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REVIEW ARTICLE

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THERAPEUTIC EFFECTS OF HERBS ON MYCOBACTERIUM TUBERCULOSIS: A SYSTEMATIC REVIEW

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ABSTRACT

Mycobacterium tuberculosis is one of the agents responsible for tuberculosis in human and animals. This bacterium damages the lungs, central nervous system, lymphatic system, and blood circulating system. The aim of this study was to provide information about the herbs which are effective on *Mycobacterium tuberculosis*. In order to gather the information, keywords of "extract", "plants" and "*Mycobacterium tuberculosis*" were searched in scientific databases including ScienceDirect, Pubmed, Scopus, Medline, SID, Iranmedex, and Medlib. In vivo and in vitro studies were included. 380 articles were collected in general. After exclusion of non-relevant and repetitive articles, 24 herbs were studied in this review. Effective herbs have shown their antibacterial effects through mechanisms such as increasing inflammatory cytokines like IFN- γ , IL-12, regulating the balance between Th1/Th2 and leading this ratio toward Th1, disturbing transcription from SP1 gene in promoter region of TACO regulatory gene and decreasing its expression, disturbing the ion balance in bacterial membrane and forming pores in the two-plants could provide scientists who work on medicine and treatment with useful information.

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INTRODUCTION

Mycobacterium tuberculosis is a gram positive, non spore-forming bacterium which is among tuberculosis disease agents both in human and animals (1). This bacterium damages the lungs, central nervous system, lymphatic system, and blood circulating system. Infection with this bacterium depends on several factors including host genetic characteristics, environmental factors, and genetic polymorphisms (2). This bacterium is currently more common in patients with immune system deficiency especially in developing countries. According to the statistics of world health organization (WHO), about one third of world population are infected with this bacterium, and approximately half to one million die yearly due to infection with this bacterium and this number may even reach nine million people a year (3). A significant decrease in people mortality as a result of correct diagnosis and early treatment was seen during the years 2000 to 2013. However the infection rate and mortality due to *Mycobacterium tuberculosis* are still high (4).

Tuberculosis (TB) signs depend on the part of the body that is infected with the bacterium. In pulmonary cases of TB, signs including angina, chronic coughing, weight loss, fever, and night sweating might be observed (5). Men get affected more than women and the infection ratio for women to men is 47 to 67%. Infection with this bacterium is correlated with several factors such as poverty, and a high rate of infection is seen in poor parts of the society especially among people with low income level, those who live in crowded regions and people with low literacy. Malnutrition, lack of proper air ventilation, hygienic facilities deficiency, and life conditions all increase the risk for TB infection (6). TB resistance to several drugs is a warning and threatening factor for controlling this disease throughout the world (7). Disease condition would be complicated in patients who are simultaneously affected by the two infections of immunodeficiency virus (HIV) and multidrug-resistant tuberculosis. Immune system weakening in patients affected by HIV may lead into reactivation of TB which existed as latent before, and also getting affected by TB is common in people who acquire HIV. Multidrug-resistant tuberculosis accompanied by HIV has a high mortality and treating those patients affected by both infections is a great challenge (8). The resistance of this bacterium results from genetic alterations and mutation in bacterial genes when antibiotics are administered. Mutation occurrence in those genes which are the targets for antibiotic and

bacterial resistance due to human mistakes in irrational antibiotic administration are among other challenges for fighting against this disease (9).

Antibiotics used for treating people infected with *Mycobacterium tuberculosis* in patients with latent and active tuberculosis include Isoniazid, Rifampin, Pyrazinamide, Ethambutol, Streptomycin, Amikacin and Kanamycin, Capreomycin, Quinolone and Ethionamide (9). New changes in *Mycobacterium tuberculosis* resistance to antibiotics have recently been observed. *Mycobacterium tuberculosis* has widely become resistant against Fluoroquinolones, and three intramuscular antibiotics including Kanamycin, Amikacin, and Capreomycin, in addition to Isoniazid and Rifampin. This wide resistance leads into a serious concerns for fighting TB in future which requires discovery and diagnosis of drug-resistance mutations and development of novel drugs against this bacterium (10).

