. However, if the administration of OAT is not carried out rationally, this can lead to new problems, namely the emergence of resistant pathogens (Tang & Johnston, 2017).

This increased rate of antibiotic resistance is one of the main obstacles to achieving successful treatment outcomes and control of microbial pathogenicity. Therefore, growing drug resistance and increasing consumer interest in drugs with minimal side effects compel us to develop new antimicrobial agents. Therefore, alternative medicine using herbal ingredients and plants is now widely used and believed to play a role in treating various diseases, including infectious diseases.This study aims to discuss the potential of herbal plants spread in Indonesia as herbal medicines that have the potential to treat tuberculosis infection.

Method

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Result

One of the components that are currently being developed in TB infection intervention methods is the development of herbal medicines for tuberculosis control. The herbal medicines used come from garlic (Allium sativum), Centellaasiatica, beluntas leaves, Hibiscus rosasinensis L., Boechmeria virgate (Forst) Guill, tobacco leaves, Morindacitrifolia L., Javanese wood bark, Spondiaspinnata (Lf) Kurz.

Discussion

Results for this studies are about the potential of herbal plants spread in Indonesia as herbal medicines that have the potential to treat tuberculosis infection:

a. Garlic (Allium sativum)

Indonesia has very high plant diversity. Various types of plants can be used as traditional medicines and are even more popular today. This is because traditional medicines are considered to have relatively less side effects than chemical drugs, and they are also more affordable. Several studies have been carried out at this time to prove the potential of herbal plants against Mycobacterium tuberculosis infection (Gautam et al., 2012). Among them is the potential for garlic (Allium sativum) as an alternative treatment for tuberculosis. Garlic (Allium sativum) has been known by the public as a traditional medicine. Garlic is an antibacterial agent against gram-positive and gram-negative bacteria. The main component in garlic that is believed to be responsible for the antibacterial and other therapeutic potential of garlic is the sulfur content in garlic. Among them are Diallylthiosulfinate (alicin) and Diallyl disulfide (ajoene). Alisin is formed from the main organosulfur compounds in garlic, namely gamma-glutamyl-s-allylcysteine and Sallyl-L-cysteins sulfoxides (alliin) through enzymatic reactions with the help of the alinase enzyme. As an antibacterial, Allicin works by changing the composition of proteins, lipids and polysaccharides in bacterial cell membranes (Hanif&Carolia, 2019).

In a joint study conducted by Aligarh University in India and the University of Cleveland in the US, Allicin has proven to be a potential agent against TB infection, through its strong anti-inflammatory effect on host mononuclear cells infected with Mycobacterium tuberculosis (MTB). Alisin increases the activity of the enzyme glutathione peroxidase thereby decreasing the production of reactive oxygen species and ultimately decreasing the production of inflammatory mediators. This phenomenon is reported to occur due to the cessation of transcription of the 85B antigen at the gene and protein levels. The 85B antigen is widely released by Mycobacterium tuberculosis and is responsible for the induction of TNF-α as an inflammatory mediator. The suppression of 85B expression by Allicin appears to be mediated through inhibition of glutathione. Researchers therefore suggest that the garlic compound should be tested in an in-vivo model to evaluate its therapeutic potential in the pathogenesis of tuberculosis. An

interesting in vitro test of the anti tuberculosis activity of Allium sativum was carried out in Nigeria in 2010, where the extract of Allium sativum was expressed as a disc diffusion method and compared with standard antibiotics. The anti-tuberculous activity of garlic on multi-drug resistant Mycobacterium was investigated among HIV-infected individuals and showed maximal activity against all isolates even at concentrations reduced by the zone of inhibition diameter (IZD).

b. Centellaasiatica

The next potential herbal plant is the Centellaasiatica plant which is a plant that grows throughout the year. The chemical ingredients contained in it include asiaticoside, thankuniside, isothankuniside, madecassoside, brahmoside, brahminoside, brahmic acid, madasiatic acid, meso-inositol, centellose, carotenoids, hyrdocotylin, vellarine, tannin and mineral salts such as potassium, sodium magnesium, calcium, iron, vellarine, and tannin. The main pharmacological effects of gotu kola are known to come from the content of triterpenoid compounds, namely asiaticoside, asiatic acid, madecassic acid, and madecassoside. Centellaasiatica has antiseptic properties against various bacteria. In the M. tuberculosis experiment, it was found that the effects of these compounds were similar to those of dihydrostreptomycin. While beluntas leaves also contain active substances that can inhibit bacterial growth. Plants that have similar benefits to Centellaasiatica are PlucheaindicaLess which contains essential oils consisting of betlephenol, kavikol, sesquiterpenes, hydroxycicvicol, cavibetol, estragol, eugenol, and carvacol (Amilah&Ajiningrum, 2015).

