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Review

A review of medicinal plant of Middle East and North Africa (MENA) region as source in tuberculosis drug discovery

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ABSTRACT

Tuberculosis (TB) is a disease that affects one-third of the world's population. Although currently available TB drugs have many side effects, such as nausea, headache and gastrointestinal discomfort, no new anti-TB drugs have been produced in the past 30 years. Therefore, the discovery of a new anti-TB agent with minimal or no side effects is urgently needed. Many previous works have reported the effects of medicinal plants against *Mycobacterium tuberculosis* (MTB). However, none have focused on medicinal plants from the Middle Eastern and North African (MENA) region. This review highlights the effects of medicinal plants from the MENA region on TB. Medicinal plants from the MENA region have been successfully used as traditional medicine and first aid against TB related problems. A total of 184 plants species representing 73 families were studied. Amongst these species, 93 species contained more active compounds with strong anti-MTB activity (crude extracts and/or bioactive compounds with activities of 0–100 μg/ml). The extract of *Inula helenium, Khaya senegalensis, Premna odorata* and *Rosmarinus officinalis* presented the strongest anti-MTB activity. In addition, *Boswellia papyrifera* (Del) Hochst olibanum, *Eucalyptus camaldulensis* Dehnh leaves (river red gum), *Nigella sativa* (black cumin) seeds and genus *Cymbopogon* exhibited anti-TB activity. The most potent bioactive compounds included alantolactone, octyl acetate, 1,8-cineole, thymoquinone, piperitone, α- verbenol, citral b and α-pinene. These compounds affect the permeability of microbial plasma membranes, thus kill the mycobacterium spp. As a conclusion, plant species collected from the MENA region are potential sources of novel drugs against TB.
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1. Introduction

Tuberculosis (TB) is one of the most infectious deadly diseases. The main aetiology of *Mycobacterium tuberculosis* (MTB) infection can occur in anyone without distinction amongst sex, age or localisation (Adaikkappan et al., 2012; Akintola et al., 2013; Sabran et al., 2016). In 1993, the World Health Organisation (WHO) declared TB as a public health emergency (Abdallah and Ali, 2012; Rennie et al., 2011). Even though TB is endemic in all countries worldwide, in developing countries, it is more likely to cause deaths than other infectious diseases (Akintola et al., 2013; Gan et al., 2019). The WHO reported numerous deaths due to TB in 2018; approximately 1.2 million (1.1–1.3 million) out of the 10.0 million (9.0–11.1 million) people afflicted with this disease are found in endemic countries. In 2018, 53,620 cases of TB were identified in the Middle Eastern and North African (MENA) region; most of these cases were detected in three countries, namely, Iraq, Egypt and Sudan (World Helath Organisation and Geneva, 2019). The MENA region includes the following countries: Algeria, Bahrain, Djibouti, Egypt, Iran, Iraq, Jordan, Kuwait, Lebanon, Libya, Malta, Morocco, Oman, Qatar, Saudi Arabia, Syria, Tunisia, Turkey, United Arab Emirates, Palestine, Yemen, Ethiopia and Sudan; all of these countries have a long history of plant use for traditional medicine (Azaizeh et al., 2003). The estimated incidences of TB in the MENA region vary due to gaps in case detection because of under-reporting and under-diagnosis (Ahmed et al., 2016).

TB is a public health problem that mainly affects the respiratory system, primarily the lungs; however, it can also infect other systems and organs, such as the reproductive system (Thangappah et al., 2011). Chemotherapy drugs, like rifampicin and isoniazid, are used to treat infectious TB diseases and are the first line of defence against this disease. Other chemical-based drugs include ethambutol and pyrazinamide, which have adverse effects. Failure to adhere to treatment through the irregular and noncontinuous use of medication results in bacterial resistance. As a result, a patient may be at risk of developing multidrug-resistant TB within a year of treatment. TB drugs with high side effects and low activity include amikacin, capreomycin, streptomycin and fluoroquinolones (Adaikkappan et al., 2012; Chetty et al., 2017; Lienhardt et al., 2012). Drug-resistant TB can be classified into two types: multidrug resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB). Approximately 4% of patients with TB worldwide are suffering from MDR-TB strains that resist standard first-line TB drugs; XDR-TB occurs when bacterial strains are resistant to all first-line and second-level TB drugs (Garaniya and Bapodra, 2014; Hoagland et al., 2016; Shashidhar et al., 2015).

The 2014 WHO report on MDR-TB and XDR-TB screening discovered approximately 480,000 cases of MDR-TB in different locations worldwide; more than half of these cases are found in India, China and the Russian Federation, with the highest number of cases of MDR-TB recorded in China (Ganihigama et al., 2015; Islam et al., 2017). The disadvantages of chemotherapy have motivated researchers and doctors to use medicinal plants and traditional medicine to treat infectious and chronic diseases, such as TB (Jalil et al., 2012). The actual need to resolve chemotherapy drawbacks has resulted in the search for new, easily obtainable solutions with good activity against MTB strains and few disadvantages (Blanco et al., 2015; Riccardi and Pasca, 2014). Medicinal plants have been used in many different fields, and many have been comprehensively investigated (Gemechu et al., 2013; Kaur and Kaur, 2015). Approximately 75% of the world population uses medicinal plants for traditional treatment and healthcare for different diseases (Karunamoorthi and Tsehaye, 2012).

In 2007, Gautam et al. reviewed different families of medicinal plants from India with potential anti-TB activities and identified 25 species with the highest anti-TB activity (Gautam et al., 2007). Many medicinal plants from different families have been found to have activity against TB (Gupta et al., 2010). Recent reviews published in 2016 focused on anti-TB medicinal plants that originated from different locations, such as Africa, Asia, Europe, South America and Canada; several of these medicinal plant species exhibit putative antimycobacterial activity and yielded numerous bioactive compounds (Chinsembu, 2016). Several anti-TB plants from Southeast Asia have been reviewed by Sanusi. Most recent reviews described anti-TB natural products based on medicinal plants with activities of 0–<10 μg/ml in their crude or pure forms (Sanusi et al., 2017).

Another review article reported that in Northern Iraq, 63 medicinal plants are used to treat 99 different types of diseases (Ahmed, 2016). Some medicinal plants from Turkey, particularly one member of the mint family that contains different phytochemicals, such as flavonoids, phenolics and other ingredients, have shown good results in the treatment of TB (Askun et al., 2012). All previous reviews included scientifically reviewed studies that focused on plants that are used as traditional medicine against respiratory disease problems and are sourced from the MENA region (Ahmed, 2016; Sharifi-Rad et al., 2017). The many traditional uses of plants from the MENA region are listed in Table 1.

2. Methodology

This review included all related published scientific articles as illustrated in Fig. 1. This research was conducted by searching the electronic databases NCBI, Google Scholar, Scopus and Science Direct for relevant studies from the year 2000 to 2018. Relevant studies were reviewed through numerous steps. In the first step, target published articles were identified by using general related terms, such as 'medicinal plants' and 'Middle Eastern and North African area.' The second step involved screening the resulting articles by using highly specific keywords, including 'anti-*Mycobacterium tuberculosis*,' '*in vitro*' and '*in vivo*.' The last step of the review focused on selected studies involving native medicinal plants and their related contributions.

3. Bioassay guidance for evaluating anti-TB activity

Modern reviews show that the bioassay-guided method is used in TB drug discovery to identify bioactive compounds from natural crude extract(s). This process includes alternating steps to identify the bioactive compounds of natural compounds by using bioassays and chemical fractionation; hence, multiple samples are taken for

Table 1
MENA region medicinal plants with antimycobacterial activity.

Plant Family	Botanical Name	Englishname	location	Part used: Preparation Extract / Active Compound	Mode of Action	**Local medicinal uses**
Acanthaceae	*Adhatoda vasica* Nees L	Arusha	Egypt	Leaf: methanol extract	The methanol extract of leaf exhibited activity against *M. bovis* BCG at MIC of >500 μg/mL (Abou El Seoud et al., 2003).	Colds, cough (P Singh et al., 2011; Santhosh and Suriyanarayanan, 2014).
Apiaceae	*Apium graveolens*	Celery	Iraq	Ethanol extract 70%	Ethanol extract of plant showed activity at 200 mg/ml concentration and growth MTB 20 colonies in 4 week incubation (Abbas, 2011).	Nil
	Cuminum cyminum L.	Peanut	Iraq	Ethanol extract 70%	The crude plant extract was active at 200 mg/ml concentration and showed no growth MTB (Abbas, 2011)	Antibacterial (Parekh and CHANDA, 2008)
	Pimpinella anisum	Flax	Iraq	Ethanol extract 70%	At 200 mg/ml, the plant crude extract showed activity against MTB and 3 colonies presented after 4 week incubation time (Abbas, 2011).	Nil
Apocynaceae	*Nerium oleander* L.	Oleander	Egypt	Leaf: methanol extract	The methanol extract of leaf exhibited activity against *M. bovis* BCG at MIC of >500 μg/mL (Abou El Seoud et al., 2003).	Antibacterial(Hase et al., 2016)
	Thevetia neriifolia Juss ex ADC.	Yellow oleander	Egypt	Leaf: methanol extract	Methanol extract of leaf plant showed inhibition against *M. bovis* BCG at MIC of >500 μg/mL (Abou El Seoud et al., 2003).	Antibacterial, insecticides (Bandara et al., 2010; Kareru et al., 2010)
Asphodelaceae	*Aloe. vera*	Aloe perfoliata	Iran	Aqueous extracts	The extract inhibit cell growth activity at 1 mg/mL concentration by time kill 95% in 1 week and 60 mm inhibition zone by disk diffusion method (Arjomandzadegan et al., 2016).	Skin treatment (Reynolds, 2004).
Asteraceae	*Ambrosia maritima* L.	Ragweeds	Egypt	Leaf : methanol extract	The extract was active against *M. bovis* BCG at MIC 250 μg/mL (Abou El Seoud et al., 2003).	Nil
	Centaurea depressa Bieb.	knapweed	Turkey	Aerial: ethanol extracts 70%	The ethanol crude extract exhibited activity against growth H37Rv strain at concentrations 100 μg/ml with MIC 6% (Tosun et al., 2005).	Anti-inflammatory (Demir et al., 2009).
	Cichorium intybus L	Chicory	Egypt	Herb: methanol extract	The plant crude extract showed activity against *M. bovis* BCG at MIC > 500 μg/mL (Abou El Seoud et al., 2003).	Local food & plants in Europe (Heinrich et al., 2016).
	Echinops purgens Trautv.	Thistles	Turkey	Aerial: ethanol extracts 70%	At 100 μg/ml of the ethanol extract showed 21% Inhibition of growth against H37Rv (Tosun et al., 2005).	Antipyretic (Maurya et al., 2015).
	Helianthus annuus L.	Sunflower	Turkey	Leaf: ethanol extracts 70%	Crude plant extract was active against growth of H37Rv strain at 100 μg/ml with MIC 35% (Tosun et al., 2005).	Antibacterial (Guo et al., 2017).
	Helianthus annuus L.	Sunflower	Egypt	Flower: methanol extract	The methanol flower extract was active against *M. bovis* BCG at MIC > 500 μg/mL (Abou El Seoud et al., 2003).	Antibacterial (Guo et al., 2017).
	Helichrysum plicatum DC. subsp. pseudoplicatum (N; ab.)	Altınotu	Turkey	Aerial: ethanol extracts 70%	Arial ethanol plant extract showed activity against growth of H37Rv strain at concentrations >100 μg/ml with MIC 8% (Tosun et al., 2005).	Cough (Yildirim et al., 2017).
	Inula helenium L. subsp. *turcoracemosa*	Horse-heal	Turkey	Root: maceration by ethanol extracts 70%, fractionation by with petroleum ether, chloroform, methanol and water/Alantolactone	The crude ethanol extract exhibited activity against H37Rv strain at MIC < 100 μg/ml with MIC 100% Inhibition activity. The fractionation and isolation compound have been screening against *M. tuberculosis* H37Rv and showed activity at MICs 3.125 μg/ml (Tosun et al., 2005).	Nil

(*continued on next page*)

Table 1 (*continued*)