Insufficient drug, excessive use of Isoniazid and Rifampin, and the consequent multidrug-resistance of TB bacterium are among the most important limitations in treating patients with TB. Control and treatment of patients with multidrug-resistance, supporting these patients and finding suitable drugs are difficult. TB patients get cured by Isoniazid, Rifampin, Pyrazinamide, and Ethambutol in two months and by Pyrazinamide, and Ethambutol in four months, while patients resistant to multiple drugs face destructive side effects after two years of chemotherapy (11, 12).

Regarding the multidrug-resistance of *Mycobacterium tuberculosis* and active ant latent infections in people, and sometimes its accompaniment with HIV infection, a need for discovery and production of novel effective drugs against TB is being felt. In this regards, isolation of herbs effective for treatment of patients affected by TB can be important for replacing the antibiotics. Actually medicinal plants are valuable resources for discovering new drugs. Many research studies have shown the positive effects of herbs and medicinal plants on various disorders and diseases such as inflammatory diseases (13, 14), cancers (15-17), liver diseases (18, 19), diabetes (20-24), neurological and learning disorders (25, 26). The aim of this study was to provide information about natural and herbal compounds effective on *Mycobacterium tuberculosis*.

For conduct this study, 380 articles were collected in general in the primary search based on keywords. In this stage, the data of articles were extracted and evaluated in a checklist based on inclusion criteria. Investigation of the effect of one or more plants or a herbal compound on *Mycobacterium tuberculosis*

was among the inclusion criteria. Both the in vivo and in vitro studies entered the study. Evaluation of alga, fungi or non-herbal compounds was the exclusion criterion. In addition, if a bacterium from another species had been studied, the article was excluded. After exclusion of non-relevant and repetitive articles and those studies which were not available, 24 plants were finally included in the current study.

Phytotherapy for *Mycobacterium tuberculosis*

24 plants effective on *Mycobacterium tuberculosis* were evaluated in this study. The articles had been published during 1999 until 2016. The effective plants included *Citrullus colocynthis*, *Alnus incana*, *Mentha spicata*, *Aralia nudicaulis*, *Juniperus communis*, *Heracleum maximum*, *Premna odorata*, *Mollugo verticillata*, *Ajuga remota*, *Centella asiatica*, *Clavija prostrata*, *Dioscorea bulbifera*, *Allium ursinum*, *Lantana camara*, *Croton tonkinensis*, *Flourensia cernua*, *Euodia rutaecarpa*, *Hypericum olympicum*, *Dodonaea angustifolia*, *Allium ascalonicum*, *Prunella vulgaris*, *Camellia sinensis*, *Hypericum perforatum*, and *Eucalyptus camaldulensis*.

Citrullus colocynthis

This small plant with climbing stem, trailing glandular plant and smooth, spherical fruit with green spots belongs to Cucurbitaceae family. Its ripe fruit is yellow and too bitter. This plant grows in Africa and Asia especially India and hot regions. Indians use it for treating Tuberculosis and respiratory discomforts and diabetic patients. This plant has different compounds effective on Tuberculosis including colocynthoside, phytosterols, pectin, albumin, ursolic acid, and cucurbitacin (27). In the study performed by Mehta et al, evaluation of several extracts from different aerial parts of the plant with the dose of 1000 µg/mL showed that extract of this plant generally does not have an effect on *Mycobacterium tuberculosis* with multidrug-resistance, but the methanolic extract of its fruit in doses of 62.5 µg/mL to 1000 µg/mL influences multidrug-resistant tuberculosis and the lowest inhibitory dose for methanolic extract of the fruit was reported as 62.5 µg/mL (28).

