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A Systematic Review on the Anti-Mycobacterial Activities of Plant Essential Oils

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Introduction

According to the World Health Organization, the number of people developing active tuberculosis (TB) is increasing yearly.[20] It is ranked as a major cause of death after human immunodeficiency virus.[6] A third of the world population was estimated infected with *Mycobacterium tuberculosis* annually[12] worsen by the emergence of multi-drug resistant (MDR) bacterial strains.[6]

Multi-drug resistant TB (MDR-TB) develops when the bacteria, *Mycobacterium tuberculosis* failed to respond to the first line anti-TB drugs. The resistance phenomenon continues to spread due to the improper use of anti-TB drugs or antibiotics and the mismanagement of the disease resulted in person-to-person transmission.[11] High emergence of antibiotic-resistant bacteria increases the TB-associated morbidity and mortality, posing a major concern to global public health. This imminent concern requires a new and safe anti-TB agent, with less resistance and side effects. Therefore, numerous studies have been conducted on the effectiveness of natural products to combat drug resistance.

The use of essential oils (EO) is currently blooming in our community. The complexity of the molecular structure in EO is a promising element required to inhibit microbial protein targets in bacteria.[4] Complementary therapy combining antibiotics and EO represents a high potential as an alternative treatment.

Methods

The literatures were obtained from databases in National Center for Biotechnology Information. The search terms included were “MDR tuberculosis” OR “multi-drug resistant tuberculosis”, “essential oils” OR “volatile oils”, “anti-mycobacterial agents” OR “anti-tubercular agents”, and “Mycobacterium tuberculosis” OR “M. tuberculosis”. All retrieved articles were reviewed by the titles and abstracts before included into the reference lists.

Studies included in the systematic review met the following criteria: (a) papers were written in English-language title; (b) papers published between year of 2000 and 2016. The process of screening the abstracts was performed by two independent researchers. Subsequently, the relevant full text articles were reviewed to extract the results. A quality assessment was conducted by using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) tool.

Results and Discussions

Table 1 Plant essential oils which have been studied for anti-mycobacterial activity

Plant	Reference	Part Used	Route of Administration	Activity
Citrus sinensis L.	Egharevba et al., 2016	Peel	*Mycobacterium tuberculosis*	MIC 0.25 mL/mL
Cymbopogon citratus *Cymbopogon nervatus* *Cymbopogon proximus*	Elhassan et al., 2016	Leaves	*Mycobacterium tuberculosis*	MIC 15.0 µL/mL
Hyptis suaveolens Lamiceae	Runde et al., 2015	Leaves	*Mycobacterium bovi*	MIC 3.13% v/v
Lippia Americana	Bueno et al., 2011		*Mycobacterium tuberculosis*	MIC 62.5 to 125.0 µg/mL
			Mycobacterium chelonae	MIC 198.4 µg/mL
			Mycobacterium abscessus *Mycobacterium fortuitum* *Mycobacterium intracellulare* *Mycobacterium terrae*	MIC >500.0 µg/mL
			Mycobacterium szulgai	MIC 125.0 µg/mL
Mutellina purpurea L.	Sieniawska et al., 2015		*Mycobacterium tuberculosis*	MIC 64.0 µg/mL
Myrtus communis L.	Zanetti et al., 2010	Leaves	*Mycobacterium tuberculosis*	MIC 0.17% (v/v)
Piper species	Bernuci et al., 2016	Leaves	*Mycobacterium tuberculosis*	MIC 125.0 to 250.0 µg/mL
Pistacia atlantica Desf	Sifi et al., 2015	Gall	*Mycobacterium smegmatis*	MIC 0.31 to 0.62 mg/mL
			Mycobacterium aurum	MIC 0.16 to 1.25 mg/mL
			Mycobacterium fortuitum	MIC 1.25 to 2.50 mg/mL
Salvia aratocensis	Bueno et al., 2011	Leaves	*Mycobacterium tuberculosis*	MIC 62.5 to 125.0 µg/mL
			Mycobacterium chelonae	MIC 79.0 µg/mL
			Mycobacterium abscessus *Mycobacterium intracellulare*	MIC 315.0 µg/mL
			Mycobacterium fortuitum *Mycobacterium terrae*	MIC 397.0 µg/mL
			Mycobacterium szulgai	MIC 99.2 µg/mL
Solanum spirale Roxb.	Keawsa-ard et al., 2016	Fruits	*Mycobacterium tuberculosis*	MIC 50.0 µg/mL
Thymbra spicata var.	Kilic, 2005	Leaves	*Mycobacterium smegmatis*	MIC 256.0 µg/mL
			Mycobacterium terrae	MIC 128.0 µg/mL
			Mycobacterium intracellulare	MIC 512.0 µg/mL
Turnera diffusa	Bueno et al., 2011	Leaves	*Mycobacterium tuberculosis*	MIC 62.5 to 125.0 µg/mL
			Mycobacterium chelonae *Mycobacterium szulgai*	MIC 198.4 µg/mL
			Mycobacterium fortuitum	MIC 397.0 µg/mL
			Mycobacterium intracellulare *Mycobacterium terrae*	MIC 500.0 µg/mL