Plant Family	Botanical Name	Englishname	location	Part used: Preparation Extract / Active Compound	Mode of Action	**Local medicinal uses**
	Inula peacockiana (Aitch. et Hemsl.) Krovin	Nil	Turkey	Aerial: ethanol extracts 70%	The plant crude extract showed activity against H37Rv at concentrations >100 μg/ml with MIC 6% (Tosun et al., 2005).	Expectorant (Gokbulut et al., 2016).
	Jasonia candicans(Delile) Botsch	Candicans	Egypt	Aerial part: maceration with 70% methanol	Methanol extracts of plant showed activity against the *M. phlei, M. smegmatis* and *M. tuberculosis* H37Rv with MIC 1.95, 6.25 and 7.8 mg/ml & DIZ 27,29 and17 mm, respectively (Safwat et al., 2018).	Antitussive & antimicrobial (Cushnie and Lamb, 2011).
	Onopordum acanthium L	Scotch	Egypt	Roots: maceration with 70% methanol	The root plant extracts showed activity against *M. phlei, M. smegmatis* and *M. tuberculosis* H37Rv with MIC 15.6, 25 and 62.5 mg/ml & DIZ 15.5, 25 and 13 mm, respectively (Safwat et al., 2018).	Antiseptic (Safwat et al., 2018).
	Onopordum anatolicum (Boiss.) Eig	Koufoti	Turkey	Aerial: ethanol extracts 70%	The extract exhibited activity against H37Rv at concentrations >100 μg/ml with MIC 22% (Tosun et al., 2005).	Nil
	Pulicaria gnaphalodes	False fleabane	Iran	Leaves, stem and flower: hydro-distillation water	At 640 μg/ml, the oil plant parts extract showed activity against H37RV and MTB sensitive isolates and observed 58.1% inhibition percentage (Hozoorbakhsh et al., 2016).	Allopathic potential (Azizi et al., 2009).
	Sonchus oleraceus L.	Sow thistle	Egypt	Flower: methanol extract	Methanol flower extract exhibited activity against *M. bovis* BCG at MIC > 500 μg/mL (Abou El Seoud et al., 2003).	Cough &asthma (Upadhyay et al., 2013).
	Tagetes patula L.	Mexican marigold	Egypt	Flower: methanol extract	The flower extract showed activity at MIC > 500 μg/mL against *M. bovis* BCG (Abou El Seoud et al., 2003).	Antifungal (Dutta et al., 2007).
	Tanacetum sinaicum Delile ex DC.		Egypt	Flower: methanol extract	The crude extract was active against *M. bovis* BCG at MIC > 500 μg/mL (Abou El Seoud et al., 2003).	Antimicrobial (Marzouk et al., 2016).
	Tripleurospermum conoclinium (Boiss. et Ball.) Hayek	Mayweed	Turkey	Aerial: ethanol extracts 70%	At 100 μg/ml, crude plant extract exhibited 95% inhibition activity against growth of H37Rv (Tosun et al., 2005).	Asthma &cold (Servi et al., 2018).
Balanitaceae	*Balanites aegyptiaca*(L.) Del.	Desert date	Sudan	Leaf, bark and root: sonication dichloromethane, ethyl acetate and ethanol (10 mg/ml)	The plant parts extract exhibited strong activity against *Mycobacterium aurum* A^+ (Eldeen and Van Staden, 2008).	Headache& cough (Al-Thobaiti and Abu Zeid, 2018).
Berberidaceae	*Mahonia aquifolium* (Pursch.) Nutt	Oregon Grape	Turkey	Branches, leaves and flowers : ethanol extracts 70%	All the parts ethanol extraction showed activity against H37Rv at concentration 100 μg/ml with 49% Inhibition percentage (Tosun et al., 2005).	Fever& diarrhea (He and Mu, 2015).
Bignoniaceae	*Kigelia Africana*(Lam.) Benth.	Kigelia	Sudan	Leaf, bark: sonication dichloromethane, ethyl acetate and ethanol (10 mg/ml)	The plant parts extract exhibited activity against *Mycobacterium aurum* A^+ at different concentration (Eldeen and Van Staden, 2008).	Skin fungal infections (Saini et al., 2009)
Boraginaceae	*Anchusa azurea* Miller var. azurea	Nil	Turkey	Aerial: ethanol extracts 70%	At 100 μg/ml, the ethanol plant extract showed 35% inhibition of growth against H37Rv (Tosun et al., 2005).	Anti-inflammatory (Kuruuzum-Uz et al., 2012).
	Cerinthe minor L. auriculata (Ten.) Domac	Honeyworts	Turkey	Aerial: ethanol extracts 70%	The crude extract exhibited activity against H37Rv at 100 μg/ml with inhibition growth 18% (Tosun et al., 2005).	Cough (Korkmaz and Karakuş, 2015).
	Echium Plantagineum L.	Purple viper's-bugloss	Turkey	Aerial: ethanol extracts 70%	The crude extract exhibited Inhibition against H37Rv at concentrations 100 μg/ml with 65% inhibition growth (Tosun et al., 2005).	Colds, coughs and fever (Kitessa et al., 2011).
	Echium italicum L.	Lady Campbell weed	Turkey	Aerial: ethanol extracts 70%	The plant extract exhibited activity against growth of H37Rv strain at concentrations 100 μg/mL with	Wound healing (Al-Snafi, 2017).

Table 1 (*continued*)

Plant Family	Botanical Name	Englishname	location	Part used: Preparation Extract / Active Compound	Mode of Action	**Local medicinal uses**
					MIC 37% inhibition growth (Tosun et al., 2005).	
	Heliotropium dolosum De Not.	Heliotrope	Turkey	Aerial and seeds: ethanol extracts 70%	At 100 μg/ml, the ethanol extract showed 4% & 85% inhibition against growth of H37Rv strain, respectively (Tosun et al., 2005).	Cough and treat wounds (Muthu et al., 2006; Roy, 2015).
	Moltkiopsis ciliata(Forssk.)I. M	Nil	Egypt	Aerial part: maceration with 70% methanol	The crude extracts was activate against the *M. phlei M. smegmatis* and *M. tuberculosis* H37Rv at MIC 40, 10 and7.8 mg/ml & DIZ 26, 22 and 17 mm, respectively (Safwat et al., 2018).	Cough, wound healing (Al-Harbi et al., 2016; Safwat et al., 2018).
	Myosotis olympica Boiss.	forget-me-nots	Turkey	Aerial: ethanol extracts 70%	The ethanol extract at concentration of 100 μg/ml showed 14% inhibition against H37Rv strain (Tosun et al., 2005).	Nil
Brassicaceae	*Alyssum fulvescens* Sibth. et Sm. var. fulvescens	Sweet alyssum	Turkey	Aerial: ethanol extracts 70%	At 100 μg/ml, the ethanol extract showed anti-TB activity against H37Rv with 1% inhibition growth (Tosun et al., 2005).	Nil
	Cheiranthus cheiri L.	Wallflower	Turkey	Aerial: ethanol extracts 70%	At 100 μg/ml, the ethanol extract showed activity against H37Rv with 13% inhibition growth (Tosun et al., 2005).	Dry bronchitis (Erum et al., 2017).
	Crambe orientalis L.	Crambe	Turkey	Aerial: ethanol extracts 70%	The ethanol plant extract showed activity against H37Rv at 100 μg/ml with 21% inhibition growth (Tosun et al., 2005).	Industrial herbs (Razavi and Nejad-Ebrahimi, 2009).
	Erysimum cuspidatum (Bieb.) DC	Nil	Turkey	Aerial: ethanol extracts 70%	At 100 μg/ml, was active against H37Rv strain with 55% Inhibition of growth (Tosun et al., 2005).	Nil
	*Isatis microcarpa*J. Gay ex Boiss.	Nil	Egypt	Whole plant: maceration with 70% methanol	Methanol extracts of whole plant showed activity against *M. phlei M. smegmatis* and *M .tuberculosis* H37Rv strain with MIC 50, 12.5 and 62.5 mg/ml & DIZ 18, 20 and 12 mm, respectively (Safwat et al., 2018).	Nasal infections &cold (Safwat et al., 2018).
	Lepidium sativum	Cumin	Iraq	Ethanol extract 70%	The ethanol extract at 200 mg/ml was active with no growth against MTB (Abbas, 2011).	Nil
	Lepidium vesicarium L.	Cruciferae	Turkey	Aerial: ethanol extracts 70%	The crude plant extract exhibited against growth H37Rv at 100 μg/ml with 3% Inhibition of growth (Tosun et al., 2005).	Antimicrobial (Bona, 2014).
	Moricandia nitens(Viv) E.A. Durand&Barratte	Violet cabbage	Egypt	Aerial part: maceration with 70% methanol	The extract showed activity against the *M. phlei M. smegmatis and M. tuberculosis* H37Rv with MIC 31.3, 25 and 125 mg/ml & DIZ 15, 25 and 10 mm, respectively (Safwat et al., 2018).	Bacterial infectious (Cushnie and Lamb, 2011).
	Nasturtium africanum (Braun-Blanq)	Moroccan watercress	Egypt	Aerial part: maceration with 70% methanol	Methanol extracts methanol of plant exhibited activity against *M. phlei* at MIC of 80 mg/ml & DIZ 26 mm (Safwat et al., 2018).	Bronchitis (Safwat et al., 2018).
	Raphanus raphanistrum L.	Wild radish	Turkey	Aerial: ethanol extracts 70%	The aerial ethanol extract at concentrations 100 μg/ml showed 19% Inhibition of growth against H37Rv strain (Tosun et al., 2005).	Anti-rheumatic &antioxidant (Küçükboyaci et al., 2012).
Burseraceae	*Boswellia papyrifera* (Del) Hochst olibanum	Olibanum	Sudan	hydro-distillation / 1) Octyl acetate 37.26% 2) Octyl formate 13.25% 3) verticilla-4(20),7,11-triene 6.85%	The oils extract with isolated compound (1,2 and 3) all was active against nine clinical isolates and H37Rv of *tuberculosis* at 15 μl/ml (Elhassan et al., 2017).	Antibacterial, diarrhea (Abdoul-latif et al., 2012; Assefa et al., 2012).
	Boswellia serrata	Frankincense	Iran	Powder: percolation extraction 80% ethanol	The plant crude extract showed activity result against *M. bovis* at 125.0 μg/ml (Rahgozar et al., 2018).	Anti-inflammatory (Krohn et al., 2001; Poeckel and Werz, 2006).
	Commiphora molmol	Myrrh	Iraq	Ethanol extract 70%	Ethanol extract at 200 mg/ml concentration exhibited activity with no growth against MTB (Abbas, 2011).	Antibacterial (Abdallah et al., 2009).
Capparaceae	*Capparis spinosa* L.	Caper	Iran	Fruits: methanol extraction	At 25 mg/mL, the methanol extract of the fruit was activate against	Antibacterial (Ehsanifar et al.,

(*continued on next page*)

Table 1 (*continued*)