Alnus incana

This species grows as a deciduous tree in north-east of America and is used for treating skin lesions, mouth and gingival disease, and syphilis. Researches demonstrate that this plant inhibits formation of glucose-6-phosphate in hepatic cells. Hence, it could be also useful for diabetic patients' management. Extracts of

leaf, skin, and seed of this tree have antibacterial, antioxidant, and cytotoxic effects. Alcoholic extract of this plant strongly inhibits intracellular fat accumulation. The alcoholic extract contains arginine and diarylheptanoid compounds, to which the anti-fat characteristics of the plant are attributed. Other compounds such as betulin and betulinic acid are also found in this plant (29). Feng et al, with the aim of studying the effect of *Alnus incana* tree skin compounds and using these compounds on TB, isolated lupane triterpene compounds including betulin, betulinic acid, betulonolupenone from Alder tree skin and evaluated their effects on TB. Just betulin affected TB among these four isolated compounds (30).

Mentha spicata

This herbal species belongs to Lamiaceae family and *Mentha* genus. This plant is among those that produce flowers, and is a firm and stable plant which sometimes reaches one meter. It is cultured in most regions of the world (31). This herbaceous species with penetrating, cool odor and flavor, is widely utilized in pharmaceutical, food, confectionery and beauty productions industries (32, 33). It is also stomach strengthening, analgesic, anti-convulsion, and relaxer (34). Mint oil contains antifungal, antimicrobial, anti-inflammatory, and anti-tumor properties (35). Mint could be a suitable replacement for anti-androgen agents in treating abnormal hair growth (36). A previous study investigated the effects of aquatic, methanol, acetone, and hexane extracts of several plants including mint on *Mycobacterium tuberculosis* sensitive to drug and resistant to drug such as Rifampin, Isoniazid, Ethambutol, Streptomycin, and Pyrazinamide. The results indicated that herbal extract of mint has inhibitory effect in concentrations higher than 200 µg/mL (35).

Aralia nudicaulis

This species is a member of Araliaceae family which is known as Sarsaparilla wild. It is seen as rhizome and grows abundantly in shadowed jungles of America and Canada (37). Chewed or stewed rhizome is used for treating stomachache, chronic thoracic diseases, stomach disease, hepatic problems and sore throat. Its ptisan is also consumed in children gingival disease, pneumonia, mothers with low milk and venereal disease (38). This herbal species has anti-inflammatory cerebroside and diterpene or triterpene saponin compounds which act against cancerous cells. Falcarinol in this plant has anti-*Mycobacterium tuberculosis* property and this herb is also used for tuberculosis

treatment in traditional medicine. Haoxin Li et al, performed a study with the aim of isolating and applying medical compounds from *Aralia nudicaulis* rhizome for *Mycobacterium tuberculosis*. They isolated faltarinol and panax, and the minimum inhibitory concentration of these two compounds was determined as 25.6 μm and 30 μm , respectively (39).

Juniperus communis

This arboreal species is shrub-shape, and has needle-like leaves which are resistant to cold and dryness. It grows in cold regions of the world and also in northern part of Iran. This plant causes snake, scorpion, and insects to scape (33, 40). Biological and pharmacological properties of this plant are numerous. Its essence has terpinene and shows pharmacological effects such as anti-blow, antibacterial characteristics, treating maldigestion and reducing blood pressure and is also applied in beauty and hygiene industry. Its most important chemical compound is α -pinene and limonene (41). Its branch and stem are used to treat blood pressure, its root is applied for treating tuberculosis, and the gum could be used for wound repair. This plant contains ligandoxypodophyllo toxin and indices that affect tuberculosis bacterial infection (28, 42). Carpenter et al. performed a study in order to isolate and diagnose the effects of aerial parts of cedar tree on TB. They extracted isocasperic diterpenes, common acids (cis and trans) and deoxypodophyllo toxin, and the minimum inhibitory concentration for these compounds was determined as 78 μm , 31 μm , and 1004 μm , respectively. Isocasperic diterpenes and common acids had a favorable effect on TB, but deoxypodophyllo toxin compounds had a weak impact on TB (43).