All 10 studies on anti-TB properties of EO found were in-vitro tests. Table 1 illustrated a number of plant EO exhibiting anti-mycobacterial properties. According to Bueno[3], crude extract shows a good anti-mycobacterial activity when the MIC value is below than 100 µg/mL. The example of the plants which appeared to be significantly active are including *Cymbopogon* sp., *Myrtus communis* L., *Mutellina purpurea* L., *Salvia aratocensis*, *Solanum spirale* Roxb. and *Turnera diffusa*. The study on *Solanum spirale* EO demonstrated good activities at the concentration of 50 µg/ml, probably due to the synergistic action of its compounds; 56.01% of n-hexadecanoic acid, 9.71% of linolenic acid, 4.41% of octadecanoic acid, 1.69% of methyl plamitate, 1.55% of tetradecanoic acid, 1.18% of (E) phytol, 0.91% of hexanal 0.83% of methyl salicylate, 0.81% of 4-hydroxy-4-methylpentan-2-one, 0.71% of pentadecanoic acid and 0.56% of β-selinene. While in *Hyptis suaveolens* EO, there was no growth of *Mycobacterium Bovi* at the concentration of 3.125% to 25% can be attributed to the high percentage of caryophyllene, sabinene and terpinolene presented in the EO.[15]

High anti-microbial activity in EO is mostly due to the presence of terpenoid; monoterpenes and sesquiterpenes. The character of hydrocarbon skeleton (lipophilic) and the functional groups (hydrophilic) of the EO are important to determine the level of anti-microbial activities[6] which may penetrate the microorganism lipid fraction in plasma membrane and alter the membrane permeability.[3] In another study published recently in 2014, the gaseous contact assay have been optimized to assess the susceptibility of *Mycobacterium tuberculosis* by *Eucalyptus citriodora* EO. The volatile fractions exerted their inhibitory effects on the inoculated microorganisms and resulted in a high growth inhibition in the bacterial strain. One of the constituents, citronellol exerted a 100% inhibition, while the major constituent showed only 18% growth inhibition properties.[14]

These results highlighted the potential of EO as a supplemental treatment for TB in the form of inhalation due to its volatile properties. The effectiveness and efficacy of the plant materials and its active constituents in MDR-TB should further be explored in additional in-vitro testing. Further studies can be performed by using in-vivo animal models to evaluate the possible adverse effects.[14,20]

Apart from EO, there were many in-vitro studies conducted to identify the active compounds from natural plants extraction that can potentially inhibit the growth of *Mycobacterium* species. A study on Mexican traditional medicine previously has described the anti-mycobacterium activity of the compounds in several plants. Of the tested plants, *Citrus aurantifolia*, *Citrus sinensis*, *Nasturtium officinale* and *Olea europaea* showed best activity against *Mycobacterium tuberculosis* H37Rv drug-resistant variants.

Conclusion

The review suggests that EO from plants have potential in-vitro anti-mycobacterial activities, mainly from the monoterpene compounds and the synergistic effects of the components. Locally available plant in Malaysia such as *Cymbopogon citratus* (lemongrass) EO was also found effective against *Mycobacterium tuberculosis*, posing a good opportunity to the export industry. Nonetheless, further trials are warranted to assess the safety and efficacy of EO to complement anti-TB treatment in the clinical setting.

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