Plant Family	Botanical Name	Englishname	location	Part used: Preparation Extract / Active Compound	Mode of Action	**Local medicinal uses**
					seven clinical samples & H37Rv strain (Ehsanifar et al., 2017).	2017).
Capparidaceae	*Capparis decidua*(Forssk.) Edgew.	Karira	Sudan	Twigs and root: Sonication dichloromethane, ethyl acetate and ethanol (10 mg/ml)	The plant extract exhibited activity against *Mycobacterium aurum* A^+ with (MIC) values Twigs extract 12.5, 25 & 6.25 mg/ml Root extract 25, na & 6.25 mg/ml (Eldeen and Van Staden, 2008).	Asthma (Singh et al., 2011).
Caryophyllaceae	*Silene arguta* Fenzl.	Givisganotu	Turkey	Aerial: ethanol extracts 70%	At 100 µg/ml, the plant extract showed activity against H37Rv with 24% Inhibition of growth (Tosun et al., 2005).	Nil
	Silene chlorifolia Sm.	Nil	Turkey	Aerial: ethanol extracts 70%	The extract at concentrations 100 µg/ml exhibited anti-TB activity against growth H37Rv with 10% Inhibition of growth (Tosun et al., 2005).	Antimicrobial &antifungal (Mamadalieva et al., 2014).
	Silene dichotoma Ehrh. subsp. sibthorpiana (Reichb.) Rech	Forked catchfly	Turkey	Aerial: ethanol extracts 70%	Ethanol extract at 100 µg/ml concentrations showed activity 42% Inhibition of growth against H37Rv strain (Tosun et al., 2005).	Cold & cough (Chandra and Rawat, 2015).
	Silene vulgaris (Moench) Garcke var. commutata (Guss.)Coode et Cullen	Bladder campion	Turkey	Aerial: ethanol extracts 70%	The crude extract exhibited anti-TB activity against H37Rv at concentrations 100 µg/ml with 30% Inhibition of growth (Tosun et al., 2005).	Cold & cough (Chandra and Rawat, 2015).
Chenopodiaceae	*Spinacia oleracea* L.	Spinach	Turkey	Leaves: ethanol extracts 70%	The extraction showed activity against H37Rv at concentrations of 100 µg/ml with 81% Inhibition of growth (Tosun et al., 2005).	Asthma (Gaikwad et al., 2010).
Cistaceae	*Cistus laurifolius* L.	Laurel-leaf cistus	Turkey	Aerial: ethanol extracts 70%	At 100 µg/ml, the plant extract showed activity against H37Rv with 34% Inhibition of growth (Tosun et al., 2005).	Antibacterial, antifungal (Agnieszka Stępień et al., 2018; Christodoulakis et al., 2014).
Combretaceae	*Combretumhartmannianum* Schweinf.	Nil	Sudan	Leaf, bark and root: Sonication dichloromethane, ethyl acetate and ethanol (10 mg/ml)	The plant parts extract exhibited activity against *Mycobacterium aurum* A^+ at different concentration (Eldeen and Van Staden, 2008).	Nil
Convolvulaceae	*Calystegia silvatica* (Kit.) Griseb.	Giant bindweed	Turkey	Aerial: ethanol extracts 70%	At 100 µg/ml, the plant extract showed activity against H37Rv with 69% Inhibition of growth (Tosun et al., 2005).	Herbicides (Gawn et al., 2013).
Crassulaceae	*Sedum stoloniferum* Gmeli	Stonecrops	Turkey	Aerial: ethanol extracts 70%	The extract at concentration of 100 µg/ml exhibited anti-TB activity against growth H37Rv with 21% Inhibition of growth (Tosun et al., 2005).	Antioxidative (Hajoboland, 2010).
Crucifereae	*Nasturtium officinale* R.Br	Watercress	Egypt	Seed: methanol extract	Methanol extract of seed showed activity against *M. bovis* BCG at MIC 500 µg/ml (Abou El Seoud et al., 2003).	Asthma & expectorant (Iseri et al., 2014).
Cyperaceae	*Cyperus esculentus* E. Mey	Chufa sedge	Egypt	Seed: methanol extract	The crude extract showed activity against *M. bovis* BCG at MIC > 500 µg/ml (Abou El Seoud et al., 2003).	Antimicrobial (Gambo and Da'u, 2014).
Elaeagnaceae	*Elaeagnus angustifolia* L.	Russian Olive	Turkey	Fruits, leaves: ethanol extracts 70%	At 100 µg/ml, the plant extract showed activity against H37Rv with 4% Inhibition of growth (Tosun et al., 2005).	Arthritis (Panahi et al., 2016).
Euphorbiaceae	*Euphorbia paralias* L	Sea spurge	Egypt	Whole plant: maceration withPetroleum ether, Chloroform, Ethyl acetate, Methanol and70% methanol / 1) Quercetin 3-O-glucoside	The plant fractionation by methanol showed activity against the *M. phlei M. smegmatis and M. tuberculosis* H37Rv with MIC 5.0, 2.5 and 3.12 mg/ml while DIZ 27.7, 28.3 and 18.0 mm respectively (Safwat et al., 2018). N10 isolated active compound showed activity against the *M. phlei M. smegmatis and M. tuberculosis* H37Rv with MIC 0.078, 0.312	Treat asthma, bronchitis. Used as expectorant (Safwat et al., 2018).

Table 1 (*continued*)

Plant Family	Botanical Name	Englishname	location	Part used: Preparation Extract / Active Compound	Mode of Action	**Local medicinal uses**
					and 0.15 mg/ml while DIZ 28.5, 25 and 27 mm respectively, with glutamine synthetase enzyme inhibition activity (Safwat et al., 2018).	
Fabaceae	*Arachis hypogaea*	Peanut	Iraq	Ethanol extract 70%	The extract at concentration of 200 mg/ml was active and has no growth against MTB (Abbas, 2011).	Nil
Fagaceae	*Quercus robur* L.	English oak	Egypt	Fruit: methanol extract	The methanol extract of fruit exhibited activity against *M. bovis* BCG at MIC > 500 μg/ml (Abou El Seoud et al., 2003).	Asthma (Uddin and Rauf, 2012).
Geraniaceae	*Geranium asphodeloides* Burm. Fil	Nil	Turkey	Aerial: ethanol extracts 70%	At 100 μg/ml, the ethanol extract of plant showed 12% Inhibition growth against H37Rv strain (Tosun et al., 2005).	Cooked with vegetables (Kızılarslan, 2012).
	Geranium divaricatum Ehrh.	Rose-scented geranium	Turkey	Aerial: ethanol extracts 70%	The extract at concentrations 100 μg/ml exhibited activity against growth H37Rv with 19% Inhibition of growth (Tosun et al., 2005).	Relives pain (Greenway et al., 2003).
	Geranium robertianum L.	Herb robert	Turkey	Aerial: ethanol extracts 70%	Ethanol extract of plant showed activity against H37Rv at concentrations of 100 μg/ml with MIC 10% Inhibition of growth (Tosun et al., 2005).	Anti-hyperglycaemiant (Ferreira et al., 2010).
Hypericaceae	*Hypericum triquetrifolium* Turra	Nil	Turkey	Aerial: ethanol extracts 70%	At 100 μg/ml, the ethanol extract of plant showed activity against *M. tuberculosis* H37Ra (Tosun et al., 2004).	Nil
	Hypericum perforatum L.	StJohn's wort	Iran	Aqueous extracts	The extract showed Inhibit cell growth activity at 1 mg/mL concentration by time kill 95% in 1 week and 60 mm inhibition zone by disk diffusion method (Arjomandzadegan et al., 2016).	Snake bite, antimicrobial (Asgarpanah, 2012; Shrivastava and Dwivedi, 2015).
Iridaceae	*Crocus ancyrensis* (Herbert) Maw	Ankara crocus	Turkey	Flowers: ethanol extracts 70%	The extract at concentration of 100 μg/ml exhibited activity against growth H37Rv with 30% inhibition of growth (Tosun et al., 2005).	Analgesic (Moraga et al., 2013).
Juglandaceae	*Juglans regia* L.	Walnut	Turkey	Leaves; ethanol extracts 70%	The leaves plant extraction was active at 100 μg/ml and showed 12% inhibition of growth against H37Rv (Tosun et al., 2005).	Asthma (Taha and Al-wadaan, 2011).
Juncaceae	*Juncus acutus* L.	Spiny rush	Egypt	Herb: methanol extract	Methanol extract of herbal exhibited activity against *M. bovis* BCG at MIC > 500 μg/ml (Abou El Seoud et al., 2003).	Cold (El-Shamy et al., 2015).
Labiatae	*Rosmarinus officinalis* L.	Rosemary	Egypt	Methanol extract	At > 500 μg/mL, the methanol plant extract showed activity against *M. bovis* BCG (Abou El Seoud et al., 2003).	Antimicrobial (Borrás-Linares et al., 2014).
Lamiaceae	*Saliva tomentosa* Mill.	Mint	Turkey	Aerial part: methanol extract 98%/ 1) Rosmarinic acid 2) Catechin 3) Rutin	Methanol extract and selected bioactive compound (1,2 and 3) showed activity against H37Ra at MIC 196 μg/mL by MGIT fluorometric test tube (Askun et al., 2009a).	Colds & antifungal (Pitarokili et al., 2003).
	Saliva tomentosa Mill.	Mint	Turkey	Aerial part: Hydro-distillation / 1) a-Pinene 2) 1,8-cineole 3) Camphor 4) Borneol	The essential oil extraction with all bioactive compound (1, 2, 3 and 4) showed activity against *M. tuberculosis* H37Ra at MIC 196 μg/mL by MGIT fluorometric test tube (Aşkun et al., 2010).	Colds & antifungal (Pitarokili et al., 2003).
	Saliva fruticosa Mill.	Greek sage	Turkey	Aerial part: methanol extract 98% 1) Caffeic acid 2) Rosmarinic acid 3) Apigenin 4) Carvacrol	Methanol extract and selected bioactive compound exhibited activity against H37Ra at MIC 392 μg/mL by MGIT fluorometric test tube (Askun et al., 2009a).	Colds & antifungal (Pitarokili et al., 2003).
	Saliva aucheri Bentham subsp. *aucheri*	Nil	Turkey	Aerial part: Hydro-distillation / 1) 1,8-cineole 2) Camphor	The essential oil extract with bioactive compounds (1 and 2) showed activity against *M. tuberculosis* H37Ra at MIC 196 μg/mL by MGIT fluorometric test tube (Aşkun et al., 2010).	Nil

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Table 1 (*continued*)

Plant Family	Botanical Name	Englishname	location	Part used: Preparation Extract / Active Compound	Mode of Action	**Local medicinal uses**
	Saliva verticiilata L. subsp. *amasiaca*	Hooked bristlegrass	Turkey	Aerial part: Hydro-distillation / 1) ß-Pinene 2) 1,8-cineole	The essential oil extract with bioactive compounds (1 and 2) was active against *M. tuberculosis* H37Ra at MIC 196 µg/mL by MGIT fluorometric test tube (Aşkun et al., 2010).	Colds, antibacterial (Aşkun et al., 2010; Soliman and Badeaa, 2002).
	Saliva. kronenburgii Rech.	Nil	Turkey	Aerial: ethanol extracts 70%	At 100 µg/ml, the ethanol extract of plant showed activity against *M. tuberculosis* H37Ra (Tosun et al., 2004).	Nil
	Sideritis albiflora	Mountain tea	Turkey	Aerial part: methanol extract 98% 1) Caffeic acid 2) Rosmarinic acid 3) Carvacrol	The whole plant extract with active compound showed activity against H37Ra at MIC 1568 µg/mL by MGIT fluorometric test tube (Askun et al., 2009a).	Nil
	Sideritis leptoclada	Mountain tea	Turkey	Aerial part: methanol extract 98% 1) Caffeic acid 2) Rosmarinic acid 3) Rutin	The methanol extract showed activity against H37Ra at MIC 1568 µg/mL by MGIT fluorometric test tube (Askun et al., 2009a).	Nil
	Perovskia abrotanoides Kar.	Russian Sage	Iran	Leaves, stem, and flower: hydro-distillation	The plant oil extract showed activity against H37RV and MTB sensitive isolates at MIC 640 µg / ml and observed 76.2% inhibition percentage (Hozoorbakhsh et al., 2016).	Antiseptic, antibacterial. (Beikmohammadi, 2012; Nezhadali et al., 2009).
	Mentha spicata	Spearmint	Iran	Powder: percolation extraction 80% ethanol	At 0.39 mg/ml, the ethanol extract showed activity against *M. bovis* (Maham et al., 2011).	Nil
	Mentha piperta	Peppermint	Iran	Powder: percolation extraction 80% ethanol	The extract was active against *M. bovis* at 100 mg/ml (Maham et al., 2011).	Antibacterial activity (Toroglu, 2011).
	Dracocephalum kotschyi	Zarringiah	Iran	Leaves: maceration methanol 70%	The methanol extract exhibited activity against H37Rv at 640 µg/mL concentration (Asghari et al., 2015).	Anti-spasmodic, analgesic, anti-parasite (Golshani et al., 2004; Saeidnia et al., 2005)
	Lavandula stoechas	Lavender	Iran	Powder: percolation extraction 80% ethanol	Ethanol extract of plant powder showed activity against *M. bovis* at 250 µg/ml (Rahgozar et al., 2018).	Antimicrobial (Umezu et al., 2006).
	Rosmarinus officinalis	Rosemary	Iran	Powder: percolation extraction 80% ethanol	The extract at concentration 187.5 µg/ml, was active against *M. bovis* (Rahgozar et al., 2018).	Antimicrobial (Bakkali et al., 2008; Özcan, 2003).
	Thymus vulgaris	Garden Thyme	Iran	Powder: percolation extraction 80% ethanol	The plant extract showed activity against *M. bovis* at 500.0 µg/ml (Rahgozar et al., 2018).	Antibacterial, antifungal (Millezi et al., 2012; Pourazar Dizaji et al., 2018).
	Thymus vulgaris	Garden Thyme	Iran	Leaves: hydro- distillation process	The essential oil showed strong activity against clinical isolate *M. tuberculosis* and H37Rv stander strain at below 40 µg/ml (Pourazar Dizaji et al., 2018).	Antibacterial, antifungal (Millezi et al., 2012; Pourazar Dizaji et al., 2018).
	Mint	Mint	Iran	Aqueous extracts	Aqueous extract of plant inhibit mycobacterium growth activity at 1 mg/mL concentration by time kill 95% in 1 week (Arjomandzadegan et al., 2016).	Nil
	Thymus sibthorpii Benth.	Thymus	Turkey	Aerial part: maceration by petroleum ether, ethyl acetate, methanol and fraction: 1) Rosmarinic acid 2) Caffeic acid	The petroleum ether fraction was active against *M. tuberculosis* H37Rv and H37Ra with MIC of 12.5 and 50 µg/ml concentration respectively. The ethyl acetate fractions showed activity against *M. tuberculosis* H37Rv and H37Ra with MIC of 12.5 µg/ml concentration. The MBC value of 50–800 µg/ml (Askun et al., 2013).	Antiseptic agent (Askun et al., 2013).
	Satureja aintabensis P.H. Davis	Savory	Turkey	Aerial part: maceration by petroleum ether, ethyl acetate, methanol and	The petroleum ether fraction was active against *M. tuberculosis* H37Rv and H37Ra with MIC of 25	Antifungal, antibacterial (Askun et al., 2008;