Heracleum maximum

This species is of Apiaceae family and grows in Northern parts of America. Native people use it for eating and providing fiber and preparing color. It is also utilized for infectious and respiratory diseases. Aquatic extract of this plant has anti-*Mycobacterium tuberculosis* activity and is not toxic. It has several compounds effective against tuberculosis including sphondin, bergapten, angelicin, pimpinellin and some others. Moreover, it stimulates immune system through producing interleukin-6. The methanolic mixture of this plant also has anti-fungal and anti-tuberculosis activity (43, 44). O'Neill et al. conducted experiments with the aim of isolating and diagnosing the compounds of *Heracleum maximum* root and evaluating its influence on TB bacterium. It was found out that faltarinciol and 6-isopentenylxyisobergapten had the most effect on this

bacterium and the minimum inhibitory dose of these two compounds for TB was proposed as 27 μm and 167 μm , respectively (44).

Premna odorata

This plant is as a small shrub from Verbenaceae family. It exists in Asia especially in Philippines and grows in jungles which have limestone, and the natives of this country use it for wound lavage, vaginal lavage, and tuberculosis treatment (45). Leaves of this plant contain aglycone flavonoids, diosmetin, and oxetane compounds and also cause reduction in dopamine in cerebral neuron cells and prevention of lung carcinoma. Ptisan of this plant is utilized to treat tuberculosis and also for headaches, stomachache, and reduction of sputum and coughs. Compounds present in this plant such as heneicosylformate-1 affect TB (46). Lirio et al. performed a research in order to investigate the effects of *Premna odorata* against *Mycobacterium*. By evaluating the effect of methanolic, ethanol acetate, and N-butanol extracts of this plant on TB bacterium, they demonstrated that most of the compounds of this plant have weak influence on TB. But, compounds such as heneicosyl formate, β -sterol, and diosmetin had the most impact rate by minimum inhibitory dose of 54 mg/mL (46).

Mollugo verticillata

This plant is classified in Molluginaceae family, and is a perennial plant and weed (47) that grows as creeper in warm and damp regions in United States, and has anti-fungal, anti-inflammatory, and anti-tumor properties, and also fortifies immune system (48). Triterpenes and flavonoids in this plant have remarkable effects on immune system, and these compounds could be stimulating factors for nitrous oxide in immune system cells including macrophages (48). In the study performed by Ferreira et al, impact of *Mollugo verticillata* on immune system in mice treated by bovine tuberculosis (BCG) was investigated, and it was found out that ethanolic extract of this plant with quercetin and triterpenoid glucoside compounds caused stimulation of immune system and elevated release of nitric oxide in mouse body (47, 48).

Ajuga reptans

This plant is classified in Lamiaceae family and its height reaches 5-50 cm and the blue, purple, and yellow leaves of this beautiful plant are opposed. The petals of this plant are continuous in the upper and lower edges. It is used to control the insects in traditional medicine (49). This plant grows as weed in Africa and Asia and is used for fever recovery, contamination

elimination, and treatment of malaria and Mycobacteriosis (50). It contains neoclerodan diterpenoids, phytoecdysteroids, flavonolglycoside, iridoidglycosides, and ergosterol-5,8-endoperoxide. In the study conducted by Cocquyt et al, impact of *Ajuga remota* methanolic extract on *Mycobacterium* was investigated and it was determined that this plant has anti-mycobacterial activity, and ergosterol-5,8-endoperoxide with the minimum inhibitory dose of 1 μm exerts the highest effect on *Mycobacterium tuberculosis* (49).

Centella asiatica

This species which belongs to Apiaceae family is grassy, perennial, climbing, rooting, villous, and semiaquatic. It grows in humid margins, and has climbing and creeping stem with leaves which are arranged as clumps (51, 52). It is used in traditional medicine in countries of eastern Asia such as India, China, and Malaysia; its extract and ointment are utilized for treating syphilis, leprosy, rheumatism, and epilepsy. It is also used as lotion, and is applied for treating skin lesions, reducing skin inflammation, improving insomnia, and repairing peptic ulcers and treating blood pressure (53-55). This plant contains steroids, volatile and flavonoids, alkaloids, centellasaponin and madecassic acid, phenolic acid, s caffeoyl ester, and asiaticoside compounds (56). Radji et al. evaluated the impact of *Centella asiatica* aquatic extract on *Mycobacterium tuberculosis* H37Rv and the multidrug-resistant type. The inhibitory ratio of this herb on the two bacterial species was reported as 70% and 50%, respectively. Furthermore, effective compounds of flavonoids, alkaloids, saponin, tannin, and glycosides were distinguished (57).