c. Plucheaindica Less

Plucheaindica Less also contains alkaloids, flavonoids, saponins, tannins, chlorogenic acids, sodium, aluminum, calcium, magnesium and phosphorus. Plucheaindica Less has bactericidal properties that can kill bacteria. Because of the potential of gotu kola plants and PlucheaindicaLess as bactericides, further research is needed to test the effectiveness of the inhibition of Centellaasiatica and Plucheaindica Less against the growth of M. tuberculosis and seek effective concentrations of Centellaasiatica and Plucheaindica Less extracts in inhibiting growth M.tuberculosis.

d. Hibiscus rosasinensis L.

Another potential herbal plant that has been researched is the ethanol extract of Hibiscus rosasinensis L. which can inhibit growth and kill the Mycobacterium

tuberculosis bacteria. Laboratory tests showed that Plucheaindica Less contains alkaloids, flavonoids, tannins, saponins, phenolics, and triterpenoids. In the observation of M. tuberculosis test bacteria, a 50% concentration of PlucheaindicaLess extract solution showed an inhibition of the growth of M. tuberculosis. This proves the antibacterial effect of PlucheaindicaLess extract against M. tuberculosis (Rendeng et al., 2019).

e. Boechmeria virgate (Forst) Guill

Another plant that is often used as a herbal medicine is the roman machete Boechmeria virgate (Forst) Guill. Boechmeria virgate (Forst) Guill is often used by the public as a herbal medicine to treat several diseases. The ability of Boechmeria virgate (Forst) Guill to heal boils, for example, is due to the presence of antibacterial substances which act as antimicrobial and antifungal. With these substances as antibacterial, it can suppress the growth of pathogenic bacteria by preventing infection so that healing can be accelerated. The results of Boechmeria virgate (Forst) Guill root extraction showed that the Boechmeria virgate (Forst) Guill root contained alkaloids, terpenoids, phenolics and flavonoids. In flavonoid compounds, quercetin compounds are reported to be able to inhibit Mycobacterium tuberculosis by inhibiting the ICL (Isocitratelysase) enzyme, where the ICL enzyme has an important role in the survival of Mycobacterium tuberculosis. In addition, the phenolic compounds in the roots of Boechmeria virgate (Forst) Guill have activity as an inhibitor of Mycobacterium tuberculosis by inhibiting the carbonic anhydrase enzyme in Mycobacterium tuberculosis (Ramadani, 2018).

f. Tobacco leaves

Among the tobacco leaves contain active ingredients, the active ingredients include the phenol group in the form of flavonoids, the alkaloid group in the form of nicotine 3, the saponin group in the form of steroids and also contains the essential oil group in the form of terpenoids. In general, tobacco leaves are used as raw material for making cigarettes and has become controversial because they can cause negative health impacts at the 56th World Health Assembly in 2003. The FCTC (Framework Convention on Tobacco Control) provides a reference on how important tobacco control is in cigarette production worldwide. However, from a medicinal perspective, tobacco leaves have a great opportunity to be used as an alternative ingredient for herbal medicine. It has been proven from several studies that tobacco leaves can be used as antibacterial or

antimicrobial for some bacteria. The identification results of the tobacco leaf extract compound (Nicotianatabacum L) have inhibitory activity against Mycobacterium tuberculosis because they contain the following compounds: 1) n-hexan extract contains flavonoid compounds, 2) ethyl acetate extract contains steroid and phenolic compounds, 3) ethanol extract 96% contains alkaloid, flavanoid, terpenoid, and phenolic compounds, 4) water extract contains alkaloids and phenolics with a concentration of 2000 ppm (Adyaksyah, 2018; Rusli et al., 2011).

g. Morindacitrifolia L. Leaves

Another study reported that several plant species that have anti-Mycobacterium tuberculosis activity are also abundant in Indonesia, one of which is Morindacitrifolia leaves. L. Morindacitrifolia L. is one type of medicinal plant. These medicinal plants contain active ingredients, including in the leaves of Morindacitrifolia, there is a scopoletin compound. Scopoletin functions to widen the narrowed blood vessels and smoothen blood vessels. In addition, scopoletin has also been shown to kill several types of bacteria. The concentration of Morindacitrifolia leaf extract can kill 89% of bacteria in the test tube, almost the same effect as the anti-tuberculosis drug, which has an inhibition rate of 97% at the same concentration. Morindacitrifolia leaves contain compounds, such as flavonoids, alkaloids and anthraquinones, essential oils, triterpenoids, phenols, tannins, and glycosides which function as antibacterials. In plants, flavonoids are the largest group of phenolic compounds in nature found in plants that have antimicrobial properties. In addition, flavonoids that are lipophilic can damage microbial membranes. It is possible that the antibacterial activity of flavonoids, which is one of the phenol groups, causes damage to the protein structure contained in the cytoplasm of bacteria (Kameswari et al., 2013).