Table 1 (*continued*)

Plant Family	Botanical Name	Englishname	location	Part used: Preparation Extract / Active Compound	Mode of Action	**Local medicinal uses**
				fraction: 1) Rosmarinic acid 2) Naringenin 3) Hesperidin 4) Luteolin 5) Caffeic acid	and 50 μg/ml concentration respectively. The ethyl acetate fractions showed activity against *M. tuberculosis* H37Rv and H37Ra with MIC of 12.5 μg/ml concentration. The MBC value of 50–100 μg/ml against four tested organism (Askun et al., 2013).	De Oliveira et al., 2011).
	Micromeria juliana (L.) Benth. ex Reich	Meris	Turkey	Aerial part: maceration by petroleum ether, ethyl acetate, methanol and fraction: 1) Rosmarinic acid 2) Chlorogenic acid 3) Rutin hydrate 4) Caffeic acid	The ethyl acetate fractions was active against *M. tuberculosis* H37Rv and H37Ra with MIC of 100 and 50 μg/ml concentration respectively (Askun et al., 2013).	Tonsillitis and common cold (Askun et al., 2013).
	Ballota acetabulosa (L.) Benth	Nil	Turkey	Aerial part: maceration by petroleum ether, ethyl acetate, methanol and fraction	The petroleum ether fraction showed activity against *M. tuberculosis* H37Rv and H37Ra with MIC of 200 and 400 μg/ml concentration respectively. The MBC value of 800 μg/ml (Askun et al., 2013).	Cough (Askun et al., 2013).
	Thymbra spicata L. var. *spicata*	Kekik	Turkey	Aerial parts: methanol extracts (98%)/ 1) Carvacrol 2) Rosmarinic acid 3) Hesperidin 4) Naringenin	At 196 μg/ml, the methanol extract exhibited high level of activity against *M. tuberculosis* H37Ra by MGIT indicator tubes (Askun et al., 2009b).	Antimicrobial (Soylu et al., 2006).
	Origanum minutiflorum O. Schwarz and P.H. Davis	Endemic	Turkey	Aerial parts: methanol extracts (98%)/ 1) Carvacrol 2) Rosmarinic acid 3) Eriodictiol 4) Luteolin	The methanol plant extract with active compound was active against *M. tuberculosis* H37Ra with MIC 392 μg/ml concentration by MGIT indicator tubes (Askun et al., 2009b).	Antibacterial (Dadalioğlu and Evrendilek, 2004).
	Clinopodium vulgare L. subsp. arundanum(Boiss.) Nyman	Wild basil	Turkey	Aerial: ethanol extracts 70%	The crude plant extract showed inhibition against H37Rv extract at concentrations 100 μg/ml with 12% (Tosun et al., 2005).	Anti-inflammatory (Batsalova et al., 2017).
	Eremostachys laciniata (L.) Bunge	Bunge	Turkey	Aerial: ethanol extracts 70%	The plant extraction showed Inhibition of growth H37Rv at concentrations 100 μg/ml with 54% (Tosun et al., 2005).	Headaches (Hadipour et al., 2016).
	Lamium purpureum L.	Red deadnettle	Turkey	Aerial: ethanol extracts 70%	At 100 μg/ml, plant ethanol extract showed 48% inhibition against H37Rv (Tosun et al., 2005).	Fracture (Yalçin and Kaya, 2006).
	Lavandula stoechas L. subsp. cariensis (Boiss.) Rozeira	French lavender	Turkey	Aerial: ethanol extracts 70%	The ethanol extract showed 17% Inhibition of growth against H37Rv at 100 μg/ml (Tosun et al., 2005).	Nil
	Marrubium parviflorum Fisch. et Mey. subsp. oligodon(Boiss.) Seybold	Horehound	Turkey	Aerial: ethanol extracts 70%	At 100 μg/ml, plant ethanol extract showed 3% inhibition against H37Rv (Tosun et al., 2005).	Nil
	Mentha longifolia (L.) Hudson subsp. longifolia	Horse mint	Turkey	Aerial: ethanol extracts 70%	The crude plant extract showed activity against H37Rv at concentrations 100 μg/ml with 33% inhibition (Tosun et al., 2005).	Antispasmodic (Mikaili et al., 2013).
	Phlomis lunariifolia Sm.	Jerusalem sage	Turkey	Aerial: ethanol extracts 70%	At 100 μg/ml, the extract of plant was active against H37Rv with 8% Inhibition of growth (Tosun et al., 2005).	Nil
	Rosmarinus officinalis L.	Nil	Turkey	Leave and flower: ethanol extracts 70%	The extract at concentrations 100 μg/ml showed 66% Inhibition of growth against H37Rv strain (Tosun et al., 2005).	Nil
	Sideritis libanotica Labill. subsp. linearis(Bentham) Bornm.	Mountain tea	Turkey	Aerial :ethanol extracts 70%	Ethanol extract showed activity against of growth H37Rv at concentrations 100 μg/ml with 4% Inhibition of growth (Tosun et al., 2005).	Nil
	Teucrium parviflorum Schreber	Germanders	Turkey	Aerial: ethanol extracts 70%	The crude plant extract showed activity against H37Rv at concentrations 100 μg/ml with 2% inhibition (Tosun et al., 2005).	Antimicrobial (Türkoğlu et al., 2010).

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Table 1 (*continued*)

Plant Family	Botanical Name	Englishname	location	Part used: Preparation Extract / Active Compound	Mode of Action	**Local medicinal uses**
	Origanum onites	Pot marjoram	Turkey	Aerial part: methanol extract 98% 1) Rosmarinic acid 2) Carvacrol 3) Apigenin	The plant methanol extract and all bioactive compound (1, 2 and 3) exhibited activity against H37Ra at MIC 784 μg/mL concentration by MGIT fluorometric test tube (Askun et al., 2009a).	Colds and sore throat (Askun et al., 2009a).
	Origanum acutidens(Hand.-Mazz.) Ietswaart.	Nil	Turkey	Aerial parts: sequential extraction method chloroform (CL),ethyl acetate (EA) and methanol (ME)/ 1) Rosmarinic acid 2) Vanillic acid	The crude chloroform, ethyl acetate and methanol extracts of plant have screened against H37Ra with MIC 0.4 mg/mL in chloroform extract (Askun et al., 2012).	Colds and sore throat (Askun et al., 2009a).
	Origanum sipyleum L.	Perennials	Turkey	Aerial parts: sequential extraction method chloroform (CL),ethyl acetate (EA) and methanol (ME)/ 1) Rosmarinic acid 2) Rutin hydrate 3) Vanillic acid	The crude chloroform, ethyl acetate and methanol extracts of plant have screened against H37Ra with MIC 1.6 mg/mL in ethyl acetate extract (Askun et al., 2012).	Antispasmodic & antibacterial (Baser, 2002).
	Salvia viridis L.	Orval	Turkey	Aerial parts: sequential extraction method chloroform (CL),ethyl acetate (EA) and methanol (ME)/ 1) Rosmarinic acid 2) Hesperidin	The crude chloroform, ethyl acetate and methanol extracts of plant have screened against H37Ra with MIC 6.3 mg/mL in chloroform extract (Askun et al., 2012).	Antimicrobial, common cold, throat infections (Ribeiro et al., 2010; Takayama et al., 2011).
	*Salvia microstegia*Boiss&Bal.	Nil	Turkey	Aerial parts: sequential extraction method chloroform (CL),ethyl acetate (EA) and methanol (ME)/ 1) Rosmarinic acid 2) p-coumaric acid 3) Luteolin	The crude chloroform, ethyl acetate and methanol extracts of plant have screened against H37Ra with MIC 0.4 mg/mL in chloroform extract (Askun et al., 2012).	Antimicrobial, common cold, throat infections (Ribeiro et al., 2010; Takayama et al., 2011).
	Salvia aethiopis L.	Nil	Turkey	Aerial: ethanol extracts 70% and fraction with petroleum ether, chloroform, methanol and water	The plant extraction and fraction by petroleum ether and chloroform was active at 50 μg/ml MIC against *M.tuberculosis* H37Ra (Tosun et al., 2004).	Nil
	Satureja boissieri Hausskn. ex Boiss.	Thyme	Turkey	Aerial parts: sequential extraction method chloroform (CL),ethyl acetate (EA) and methanol (ME)/ 1) Rosmarinic acid 2) Naringenin 3) Hesperidin	The crude chloroform, ethyl acetate and methanol extracts of plant have screened against H37Rv with MIC 0.4 mg/mL in chloroform extract (Askun et al., 2012).	Antimicrobial, common cold, throat infections (Ribeiro et al., 2010; Takayama et al., 2011).
	Stachys sylvatica L.	Nil	Turkey	Aerial: ethanol extracts 70% and fraction with petroleum ether, chloroform, methanol and water	The plant extraction and fraction by petroleum ether showed activity at 50 μg/ml MIC against *M.tuberculosis* H37Ra (Tosun et al., 2004).	Nil
	*Stachys byzantine*C.Koch.	Lamb's-ear	Turkey	Aerial parts: sequential extraction method chloroform (CL),ethyl acetate (EA) and methanol (ME)/ 1) Rosmarinic acid 2) Naringenin	The crude chloroform, ethyl acetate and methanol extracts of plant have screened against H37Ra with MIC 0.8 mg/mL in chloroform extract (Askun et al., 2012).	Antimicrobial, common cold, throat infections (Loizzo et al., 2010; Takayama et al., 2011).
	Stachys cretica L.	self-heal	Turkey	Aerial parts: sequential extraction method chloroform (CL),ethyl acetate (EA) and methanol (ME)/ 1) Rosmarinic acid	The crude chloroform, ethyl acetate and methanol extracts of plant have screened against H37Rv with MIC 6.3 mg/mL in chloroform extract (Askun et al., 2012).	Antimicrobial, common cold, throat infections (Loizzo et al., 2010; Takayama et al., 2011).
	Stachys cretica subsp. *smyrnaea* Rech.fil.	betony	Turkey	Aerial parts: sequential extraction method chloroform (CL),ethyl acetate (EA) and methanol (ME)/ 1) Rutin hydrate 2) p-coumaric acid	The crude chloroform, ethyl acetate and methanol extracts of plant have screened against H37Ra with MIC 6.3 mg/mL in chloroform extract (Askun et al., 2012).	Antimicrobial, common cold, throat infections (Loizzo et al., 2010; Takayama et al., 2011).
	Thymus syriacus Boiss.	Thymes	Turkey	Aerial parts: sequential extraction method chloroform (CL),ethyl acetate (EA) and methanol	The crude chloroform, ethyl acetate and methanol extracts of plant have screened against H37Ra with MIC 0.4 mg/mL in chloroform	Antimicrobial, common cold, throat infections (Loizzo et al.,