Clavija procera

This herbal species grows as small wooden tree in Africa and also Peru and Australia (58, 59). Native people use it to repair the wound resulting from *Leishmania* infection (43). It contains the important compounds such as triterpenes. The ethanolic extract of this tree in combination with orinane terpenoids has a good activity against multidrug-resistant *Mycobacterium tuberculosis* (60). In the study of Rojas et al, Aegicerin compound obtained from *Clavija procera* had an acceptable influence on species of *Mycobacterium tuberculosis* H37Rv and the multidrug-resistant type (61).

Dioscorea bulbifera

This medical herb is from Dioscoreaceae family, and is a weed with climbing stem. Additionally, it is a perennial plant that grows as shrubs. The leaves are usually simple and alternate, but sometimes they are compound and their length reaches 1-8 cm (62). It grows in hot tropical regions of Africa like Cameroon (63). It has medical properties for treating microbial infections and is also a traditional therapy for conjunctiva, dysentery, sore throat, goiter, wound infection, pimple, and abscess (64). Its extract and bafoudiosbulbins A and B compounds affect *Salmonella* infection and has different compounds including steroids, phenanthrene, 2,7-dihydroxy-4-methoxyphenanthrene, and flavonoids. Terpenoids in this herb show antibacterial activity (65). In the previous studies the effects of *Dioscorea bulbifera* extract and compounds on *Mycobacterium* isolates were investigated. They found out that the minimum inhibitory dose of methanolic extract and its components on *Mycobacterium tuberculosis* MTCS2 is 16 $\mu\text{g/ml}$, and the diterpenoids bafoudiosbulbins component has the lowest inhibitory dose (8 $\mu\text{g/mL}$) on *Mycobacterium smegmatis* and the isolates of ATCC and MTCS2 (65, 66).

Allium ursinum

Mountain garlic from the Liliaceae family has long roots (67), narrow and long gland that is about 1-6 cm. It is covered by thin fiber layers. The aerial part of this plant has a triangular and straight stem with umbel inflorescence. At the flowering time, the flower consists of 6 segments (68, 69) and the leaves are soft and plane with short tips and it produces black grains (70, 71). It grows in Asia and Europe (68). This plant contains numerous compounds including sulphuric, phenolics, glycoside steroids, lectin, sugars and polypeptides, palmitic acid, linoleic acid, steric acid, meristic acid, and oleic acid. This plant could be used for controlling and preventing cardiovascular diseases, respiratory diseases, bronchitis, and wound repair. It also stimulates appetite and reduces fever (69). Yirga et al. performed a research with the purpose of evaluating medical herbs. They demonstrated that fruit and leaf of mountain garlic has medical properties and could be administered for patients with bronchitis. Its chopped fruit is also used as mixture with honey and butter for treating *Mycobacterium tuberculosis* infection (72).

Shrub verbenas (Lantana camara)

This plant belongs to Verbenaceae family and grows in tropical regions especially in Africa, America, India, Mexico, and Brazil (73). This plant has small triangular stem with cluster inflorescence, and its flower

has four petals colored red, pink, and orange (74). Its leaves are arranged oppositely, and are simple, rectangular and elliptically. Its fruit is strawberry-like with green color and dark purple when ripe. Its medical usage is for treating intestinal discomforts, cardiac diseases, biliary fever, asthma, eczema, wound infection, rheumatism patients, malaria infection, and lockjaw (75, 76). It contains folic compounds, flavonoids, alkaloids, glucosides, phenol etanoid, saponins, steroids, triterpene and tannin (77, 78). In the study performed by Kirimuhuzya et al. in order to investigate the antimycobacterial activity of methanolic extract of shrub verbenas, it was identified that the minimum inhibitory dose for H37R isolate was 20 µm/ml and for Rifampin-resistant isolates and the sensitive isolate was 15 µm/mL (79).