Alkaloids have antibacterial properties. The suspected mechanism is by disrupting the peptidoglycan constituent components in bacterial cells, so that the cell wall layer is not formed completely and causes the cell's death. The cause of bacterial inhibition of Mycobacterium tuberculosis is due to the presence of compounds from noni leaves which have antibacterial activity. It is not known for sure which material has the greatest role in inhibiting the growth of Mycobacterium tuberculosis, the active ingredients can work alone or together in inhibiting the bacteria Mycobacterium tuberculosis. Results may differ because there is no standardization of extracts from

natural ingredients so that when fractions are prepared in different laboratories, different results will occur. Not only Morindacitrifolia leaves have compounds to reduce activity (Aryadi, 2014).

h. Javanese Wood Bark

Prawirohardjo in 2014 in Wahid 2017 in his research reported that the results of phytochemical screening reported that 70% ethanol extract and water from the bark of JawaKayu contained flavonoids, saponins, glycosides, phenols, and tannins. In plants, flavonoids as antimicrobials can form complexes with extracellular proteins and cell walls. In addition, flavonoids that are lipophilic can damage microbial membranes. Terpena or terpenoid has activity as antimicrobial. The mechanism is not fully known, but it is suspected that these compounds act on membrane damage by lipophilic compounds. The triterpenoid / steroid group is a compound that dissolves in non-polar solvents such as n-hexane, while flavonoids and tannins can dissolve in polar solvents such as methanol, ethanol, ethyl acetate or other polar solvents. Flavonoids are generally more easily dissolved in water or polar solvents because they have bonds with sugar groups (Markham, 1988).

Flavonoids are mainly water-soluble compounds and their active compounds can be extracted with 70% ethanol. Flavonoid compounds are a group of polyphenolic compounds that act as antimicrobials. This phenolic group is thought to be one of the components responsible for inhibiting the growth of the tested microbes. Although the components of phenolic compounds themselves are still relatively broad, it is not certain what specific compounds have microbial activity. The workings of phenolic compounds in killing microorganisms are by denaturing cell proteins, flavonoid compounds are thought to work mechanisms of denaturing bacterial cell proteins and irreparably damaging cell membranes. Steroids are organic compounds of sterol fat that are not hydrolyzed which can be produced from the reaction of decreasing terpenes or squalene. The mechanism of action of antibacterial steroid compounds is by damaging the bacterial cell membrane. The antimicrobial activity of phenolic compounds is by damaging the lipids in the plasma membrane of microorganisms, causing the contents of the cell to come out.

i. Spondiaspinnata (L.f.) Kurz

As an agricultural country, Indonesia is also rich in fruits and spices which have benefits in treating various diseases. One of them is the kedongdong fruit which is not only used for its fruit but also its leaves as herbal medicine which has been widely used in Indonesia. Spondiaspinnata (L.f.) Kurz has traditionally been used as a medicine for dysentery and cough. Laboratory test results showed that the leaf extract compound of Spondiaspinnata (L.f.) forest Kurz contained flavonoids, steroids and triterpenoids. The flavonoid and triterpenoid content of the leaf extract of Spondiaspinnata (L.f.) Kurz forest contributes to its activity as an anti-tuberculosis agent. Flavonoids are able to inhibit mycolic acid synthesis by inhibiting the activity of the enzyme βhydroxyacyl-ACP dehydratase and proteasome M.tuberculosis. While triterpenoids can result in bacterial cell wall lysis (Gitari et al., 2017; Uddin et al., 2016).

Flavonoids from the leaf extract of Spondiaspinnata (L.f.) forest Kurz are also able to bind to HadB so that it will inhibit the β-hydroxyacyl-ACP dehydratase enzyme and can inhibit M. tuberculosis proteasomes. In addition, triterpenoid content can cause cell wall lysis of M. tuberculosis. It is hoped that this modality can reduce morbidity and mortality caused by infection with M. tuberculosis, both resistant and sensitive, so that it can be a management of TB and MDR-TB in the future (Dong et al., 2015).

Conclusion

Several herbal plants that have been described above report that there are similarities in the content of compounds such as alkaloids, flavonoids, tannins, saponins, phenolics, and triterpenoids which are useful for bactericides and inhibit the growth of Mycobacterium tuberculosis. This provides opportunities for researchers as well as individuals in the health sector to develop anti-tuberculosis drugs.

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