Table 1 (*continued*)

Plant Family	Botanical Name	Englishname	location	Part used: Preparation Extract / Active Compound	Mode of Action	**Local medicinal uses**
				(ME)/ 1) Rosmarinic acid 2) Rutin hydrate 3) p-coumaric acid	extract and 0.8 mg/mL in ethyl acetate (Askun et al., 2012).	2010; Takayama et al., 2011).
	*Thymus cilicicus*Boiss&Bal. *(endemic)*	Thymes	Turkey	Aerial parts: sequential extraction method chloroform (CL),ethyl acetate (EA) and methanol (ME)/ 1) Rosmarinic acid 2) Rutin hydrate	The crude chloroform, ethyl acetate and methanol extracts of plant have screened against H37Rv with MIC 6.3 mg/mL in chloroform extract (Askun et al., 2012).	Antimicrobial, common cold, throat infections (Loizzo et al., 2010; Takayama et al., 2011).
	Premna odorata	Alagaw	Egypt	Leaves, young stems, and flowers: hydrodistillation process 1) Trans-caryophyllene 2) β-phellandrene 3) α-pinene	The oil extracted from leaves and young stems parts showed activity. The flowers oils separately with all active compound exhibited clear anti-TB activities with values >1.5 μg/ml MTB antigen (Elmaidomy et al., 2017).	Coughs, abdominal pains, fever (Elmaidomy et al., 2017; Lirio et al., 2014).
	Rosmarinus officinalis L	Rosemary	Sudan	Leaves: Fractionation with water, n-hexane, chloroform, ethanol, ethyl acetate and n-butane.	The fractions extract of plant by n-hexane and chloroform was active against MTB H37Ra at 6.25 μg/ml (Abuzeid et al., 2014).	Pain (Abuzeid et al., 2014).
Lamiaceaea	*Phlomis fruticosa* L	Jerusalem sage	Egypt	Leaves: maceration with70% methanol	Methanol extract showed activity against *M. phlei M. smegmatis* with MIC 25 and 25 mg/ml & DIZ 18.5 and 19 mm, respectively (Safwat et al., 2018).	Bacterial infections (Cushnie and Lamb, 2011).
Lauraceae	Camphora	Cubeb	Iraq	Ethanol extract 70%	The ethanol plant extract showed activity at 200 mg/ml against growth MTB and 18 colonies in 4 week incubation time (Abbas, 2011).	Nil
	Laurus nobilis L.	Bay laurel	Turkey	Leaves : ethanol extracts 70%	At 100 μg/ml, the leaves ethanol extract showed 57% Inhibition of growth against H37Rv (Tosun et al., 2005).	Antimicrobial (Caputo et al., 2017).
Liliaceae	*Veratrum album* L.	Falsehelleborine	Turkey	Leaves: maceration by ethanol extracts 70%, fractionation by with petroleum ether, chloroform, methanol and water/ jervine	The plant extraction showed activity against H37Rv at concentrations 100 μg/ml with 95% Inhibition of growth The chloroform fractions and isolated bioactive compound is jervine have been tested against *M. tuberculosis* H37Rv showed activity with MIC value 50 and 25 μg/ml, respectively. (Tosun et al., 2005).	Nil
Linaceae	*Linum usitatissumun*	Celery	Iraq	Ethanol extract 70%	The crude extract showed activity at 0.2 ml/10 ml concentration against growth MTB and 25 colonies in 4 week incubation (Abbas, 2011).	Arthritis (Kolarovic et al., 2009).
Magnoliaceae	*Magnolia grandiflora* L.	Southern magnolia	Turkey	Leaves: ethanol extracts 70%	Ethanol extract of the leaves showed 3% inhibition of growth against H37Rv at 100 μg/ml (Tosun et al., 2005).	Itching (Jackson and Denney, 2011).
	Liriodendron tulipifera L.	Tulip tree	Turkey	Leaves: ethanol extracts 70%	The extract showed activity against H37Rv strain at 100 μg/ml with 77% inhibition (Tosun et al., 2005).	Nil
Malvaceae	*Hibiscus syriacus* L	Hibiscus	Turkey	Arial: ethanol extracts 70%	At 100 μg/ml, the leaves ethanol extract showed 22% Inhibition of growth against H37Rv (Tosun et al., 2005).	Antipyretic (Punasiya et al., 2014).
Meliaceae	*Khaya senegalensis*(Desr.) A. Juss.	Khaya wood	Sudan	Bark: fractionation in water, n-hexane, chloroform, ethanol, ethyl acetate and n-butane.	The fractions extract by chloroform, ethanol, ethyl acetate and n-butane was active at 6.25 μg/ml against MTB H37Ra (Abuzeid et al., 2014).	Jaundice (Abuzeid et al., 2014).
Mimosaceae	*Acacia seyal* Del.	Vachellia seyal	Sudan	Leaf, bark and root: Sonication dichloromethane, ethyl acetate and ethanol (10 mg/ml)	The plant parts extract showed activity with (MIC) values against *Mycobacterium aurum* at different concentration (Eldeen and Van Staden, 2008).	Cold (El Mahi and Magid, 2014).
Moraceae	*Ficus carica* L. subsp. carica	Common fig	Turkey	leaves: ethanol extracts 70%	The extract at concentration of 100 μg/ml showed 1% inhibition	Asthma and cough (Badgujar et al.,

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Table 1 (*continued*)

Plant Family	Botanical Name	Englishname	location	Part used: Preparation Extract / Active Compound	Mode of Action	**Local medicinal uses**
					against H37Rv (Tosun et al., 2005).	2014).
	Morus alba L.	White mulberry	Turkey	leaves: ethanol extracts 70%	At 100 µg/ml, the leaves ethanol extract showed 66% Inhibition of growth against H37Rv (Tosun et al., 2005).	Throat inflammation (Soni et al., 2009).
Morinaceae	*Morina persica* L.	Morina	Turkey	Aerial: ethanol extracts 70%	The ethanol extract was active against growth of H37Rv at concentrations 100 µg/ml with 5% inhibition (Tosun et al., 2005).	Antifungal (Onaran and Sağlam, 2017).
Myrtaceae	*Eucalyptus camaldulensis*Dehnh leaves,	River red gum	Sudan	hydro-distillation / 1) 1,8-cineole 74.814 2) p-Cymene 16.710 3) β-Phellandrene 3.990	The oils extract showed activity at 15 µl/ml against nine clinical isolates and H37Rv of tuberculosis (Elhassan et al., 2017).	Antifungal (Fathi and Shakarami, 2014; Katooli et al., 2011).
Nyctaginaceae	*Bougainvillea glabra* Choisy	Paper flower	Turkey	Leaves, flower: ethanol extracts 70%	Ethanol extract of both leaves and flower at 100 µg/ml showed 24% Inhibition growth against H37Rv (Tosun et al., 2005).	Analgesic (Abarca-Vargas and Petricevich, 2018).
Oleaceae	*Jasminum officinale* L.	Common jasmine	Turkey	Leaves, flower: ethanol extracts 70%	At 100 µg/ml, the leaves ethanol extract showed 13% Inhibition of growth against H37Rv (Tosun et al., 2005).	Analgesic (Rama and Ampati, 2013).
Onagraceae	*Epilobium angustifolium* L.	fireweed	Turkey	Aerial: ethanol extracts 70%	The ethanol of plant extract exhibited 7% inhibition against H37Rv at concentrations 100 µg/ml (Tosun et al., 2005).	Nil
Orobanchaceae	*Cistanche tubulosa*(Schrenk) Hook.f	Cistanche tubulosa	Egypt	Aerial part: maceration with 70% methanol	Extracts showed activity against the *M. phlei M. smegmatis and M. tuberculosis* H37Rv with MIC 62.5, 25 and 125 mg/ml with DIZ 18.5, 20 and 11 mm, respectively (Safwat et al., 2018).	Antibacterial agent (Cushnie and Lamb, 2011).
Palmae	*Hyphaene coriacea* Gaertn.	Lala palm	Egypt	Epicarp and mesocarp : methanol extract	The plant extract was active against *M. bovis* BCG at MIC > 500 µg/ml (Abou El Seoud et al., 2003).	Nil
Papaveraceae	*Glaucium leiocarpum* Boiss.	Nil	Turkey	Aerial : ethanol extracts 70%	At 100 µg/ml, the ethanol extract showed 7% Inhibition of growth against H37Rv (Tosun et al., 2005).	Antimicrobial (Yıldız and Kılıç, n. d.)
	Chelidonium majus L.	Nil	Turkey	Aerial: ethanol extracts 70% and fraction with petroleum ether, chloroform, methanol and water	The plant extract and fraction inhibited the growth at 50 µg/ml MIC against *M. tuberculosis* H37Ra (Tosun et al., 2004).	Nil
Papilionaceae	*Erythrina latissima* E.Mey.	Deciduous tree	Sudan	Bark, root: Sonication dichloromethane, ethyl acetate and ethanol (10 mg/ml)	The plant parts extract exhibited result with (MIC) values against *Mycobacterium aurum* A^+ Bark extract 1.56, 1.56 & 0.39 mg/ml Root extract 0.39, 12.5 &6.25 mg/ml (Eldeen and Van Staden, 2008).	Antimicrobial (Wanjala et al., 2002).
Pinaceae	*Picea orientalis* (L.) Link	Oriental spruce	Turkey	Wood: ethanol extracts 70% Cones: ethanol extracts 70%	At 100 µg/ml, the ethanol extract of both wood and cones showed 96% and 26% inhibition of growth against H37Rv, respectively (Tosun et al., 2005).	Nil
	Pinus brutia Ten.	Nil	Turkey	Oleoresin: ethanol extracts 70% and fraction with petroleum ether, chloroform, methanol and water	The plant extraction and fraction by petroleum ether showed inhibited growth at 50 µg/ml MIC against *M. tuberculosis* H37Ra (Tosun et al., 2004).	Nil
	Pinus nigra Arn.ssp. *pallasiana* (Lamb.) Holmbae	Nil	Turkey	Cones: ethanol extracts 70%	The petroleum ether extract of the plant inhibited the growth of *M. tuberculosis* at concentration of 50 µg/ml (Tosun et al., 2004)	Nil
Piperaceae	*Piper cubeba*	Black seeds	Iraq	Ethanol extract 70%	At 200 mg/ml concentration plant extract showed activity against growth MTB and 15 colonies in 4 week incubation (Abbas, 2011).	Nil
	Piper nigrum L	Black pepper	Egypt	Fruits: maceration with 70% methanol	The methanol extracts of fruits exhibited activity against the *M. phlei* and *M. tuberculosis* H37Rv at MIC 50 and 31.3 mg/ml with DIZ 25 and 11 mm, respectively (Safwat et al., 2018).	Oral abscesses (Safwat et al., 2018).