Croton tonkinensis

This herbal species belongs to Euphorbiaceae family and is a small plant with 1-2 cm height. It grows in hot tropical regions especially in Vietnam, and is used for stomach discomfort, impetigo, and ulcers in traditional medicine (80, 81), and its dried leaves are utilized for abscess, pimple, maldigestion, psoriasis infections, leprosy, and vaginitis (82). Herbal extract of this species contains several compounds such as steroids, alkaloids, terpenoids especially it is rich in diterpenoids. Diterpenoids of this extract have anti-inflammatory, anti-tumor, and antioxidant properties (83). Extract of this plant has labdane, clerodane, and kaurane. Besides, it contains some other compounds like ent-kauran and grayanane. This plant has crotonkinensin A and B compounds that have inhibitory activity against *Mycobacterium tuberculosis* (83). Thuong et al. studied the effect of diterpenoid compounds on the three *Mycobacterium* isolates. They indicated that the extract and mixtures of this herb had minimum inhibitory doses of 1.56, 3.12, and 12.5 µg/ml for H37Ra, H37Rv, and other resistant MB isolates, respectively (84).

Flourensia cernua

This plant is from Asteraceae family. It is a flowered plant with alternate leaves and elliptical shape, and has villous akene fruit. It is seen as a small shrub and its height reaches three meters sometimes. This plant grows in Arizona desert and Mexico. It has antifungal and antibacterial activity, and has toxic effects. It contains polyphenolic compounds, lactones, benzofuran, hydrofluorensic, tetracosane, pentacosane, triacontane, and benzopyruvate (85, 86). Hexane extract of this plant has *Mycobactericidal* activity, and also has some compounds which can act against multidrug-resistant

Mycobacterium tuberculosis (87). Molina-Salinas et al. studied the bactericidal activity of hexane and acetone extracts of *Flourensia cernua* plant. The hexane extract had minimum inhibitory doses of 25 µg/ml and 50 µg/ml for sensitive and resistant isolates of *Mycobacterium tuberculosis*, respectively. The acetone extract showed the minimum inhibitory dose of 100 µg/mL for active CIBIN:UMF:15:99 isolate (87).

Euodia rutaecarpa

This herbal tree belongs to Rutaceae family (88). It is a green deciduous tree, the blossoms of which are cluster, the leaves are shining, and its ripe fruit is brown (89, 90). This tree grows in eastern-south of Asia, in Korea, and China. The unripe fruit of this herb contains quinolone alkaloid, and quinazolinone alkaloids including rutaecarpin and evodiamin (90-92). In traditional medicine it has been used for headache, stomachache, dysentery, and high blood pressure (92). Hochfellner et al. found that evodiamine compound with the minimum inhibitory dose of 10 µg had the highest activity against this bacterium (93).

Hypericum olympicum

This herb is a deciduous, prosperous shrub that belongs to Hypericaceae family, and has a variable length of about 10 cm to 12 m. the leaves are opposite and elliptical, and the color of flowers is pale to dark yellow. The dry fruit with tiny grains gets spread while split (94, 95). This plant does not have a vast environment and grows in dry and stony lands of Balkan region (96). Li Feng and colleagues showed in their study that this plant contains acyl fluo glycerol and elemicin compounds which have anti-gram positive and anti-*Mycobacterium tuberculosis* activity. This herb also possesses olympicin A that inhibits the enzyme topoisomerase-4 (the enzyme that enters the reaction after replication of bacterial DNA and separates the two skewed DNA strands) (30).

Dodonaea angustifolia

This medical herb is a shrub from Sapindaceae family, and its leaves are green, shining, simple elliptical, and narrow. It grows in semidry jungles of Southern Africa, Arabic countries, and Australia. Its skin, leaf, and root are all used in traditional medicine for treating diarrhea, fever and pain (97, 98). Chemical compounds such as fat-soluble flavonoid destroy the bacterium by penetrating into the membrane. The previous studies demonstrated that the ethanolic extract of *Dodonaea angustifolia* inhibits *Mycobacterium*

tuberculosis with the minimum inhibitory concentration of 5 µg/ml (99, 100).