Table 1 (*continued*)

Plant Family	Botanical Name	Englishname	location	Part used: Preparation Extract / Active Compound	Mode of Action	**Local medicinal uses**
	Piper nigrum L	Black pepper	Iraq	Ethanol extract 70%	Ethanol extract showed activity at 200 mg/ml concentration against growth MTB and 4 colonies in 4 week incubation (Abbas, 2011).	Oral abscesses (Safwat et al., 2018).
Poaceae	*Cymbopogen citratus* leaves	Lemon grass	Sudan	Leaves: hydro-distilled 1) citral b (32.74%) 2) citral a (26.23%) 3) β-pinene (9.36%)	Anti-TB activity of essential oils extract at 15 µl/ml against nine clinical isolated *M. tuberculosis* strains and H37Rv (Elhassan et al., 2016).	Antifungal, antibacterial (Matasyoh et al., 2011; Millezi et al., 2012; Uraku et al., 2012).
	Cymbopogen nervatus Inflorescences	Lemon grass	Sudan	Leaves: hydro-distilled 1) α- verbenol (20%) 2) transpincarveol (19.41%) 3) trans- p-menthe-2,8-dien-ol (14.14) 4) d-Limonene (8.49%)	The essential oils extract showed Anti-TB activity at 15 µl/ml against nine clinical isolated *M. tuberculosis* strains and H37Rv (Elhassan et al., 2016).	Antifungal (Abushama et al., 2013).
	Cymbopogen proximus leaves	Lemon grass	Sudan	Leaves: hydro-distilled/ 1) piperitone (43.2, 45.8%) 2) elemol (13.45, 14.43%) 3) 4-carene (7.55, 9.75%) 4) β-eudesmol (5.41, 4.32%)	The essential oils extract showed Anti-TB activity at 15 µl/ml against nine clinical isolated *M. tuberculosis* strains and H37Rv (Elhassan et al., 2016).	Antibacterial (Selim, 2011).
Portulacaceae	*Portulaca oleracea* L.	Moss-rose	Egypt	Herb: methanol extract	Methanol plant extract was active against *M. bovis* BCG at MIC > 500 µg/ml (Abou El Seoud et al., 2003).	Muscle spasms (Samad et al., 2011).
Primulaceae	*Cyclamen hederifolium* Aiton	Sowbread	Turkey	Aerial & Tuber: ethanol extracts 70%	The plant extracts showed Activity against H37Rv 100 µg/ml with 4% & 36% Inhibition, respectively (Tosun et al., 2005).	Anti-inflammatory (Mohammed et al., 2018).
	Primula vulgaris Huds. subsp. sibthorpii (Hoffmanns.) W. W. Sm. et Forrest	Primrose	Turkey	Leaves & Flower: ethanol extracts 70%	At 100 µg/ml, the ethanol extract of both leaves and flower showed 41% inhibition of growth against H37Rv (Tosun et al., 2005).	Nil
Punicaceae	*Punica granatum* L.	Anar	Iran	Peel: maceration method by 70% ethanol	Potential activity against all *M. tuberculosis*isolates & H37RV with mean inhibitory zone of 18.8 mm at 200 mg/ml (Jahanpour et al., 2015).	Anti-bacterial cold, flu (Ghaemi et al., 2011; Jahanpour et al., 2015).
	Punica granatum L.	Anar	Iran	Peel: hydro-alcoholic extracts by cold percolation method	The plant extract showed best effect against *M. bovis* strain at 4 mg/ml with 32 mm inhibition zone (Ghaemi et al., 2011).	Anti-bacterial (Ghaemi et al., 2011)
	Punica granatum L.	Anar	Turkey	Leaves & Flower: ethanol extracts 70%	At 100 µg/ml, the ethanol extract of both leaves and flower showed 36% inhibition of growth against H37Rv (Tosun et al., 2005).	Anti-bacterial (Ghaemi et al., 2011)
	Punica granatum L.	Anar	Egypt	Fruit: methanol extract	Exhibited activity of plant extract against *M. bovis* BCG at MIC > 500 µg/ml (Abou El Seoud et al., 2003).	Anti-bacterial (Ghaemi et al., 2011)
Ranunculaceae	*Adonis dentat*	Delile	Egypt	Aerial part: maceration with70% methanol	Extracts methanol plant showed activity against *M. phlei* at MIC 80 mg/ml & DIZ 25 mm (Safwat et al., 2018).	Antibacterial agent (Safwat et al., 2018).
	Nigella sativa seeds	Black cumin	Sudan	Hydro-distillation / 1) p-cymene 45.26 2) Thymoquinone 35.35 3) 1,5-decadiene 9.9	The oils extract exhibited anti-TB at 15 µl/ml against nine clinical isolates and H37Rv of *tuberculosis* (Elhassan et al., 2017).	Cough, asthma & cold (Hussain and Hussain, 2016).
Rhamnaceae	*Ziziphus spina*-christi(L.) Willd.	Jujube	Sudan	Leaf, Bark: Sonication dichloromethane,ethyl acetate and ethanol (10 mg/ml)	The plant parts extract showed result with (MIC) values against *Mycobacterium aurum* A^{+} Leaf extract 12.5, 12.5 & 6.25 mg/ml Bark extract 25, 6.25 & 0.39 mg/ml (Eldeen and Van Staden, 2008).	Nil
Rutaceae	*Citrus lemon*	Limoo	Iran	Powder, fresh juice: maceration method by 70% ethanol	Moderate inhibitory activity only against sensitive (non MDR; non multi drug resistant) strains of *M. tuberculosis* (Jahanpour et al., 2015).	Cold & fever (Jahanpour et al., 2015).
	Citrus lemon	Limoo	Iran	Powder: hydro-alcoholic	The plant extract showed best	Cold & fever

(*continued on next page*)

Table 1 (*continued*)

Plant Family	Botanical Name	Englishname	location	Part used: Preparation Extract / Active Compound	Mode of Action	**Local medicinal uses**
				extracts by cold percolation method	activity against *M. smegmatis* strain at 4 mg/ml with 27 mm inhibition zone (Ghaemi et al., 2011).	(Jahanpour et al., 2015).
	Haplophyllum schelkovnikovii Grossh.	Nil	Turkey	Aerial : ethanol extracts 70%	Ethanol extract showed activity against H37Rv at concentrations 100 µg/ml with 24% inhibition (Tosun et al., 2005).	Antimicrobial (Tekin and Eruygur, 2016).
Salicaceae	*Salix babylonica* L.	Weeping willow	Egypt	Leaf: methanol extract	The plant extract was active against *M. bovis* BCG at MIC > 500 µg/ml (Abou El Seoud et al., 2003).	Antipyretic (Dizaye and Abdulqadr, 2008).
	Salix safsaf Forsk.	Safsaf willow	Egypt	Leaf: methanol extract	Methanol plant extract showed activity against *M. bovis* BCG at MIC > 500 µg/ml (Abou El Seoud et al., 2003).	Antimicrobial (Hussain et al., 2011).
Sapindaceae	*Koelreuteria paniculata* Laxm.	Goldenrain tree	Turkey	Leaf: ethanol extracts	At 100 µg/ml, the extract of plant showed 11% Inhibition against H37Rv (Tosun et al., 2005).	Nil
Sapotaceae	*Argania spinosa* L	Argan	Iraq	Mixture of argan oil: 1.5% H2O at six different concentrations.	Concentration mixture 2.5: 7.5 and 3:7 exhibited good inhibitory effect against 17 MTB clinical isolated with percentage 64.71–82.35% (AL-Saffar and Al-Dahmoshi, 2015).	Antibacterial (Habeeb Sahib Naher, 2014)
	Argania spinosa L	Argan	Iraq	Mixture of argan oil 100% and sider extract 62.5 g\L at eight different concentrations	The mixture showed good inhibitory effect against 10 MTB clinical isolated at all different concentration during 28 days incubation time (Prof. Dr. Habeeb Sahib Naher1*, 2014).	Antibacterial (Habeeb Sahib Naher, 2014)
Scrophulariaceae	*Digitalis. Sp.*	Angoshtane	Iran	Leaf: maceration method by 70% ethanol	Ethanol extract of plant was active against five isolates MDR & non MDR *M.tuberculosis* (Jahanpour et al., 2015).	Antipyretic (Jahanpour et al., 2015)
	Scrophularia. Cryptophilai Boiss. & Heldr.	Figworts	Turkey	Arial part: Me OH extract/ 1) Cryptophilic acid C 2) Chlorogenic acid	The purified compound showed marginal significant activity against H37Rv strain with 45% and 37% inhibition at MICs 100 µg /ml (Tasdemir et al., 2008).	Antiprotozoal (Tasdemir et al., 2008).
Solanaceae	*Atropa belladonna* L.	Belladonna	Turkey	Arial & fruit : ethanol extracts 70%	The plant extract showed activity against H37Rv at concentrations 100 µg /ml with 2% Inhibition of growth (Tosun et al., 2005).	Nil
	Datura stramonium	Jimsonweed	Iran	Powder: percolation extraction 80% ethanol	The crude extract was active against *M. bovis* at 375.0 µg/ml (Rahgozar et al., 2018).	Analgesic (Rahgozar et al., 2018).
	Hyoscyamus niger L.	black henbane	Turkey	Arial: ethanol extracts 70%	The extract at 100 µg /ml exhibited 8% inhibition against H37Rv (Tosun et al., 2005).	Nil
Taxodiaceae	*Cryptomeria japonica* (L. fil.) D. Don.	Japanese cedar	Turkey	Leaves: ethanol extracts 70%	The plant ethanol extract was active against H37Rv at concentrations 100 µg /ml with 57% Inhibition of growth (Tosun et al., 2005).	Nil
Thymelaeaceae	*Thymelaea hirsuta* L	hirsuta	Egypt	Aerial part: maceration with70% methanol	Methanol extract exhibited activity against the *M. phlei M. smegmatis* and *M. tuberculosis* H37Rv with MIC 40, 40 and 62.5 mg/ml with DIZ 22, 20 and10 mm, respectively (Safwat et al., 2018).	Antibacterial agent (Safwat et al., 2018).
Ulmaceae	*Ulmus glabra* Hudson	Nil	Turkey	Leaves: ethanol extracts 70% and fraction with petroleum ether, chloroform, methanol and water	The plant extraction and fraction by petroleum ether show inhibited growth at 50 µg/ml MIC against *M. tuberculosis* H37Ra (Tosun et al., 2004).	Nil
Urticaceae	*Urtica dioica* L.	Nil	Turkey	Aerial: ethanol extracts 70% and fraction with petroleum ether, chloroform, methanol and water	The plant extraction and fraction by petroleum ether exhibited anti-TB activity against *M. tuberculosis* H37Ra at 50 µg/ml MIC (Tosun et al., 2004).	Nil
Usneaceae	*Usnea barbata* (L.) Mott	Beard lichen	Turkey	whole plant: maceration by ethanol extracts 70%, fractionation by with	Ethanol extract of whole plant exhibited activity against H37Rv at 100 µg /ml.	Nil

Table 1 (*continued*)

Plant Family	Botanical Name	Englishname	location	Part used: Preparation Extract / Active Compound	Mode of Action	**Local medicinal uses**
				petroleum ether, chloroform, methanol and water/ 1) Usnic acid	The fraction and isolated compound usnic acid as major compound inhibited *M. tuberculosis* H37Rv with Minimum inhibitory concentrations (MICs) at 12.5 μg/ml (Tosun et al., 2005).	
Verbenaceae	*Vitex agnus-castus* L.	Chaste tree	Turkey	Leaves & fruit; ethanol extracts 70%	The ethanol extracts of both leaves and fruit exhibited Inhibition of growth against H37Rv at 100 μg / ml (Tosun et al., 2005).	Nil
Vitaceae	*Vitis vinifera* L.	Common grape vine	Turkey	Leaves : ethanol extracts 70%	At 100 μg/ml, the extract of plant showed 73% Inhibition against H37Rv (Tosun et al., 2005).	Nil
Zingiberaceae	*Curcuma longa* L.	Turmeric	Egypt	Root: methanol extract	The methanol plant extract of plant showed activity against *M. bovis* BCG at MIC > 500 μg /ml (Abou El Seoud et al., 2003).	Antibacterial (Santhosh and Suriyanarayanan, 2014).
Zygophyllaceae	*Peganum harmala* L.	Esphand	Iran	Seed: maceration method by 70% ethanol	Potential activity against all *M. tuberculosis* isolates & H37RV with mean inhibitory zone of 18.7 mm at 200 mg/ml (Jahanpour et al., 2015). Mean of inhibitory zone was 18.7 ± 3.5 mm at concentration of 200 mg/ml of extract against all *M. tuberculosis* isolates & H37RV. TNF-α decrease in production after extract added in human macrophage cell line U937 with infected by H37Rv strain (Davoodi et al., 2015).	Respiratory diseases (Jahanpour et al., 2015).

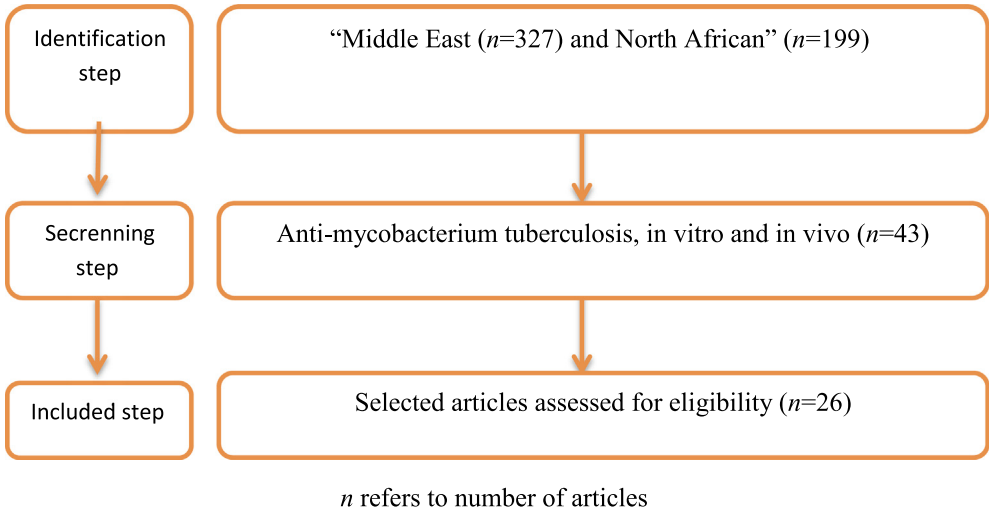

Fig. 1. Research Process.

mycobacteriology–herbal product chemistry analysis (Fadipe et al., 2017; Ibekwe and Ameh, 2014). In recent years, chromatography and spectroscopy techniques have spearheaded technological advancements that have improved the sensitivity of fractionation procedures for natural products and made way for new studies on unknown materials, previously inspected genera and unknown chemical and new bioactive compounds (Pauli et al., 2005). Thus, the development of new phytochemical approaches for bioassaying anti-TB drugs is essential to produce highly effective ways of discovering herbal resources. The terminal point must be chosen wisely to present the good orientation of bioassay steps. Bioassay-guided drug discovery has been performed for different medicinal plants, such as *Dracaena angustifolia* and *Premna odorata*, which have yielded numerous potential compounds with antimycobacterial activity (Elmaidomy et al., 2017; Gautam et al., 2007; Ibekwe and Ameh, 2014). Additional details are provided in Table 1.

3.1. Target organism

In trials for discovering new anti-TB drugs, visible results are obtained by using the actual pathogenic agent MTB. MTB H37Rv

(ATCC 27294) is the ideal target organism that is the main source of drug sensitivity in clinical sample isolates. Chemical molecules do not need to check initially when MDR-TB strains are used because these strains exhibit resistance to many drugs on the basis of a simple mechanism that is similar to the effusion pump mechanisms of several bacteria. However, genetic mutation gives rise to resistance to new bioactive compounds with novel mechanisms of action that are starkly different from the action mechanisms of currently used anti-TB drugs (Gautam et al., 2007; Ibekwe and Ameh, 2014). Given the virulence factors of the pathogenic MTB H37Rv strain, it should be carefully processed in a biosafety level 3 laboratory with specific safety requirements for workers and researchers. Most natural product researchers opt for an avirulent surrogate strain, such as *Mycobacterium smegmatis* (ATCC 607), that has exhibited good growth in many anti-TB studies (Nguta et al., 2015; Safwat et al., 2018). Other researchers use a non-pathogenic strain, such as MTB H37Ra (ATCC 25177), and vaccine strains, such as *Mycobacterium bovis* BCG (ATCC 35743) (Abou El Seoud et al., 2003). All of the above-mentioned strains are closely related to the virulent MTB H37Rv strain in terms of drug susceptibility and genetic material. Working with these kinds of strains requires a class 2 biosafety cabinet (Gautam et al., 2007; Nguta et al., 2015). Additional details are listed in Table1.

3.2. In vitro methods for evaluation of anti-TB drugs

3.2.1. Agar diffusion

The disc-and-well diffusion assay is a common method used for the evaluation of different antimicrobial agents. The capability of a natural resource to inhibit bacterial growth at an unknown concentration is screened on the basis of the length of a concentration gradient; however, this approach is insufficiently quantitative for the estimation of natural extracts and products or new crude materials. The size of the inhibition zone is a sign of microbial susceptibility or resistance to well-characterised antibiotics and can be used to calculate the mean diffusion rate of an active compound and the ratio of microbial growth (Pauli et al., 2005). Given that MTB has a cell wall with a high lipid content and that is composed of a hydrophobic area that is susceptible to less-polar compounds, its use in agar diffusion assays is not recommended (Sanusi et al., 2017). On aqueous agar, the faster diffusion rate of polar compounds than that of nonpolar compounds with identical molecular weights results in the formation of small inhibition zones and the wrong impression of weak product activity. Furthermore, active polar compounds with low molecular weight may diffuse to equilibrium before the growth of slow-growing mycobacterial colonies. In this case, a zone of inhibition is absent because the concentration of the compound is below the minimum inhibitory concentration at equilibrium (Pauli et al., 2005; Sanusi et al., 2017). Extracts of *Peganum harmala* L exhibit potential activity against all clinical MTB isolates and the H37RV strain with a mean inhibitory zone of 18.7 mm at 200 mg/ml (Jahanpour et al., 2015).

3.2.2. Micro and macro agar dilution

The activities and minimal inhibitory concentrations (MICs) of new natural plant extracts with known concentrations, fractions or materials can be quantified and evaluated in agar media. Except for many fastidious organisms, most mycobacterial strains, such as MTB, tend to produce active colonies on Middlebrook 7H10 or 7H11 agar media, which comprise oleic acid, albumin, dextrose and catalase (Gautam et al., 2007). The sample to be tested can be added to the semisolid media at 1% v/v final concentration and then, 100–200 μl, 4 ml, 1.5 ml and 20 ml of media are added to 96-well, 6-well, 24-well microplates or 150 mm diameter petri dishes, respectively. Once the agar has solidified, the inoculum is dropped on the medium surface by using a micro pipette. Then, 100 μl of inoculum is spread on Petri dishes, 10 μl of inoculum is spread on 6- or 24-well plates and 1–5 μl of inoculum is spread on 96-well plates. Incubated plates are kept overnight at 37 °C, and the plates should be inverted for the remaining incubation period. The major weakness of such a bioprocedure is that approximately a minimum of 18 days is needed for the visible growth of *Mycobacteria* colonies (Gautam et al., 2007; Nguta et al., 2015).

3.2.3. Micro-broth dilution

Small amounts of samples are required when evaluating the activities of natural products in 96-well microplates. This technique offers advantages, such as reduced cost, good overall production and automated process. The mycobacterial organism is usually cultured in Middlebrook 7H9 broth with the addition of 0.5% glycerol, 0.1% casitone, 0.05% Tween-80 and ADC (10%). The quantitative evaluation of many mycobacterial strains in liquid medium based on turbidity caused by clumping behaviour is difficult (Pauli et al., 2005). The use of alamarBlue dye indicator accelerates this technique and increases its sensitivity (Sanusi et al., 2017). The results of this method can be read visually without requiring any tools. The reduction of alamarBlue can be estimated by using a colorimeter and then subtracting the absorption measured at 600 nm from that measured at 570 nm. The microbroth dilution technique can be applied by using either resazurin or tetrazolium dye to obtain results with increased sensitivity (Martin et al., 2003). Hence, the results for partial inhibition can be obtained via high-throughput anti-TB assays by using a microplate spectrophotometer or fluorometer, making these methods perfect for determining the various activities of crude natural products at different concentrations (Sanusi et al., 2017).

3.3. Anti-TB ex vivo bioassay

The efficacies of plant natural extracts against many microorganisms and mycobacterial organisms can be profiled by using *ex vivo* models. Isolated peripheral blood mononuclear cells (PBMCs) from patients suffering from tubercular disease are an actual *ex vivo* model. The evaluation of natural compound extracts can be improved when performed on samples collected from patients with different severities of disease infection induced by various mycobacterial strains (MDR-TB or XDR-TB). Animal models provide a different immune pathological situation. For example, animal cells infected with mycobacterial strains from patients produce nitric oxide compounds that are different from those produced by noninfected animal cells (Sharma et al., 2009; Voskuil et al., 2003). The variation in gene expression in animal models accounts for the difference between plant extract activity in isolated infected PBMCs and that in noninfected PMBCs. Hence, *ex vivo* bioassays based on PMBCs for testing novel anti-TB material are more knowledge-based and less expensive than *in vivo* animal models (Nguta et al., 2015).

3.4. In vivo evaluation for anti-TB drugs

The final drug candidate for clinical evaluations must be tested at different dosages that are well tolerated in humans by using *in vivo* animal models with mycobacterial infections. Mice are exposed to virulent mycobacterial strains via aerosol; this exposure route leads to a low level of MTB accumulation in lung tissues (Falzari et al., 2005; Pauli et al., 2005). After the cellular growth of tubercule bacilli and host immune response, therapy steps are applied through two phases: the rapid multiplication phase (up to 1 month) and the latent phase, which may last for several months (Dick, 2001; Falzari et al., 2005). *In vivo* methods can be used to evaluate the activity of extracted natural products during the latent stages of infection (Franzblau et al., 2012; Lin and

Flynn, 2010). The extracts of all leaf parts and young stems and flower oils of *P. odorata* have clear anti-TB activities against >1.5 μg/ml MTB antigen with the MIC of 100 μl/ml *in vitro* and 300 μl/ml *in vivo* (Elmaidomy et al., 2017).

4. Molecular and protein studies for TB agent

This review included all of the microbial genetic content of genomics studies based on genome sequencing and bioinformatics analysis to reveal potential specific active targets for antigen discovery and support the production of known antibacterial agents and new vaccine strains. The first TB study was carried out on the MTB H37Rv strain. This study showed the attribution of specific functions (~40% of 4000 genes). Once information was available for active genes, the exact target drug was determined on the basis of its proposed metabolic production pathway (Freiberg et al., 2004). Gene expression analysis may represent a helpful tool for achieving three goals in drug discovery: (i) determining specific targets, (ii) studying antibiotic activity and (iii) proposing new types of bioassays (Freiberg et al., 2004; Kumar et al., 2013b). Extensive variations in genomic molecular targets lead to the different results of anti-TB drugs, and novel molecules should inhibit the active genes involved in the bacterial life cycle (Zhang et al., 2006). Protein production is the last step in the molecular gene process. DNA chip technology is overcoming the problems of protein production, which can be considered as a key factor in antimycobacterial drug discovery (Kumar et al., 2013b). Approximately 263 proteins from *M. bovis* BCG and MTB strains have been determined through two-dimensional gel electrophoresis coupled with mass spectrometry. This protein analysis technique provides good results with the assistance of whole-genome sequence databases (Kumar et al., 2013a; Wang and Marcotte, 2008). Different mechanisms that interrupt bacterial biosynthetic pathways, such as protein, cell wall and DNA synthesis pathways, are considered in the discovery of antitubercular agents with specific targets (Manjunatha and Smith, 2015).

5. MENA region medicinal plants with potential feature of anti-TB activity

The search results for literature on medicinal plants with anti-TB activity from the MENA region revealed few studies. The climates and traditional medicinal plants of the countries in the MENA region vary. Given the abundant biodiversity and traditional ethnomedicines available in the MENA region, a massive potential for preparing a dedicated programme for tuberculosis treatment exists.

This review included medicinal plants from different families exhibiting anti-TB activities. Table 1 shows information on these medicinal plants, including plant family, scientific name, country of origin, mode of preparation/active compound, mode of action (MIC value) and traditional uses. These plant species have different ethnomedical uses. A total of 184 plants species representing 73 families and 165 plants species (88%) show good correlations with treatment of TB or signs of respiratory disease, such as coughing, pulmonary infections, asthma and bronchitis (Table 1). A total of 93 plant species accounted for 51% of the active compounds against MTB (crude extracts and/or bioactive compounds with MICs of 0–<100 μg/ml).