Allium ascalonicum

This species is from *Allium* genus and Liliaceae family (101). Its leaves are long and narrow, the flowers are red-purple, and the inflorescence is simple clustered. It is a bulbous plant that grows in most parts of Western Asia and Iran (102). This species has a positive effect on hematological indices, and also is a stomach stimulator with antifungal and anti-parasitic activity. Chemical compounds such as organosulphures and polyphenols are present in its alcoholic-aquatic extract (103). Igboke et al. investigated the sensitivity and bactericidal activity of shallot plant ethanolic extract on *Mycobacteria* and other bacteria in the concentration range of 25 to 100 mg/ml. The minimum inhibitory concentration for the three *Mycobacterial* species of *phlei* ATCC 19240, *smegmatis* ATCC 19420, and *fortuitum* ATCC 684 has been reported as 100 mg/ml and the bactericidal activity as almost 78-92% (104).

Prunella vulgaris

It is a medical herb from Lamiaceae family and its height reaches 5-30 cm. It is a creeping plant with tough, square, reddish stem. The branches bud from the leaf place and the leaves are lance shaped, serrated, and opposite. The inflorescence is clustered and rectangular (105, 106). Leaves and trimmings of this plant are used orally as ptisan. Therapeutic effects of this herb include hemorrhoid and hemorrhage elimination, treatment of stomach diseases, respiratory tract and throat disorders, and runny nose (107). This species contains chemical compounds like oleic, butyric acid, and flavonoids (108). Components of this herb elevate the cytokines such as IFN- γ , IL-10, and IL-12 by affecting the immune system. This plant improves sight, inhibits proliferation of tumor cells, enhances transfer of anti-tumor signals and also stimulates the macrophages that results in positive effects on treatment of tuberculosis bacterium and antibiotic-resistant type. In a study conducted by John Lu and colleagues, Chinese mint extract was evaluated in mice infected by tuberculosis, and it was determined that the extract caused increased immune mediators by upregulating the expression of these mediators' genes (109).

Camellia sinensis

This plant which is a perennial is classified in angiosperms order and Theaceae family. White sweet-smelling tea flowers appear as clusters or single-flowers beside the leaves; it has sepals, petals, and some

stamens. Its fruit is like a capsule. This herb grows in Eastern Asia, Middle-East, and Africa (110, 111). This plant contains flavonoid compounds such as catechin and epicatechin, and also caffeine, vitamins, and saponins as anti-inflammatory, antioxidant, and anticancer compounds. It is also suitable for diabetic patients (112). Daily tea drinking reduces the probability for getting affected by tuberculosis among the population. Epigallocatechin and apigallocatechin-3-gallate affect tuberculosis bacterium. Anand et al. did a study to evaluate the influence of epigallocatechin-3-gallate compound from green tea on human macrophages. They concluded that this compound is naturally able to downregulate TACO gene expression (for bacterial invasion and survival), and diminished expression of this gene results in reduced TACO protein that leads into bacterial destruction in macrophages (113).

Hypericum perforatum

H. perforatum from Hypericaceae family is a grassy plant, perennial, with elliptical oppositely arranged leaves. It grows in most parts of the world such as Europe, Western Asia, and Northern Africa. This plant has pharmacological effects including analgesia, anti-inflammatory, anti-anxiety, anti-forgetfulness, anti-tumor, anti-peptic ulcer, antioxidative, anti-viral, anti-herpes, and anti-depression properties. It is also used for nervous-psychological patients, epilepsy, convulsion, migraine, sciatica pain, and headache in traditional medicine. The plant contains flavonoids, phloroglucinols, phenylpropanes, and procyanidines, and the extract compounds inhibit growth of gram negative and positive bacteria especially *Mycobacterium tuberculosis* with multidrug-resistance (114). Raju et al. examined the activity of this plant's anti-folate compounds on *Mycobacterium tuberculosis* and indicated that these compounds have the highest antibacterial activity in the range of 3-183 micrometer. Moreover, they showed that among the present compounds, epigallocatechin-3-gallate with minimum inhibitory dose of 4.25 µm had the most activity against *Mycobacterium tuberculosis* isolate H37Rv (115).