These plant species are *Alyssum fulvescens* Sibth. et Sm. var. fulvescens., *Anchusa azurea* Miller var. azurea., *Atropa belladonna* L., *Bougainvillea glabra* Choisy., *Calystegia silvatica* (Kit.) Griseb., *Centaurea depressa* Bieb., *Cerinthe minor* L. auriculata (Ten.) Domac., *Cheiranthus cheiri* L., *Cistus laurifolius* L., *Clinopodium vulgare* L. subsp. arundanum (Boiss.) Nyman., *Crocus ancyrensis* (Herbert) Maw., *Cryptomeria japonica* (L. fil.) D. Don., *Elaeagnus angustifolia* L., *Echinops pungens* Trautv., *Echium plantagineum* L., *Echium italicum* L., *Epilobium angustifolium* L., *Eremostachys laciniata* (L.) Bunge., *Erysimum cuspidatum* (Bieb.) DC., *Ficus carica* L. subsp. carica., *Geranium asphodeloides* Burm. Fil., *Geranium divaricatum* Ehrh., *Geranium robertianum* L., *Glaucium leiocarpum* Boiss., *Haplophyllum schelkovnikovii* Grossh., *Helianthus annuus* L, *Helichrysum plicatum* DC. subsp. pseudoplicatum (N;ab.), *Heliotropium dolosum* De Not., *Hibiscus syriacus* L., *Hypericum triquetrifolium* Turra., *Hyoscyamus niger* L., *Inula helenium* L. subsp. turcoracemosa., *Inula peacockiana* (Aitch. et Hemsl.) Krovin., *Inula peacockiana* (Aitch. et Hemsl.) Krovin., *Jasminum officinale* L., *Juglans regia* L., *Koelreuteria paniculata* Laxm., *Lamium purpureum* L., *Laurus nobilis* L., *Lavandula stoechas* L. subsp. cariensis (Boiss.) Rozeira., *Lepidium vesicarium* L., *Liriodendron tulipifera* L., *Magnolia grandiflora* L., *Mahonia aquifolium* (Pursch.) Nutt., *Morus alba* L., *Marrubium parviflorum* Fisch. et Mey. subsp. *oligodon* (Boiss.) Seybold., *Mentha longifolia* (L.) Hudson subsp. longifolia., *Morina persica* L., *Myosotis olympica* Boiss., *Onopordum anatolicum* (Boiss.) Eig., *Phlomis lunariifolia* Sm., *Picea orientalis* (L.) Link., *Pinus nigra* Arn.ssp. *pallasiana* (Lamb.) Holmbae., *Primula vulgaris* Huds. subsp. sibthorpii (Hoffmanns.) W. W. Sm. et Forrest., *Punica granatum* L., *Raphanus raphanistrum* L., *Rosmarinus officinalis* L., *Saliva. kronenburgii* Rech., *Scrophularia. Cryptophilai* Boiss. & Heldr., *Sedum stoloniferum* Gmeli., *Sideritis libanotica* Labill. subsp. linearis (Bentham) Bornm., *Silene arguta* Fenzl., *Silene chlorifolia* Sm., *Silene dichotoma* Ehrh. subsp. sibthorpiana (Reichb.) Rech., *Silene vulgaris* (Moench) Garcke var. commutata (Guss.) Coode et Cullen., *Spinacia oleracea* L., *Tripleurospermum conoclinium* (Boiss. et Ball.) Hayek., *Teucrium parviflorum* Schreber., *Usnea barbata* (L.) Mott., *Veratrum album* L., *Vitex agnus-castus* L and *Vitis vinifera* L.

Boswellia papyrifera (Del) Hochst olibanum, *Chelidonium majus* L, *Cymbopogen citratus, Cymbopogen nervatus* inflorescences, *Cymbopogen proximus, Eucalyptus camaldulensis, Inula helenium* L. subsp. *turcoracemosa, Khaya senegalensis, Micromeria juliana, Nigella sativa, Pinus brutia* Ten, *Premna odorata, Rosmarinus officinalis*, *Salvia aethiopis* L, *Satureja aintabensis, Stachys sylvatica* L, *Thymus sipthorpii*, *Thymus vulgaris, Ulmus glabra* Hudson, *Urtica dioica* L, *Usnea barbata* (L.) Mott and *Veratrum album* L. are widely distributed in the MENA region and have been proven to contain potential agents against MTB. The bioactive compounds extracted from these plant materials have significant *in vitro* activity. Specifically, their extracts have MICs of 1–50 μg/ml.

The oil extracts of *B. papyrifera* (Del) Hochst olibanum contained octyl acetate, octyl formate, verticilla-4(20), 7,11-triene and diterpenes exhibit activity against H37Rv with the MIC of 15 μl/ml. This activity may be attributed to octyl acetate (37.26%) and diterpene constituents (20%) given that different diterpenes extracted from various plants exert activity against MTB by acting as an efflux pump inhibitor (Jin et al., 2010; Singh et al., 2010). The ethanol extraction and fraction of *C. majus* L. by petroleum ether and chloroform have inhibited growth at 50 μg/ml MIC against *M. tuberculosis* H37Ra. Essential oils and fractions containing citral b, citral a and β-pinene from *C. citratus* leaves show anti-TB activity with the MIC of 15 μl/ml. α-Verbenol (20%), transpincarveol, trans- p-menthe-2,8-dien-ol and d-limonene have been isolated from the essential oil of *C. nervatus* inflorescences and presented activity against MTB strains with the MIC of 15 μl/ml. The active compounds isolated from *C. proximus* leaves are piperitone, elemol, 4-carene and β-eudesmol. The essential oils of this plant showed anti-MTB activity with the MIC of 15 μl/ml. All essential oils obtained from the genus *Cymbopogon* have clear antitubercular activity because they contain terpenoids, which likely disrupt the lipid layers and permeability of the microbial plasma membrane (Bueno-Sánchez et al., 2009; Koroch et al., 2007).

1,8-Cineole (74.814%), p-cymene and β-phellandrene have been isolated from *E. camaldulensis* Dehnh leaves; the oil extract of this

material exhibits activity against H37Rv with the MIC of 15 μl/ml and contains high amounts of compounds, such as oxide 1,8-cineole (75%), showing biological activities and growth inhibition against mycobacterial strains (Asanova et al., 2003; Lawal et al., 2012). The fractionation of *I. helenium* L. subsp. *turcoracemosa* and isolated alantolactone bioactive compound have been screening against *M. tuberculosis* H37Rv with Minimum inhibitory concentrations (MICs) at 3.125 μg/ml. *K. senegalensis*(Desr.) A. Juss. fractions extract by chloroform ethanol, ethyl acetate and n-butane exhibited MIC value at 6.25 μg/ml against MTB H37Ra.

M. juliana exhibits activity against four strains of *M. tuberculosis* with the MIC of 12.5–100 μg/ml and the fractions by ethyl acetate showed activity against *M. tuberculosis* H37Rv and H37Ra with MIC of 100 and 50 μg/ml respectively, depended on the quaintity of phenolic compound such as rosmarinic acid, chlorogenic acid, rutin hydrate and caffeic acid were investigated as active compound. P-cymene, thymoquinone and 1,5-decadiene have been isolated from *N. sativa* seeds at concentrations of 45.26%, 35.35% and 9.9%, respectively. The oil extracts of these compounds exhibit activity against H37Rv with the MIC of 15 μl/ml. Anti-TB activity is attributed to the bioactive compound thymoquinone, which has numerous biological activities (Randhawa, 2011). *P. brutia* Ten. ethanol extraction and fraction by petroleum ether exhibited MIC value at 50 μg/ml against *M. tuberculosis* H37Ra. Trans-caryophyllene, β-phellandrene and α-pinene have been identified as bioactive compounds with anti-TB activities from the flower oils and leaf and young stem extracts of *P. odorata* with MIC > 1.5 μg/ml at the dose of 100 μl/ml *in vitro* and 300 μl/ ml *in vivo*. Anti-TB activity can be attributed to the high content of terpene compounds, such as α-pinene (38.160%) (Esquivel-Ferriño et al., 2014).

The fractions of *R. officinalis* by n-hexane and chloroform exhibited MIC value 6.25 μg/ml against MTB H37Ra. *Salvia aethiopis* L. ethanol extraction and fraction by petroleum ether and chloroform exhibited MIC value at 50 μg/ml against *M. tuberculosis* H37Ra. *S. aintabensis* presents activity against four strains of *M. tuberculosis* with the MIC of 12.5–100 μg/ml and the petroleum ether fractions showed activity against *M. tuberculosis* H37Rv and H37Ra with MIC of 25 and 50 μg/ml respectively. The ethyl acetate fractions exhibited MIC value of 12.5 μg/ml against *M. tuberculosis* H37Rv and H37Ra, respectively. The strong properties due to present high quaintity of phenolic compound such as rosmarinic acid, naringenin, hesperidin, luteolin, caffeic acid were investigated. The ethanol extraction for *S. sylvatica* L and fraction by petroleum ether showed MIC value at 50 μg/ml against *M. tuberculosis* H37Ra.

T. sipthorpii exerts activity against four strains of *M. tuberculosis* with the MIC of 12.5–100 μg/ml and the petroleum ether fractions exhibited MIC values of 12.5 and 50 μg/ml against *M. tuberculosis* H37Rv and H37Ra, respectively. The ethyl acetate fractions showed activity against *M. tuberculosis* H37Rv and H37Ra with MIC of 12.5 μg/ml. The anti-TB properties could depend on the high content of phenolic compounds such as rosmarinic acid, caffeic acid were investigated. The essential oil extracts of *T. vulgaris* exhibited strong activity against clinical isolate *M. tuberculosis* and H37Rv stander strain at MIC value ≤40 μg/ml. Carvacol compound is consider important source from thyme oil will lead to the penetration and distraction cell membrane of bacteria. *U. glabra* Hudson & *U. dioica* L. ethanol extraction and fraction by petroleum ether exhibited MIC value at 50 μg/ml against *M. tuberculosis* H37Ra. From *U. barbata* (L.) Mott. usnic acid was isolated as major compound have been screening with exhibited MIC value at 12.5 μg/ml against *M. tuberculosis* H37Rv. Alkaloid major compound fraction of *V. album* L by chloroform and jervine isolated bioactive compound showed MICs value 50 and 25 μg/ml respectively, against *M. tuberculosis* H37Rv strain. Thus, the bioactive compound extracts of these plant species may be potentially useful against TB and are potential sources of new anti-TB drugs.

Lamiaceae is a plant family from the MENA region with potential anti-TB activity. It contains 48 different plant species that have been tested against TB. Amongst all medicinal plant families, the Lamiaceae plant family has received considerable attention from researchers because they contain different bioactive compounds and are easily soluble in various solvents, including methanol, ethanol and water (Milevskaya et al., 2019). Hydro-distilled extracts and fraction from the leaves, long stems and flowers of *P. odorata, B. papyrifera, E. camaldulensis, I. helenium, K. senegalensis, N. sativa* seeds *R. officinalis* and genus *Cymbopogon* exhibit the highest number of activities against TB.

In the MENA region, Turkey has the highest number of plant species (92) with anti-TB potential because this country possesses the richest plant biodiversity in the temperate zone and approximately 10,000 species of vascular plants (Gürdal and Kültür, 2013). Turkey has the highest levels of plant biodiversity in the temperate zone and the Mediterranean basin (Şekercioğlu et al., 2011). The high terrestrial and plant biodiversity of the MENA region may be attributed to its diverse water resources and climates that range from temperate to subtropical (Yeşilada, 2002). The unique biodiversity of the MENA region provides considerable possibilities for finding new anti-TB candidates from medicinal plants.

6. Conclusion

Natural pharmaceutical products are used worldwide because of the numerous side effects of chemical drugs. Table 1 presents numerous plants that demonstrate active properties against MTB. These plants originate from the MENA region and are members of a wide range of families and species. Their effectiveness has been clearly proven through laboratory tests. Moreover, different compounds have been isolated from these plants. 22 plant species with significant effect with the MIC of ≤50 μg/ml are distributed in the MENA region. They can be used for the synthesis and manufacture of pharmaceutical products in the future. Researchers have attempted to extract crude and bioactive compounds from these plants to develop novel anti-TB drugs. The findings of previous studies may help researchers select plants, such as *I. helenium, K. senegalensis, P. odorata* and *R. officinalis* that contain diverse pharmacological active compounds, and investigate different mechanism that can be used as supportive anti-TB drugs. Therefore, efforts should be made to further investigate and identify the anti-TB activities and toxic constituents of the plants identified in this review.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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