Eucalyptus camaldulensis

This plant grows as high trees with the height of 35 m and belongs to Myrtaceae family. It has long leaves, and is found in swampy grounds and in semi dry climate in lime and sandy soils. Eucalyptus possesses routine compounds, resin, eucalyptic acid, and a lot of tannin. Its medical properties include reducing fever, anti-diabetes, anti-gonorrhea, anti-parasite, anti-

diarrhea, and anti-asthma. It is also useful for cold, influenza, and clearance of respiratory tract, and has a favorable activity against microorganisms (116). Compounds obtained from hexane, chloroform, and methanol extracts of eucalyptus tree are effective against *Mycobacterium tuberculosis* and *Mycobacterium avium*, and has also therapeutic effects for bacteria infecting respiratory system. Gemechu et al. studied the herbs with activity against *Mycobacterium tuberculosis* and *Mycobacterium bovis*. 80% ethanol extracts of several plants were evaluated with the range of minimum inhibitory concentration of 6.25-100 µg/ml. They showed that the 80% ethanol extract of eucalyptus could inhibit the isolates of *Mycobacterium tuberculosis* including H37Rv, SIT777, SIT73, SIT26, SIT37, SIT1688, SIT336, SIT149, SIT53, and SIT54 with respective minimum inhibitory doses of 25, 25, 6.25, 50, 25, 37.5, 50, 50, 50, 37.5, and 25 µg/ml. It also inhibited isolates of *Mycobacterium bovis* such as SB1176, SB1953, SB0133 with respective inhibitory strengths of 25, 12.5, and 50 (117).

CONCLUSION

Numerous chemical drugs exist for treating tuberculosis resulting from gram positive *Mycobacterium tuberculosis*, and these chemical agents may have adverse effects. Furthermore, this bacterium becomes resistant to drugs in some cases. The findings of this study demonstrated that medicinal plants evaluated throughout the world contain natural compounds that act specifically against this bacterium. Some of action mechanisms against *Mycobacterium tuberculosis* could be summarized as follow:

- Glucopyranoside compound forms pores in the two-layer membrane of bacterium.
- Henicosyl formate compound acts as a detergent and non-ionic surfactant on cell membrane.
- TACO protein is concentrated in the membranes of macrophages infected by *Mycobacterium tuberculosis* and prevents fusion of phagosome with lysosome. The polyphenolic extract (epigallocatechin-3-gallate) of tea tree reduces TACO expression by smashing the acyl group in mRNATACO expression. In addition, it inhibits transcription of SP1 gene that is placed in the promoter region of TACO regulatory gene and causes disturbance in TACO gene.
- Pectin compound acts as an antagonist for D2 receptor of dopamine and adrenergic receptor, and reduces pain.

-Diterpenoids possess ketone groups in D ring of their structure, R1 and R5 groups present in diterpenoids structure. These compounds prevent the synthesis of soluble glucan by bacterial glucosyltransferase.

-Compounds obtained from Chinese mint extract regulate the balance between Th1/Th2 through increasing the cytokines IFN-γ, IL-10, and IL-12. Afterwards, Th1 cells increase and Th1 stimulates macrophages by secreting IFN-γ and IFN-α and destroy the intracellular *Mycobacterium*.

Each of the medicinal plants and natural compounds are able to inhibit *Mycobacterium tuberculosis* by a special mechanism due to containing secondary metabolites and biological compounds.

Results obtained from this study provide scientists of pharmacology with basic information, so that they can take steps to utilize natural and synthetic compounds besides chemical drugs for treating *Mycobacterium tuberculosis*. It is clear that each of the plants mentioned in this study require several accurate pharmacological studies to receive approval.

CONFLICT OF INTEREST

The authors declared no competing interests.

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