Review

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

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A B S T R A C T
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 heliium, 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 (Adaiikappan 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 100 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 Health 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, 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 (Adaiikappan 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 (Garanjya 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 focus 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 | (Singh et al., 2011; Sathishkumar and Suryanarayanan, 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). | Antibacterial | NagChaDA, 2008 |
|              | Cuminum cyminum| Pea nut | 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. O leander | 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 | 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. Ra gweeds | 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), Antibacterial (Guo et al., 2017). |
| Helianthus annuus L. | Sunflower| Turkey | Leaf: ethanol extracts 70% | The 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). |
| Helichrysum plicatum DC. subsp. pseudopicatum (N; ab.) | Altnotu | Turkey | Aerial: ethanol extracts 70% | The aerial 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 helelenium L. subsp. tauroracemosa | 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                  |
|--------------|--------------------------------------|-------------|----------|------------------------|--------------------------|--------------------------------------------------------------------------------|----------------------------------------|
| Bignoniaceae | Inula peacockiana (Aitch. et Hemsl.) | 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). |
|              | Jasionia 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 and 17 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 Bacthma (Upadhyay et al., 2013). |
|              | Tagetes patula L                     | Mexican marigold | Egypt    | Flower: methanol extract |                          | The flower extract showed activity against M. bovis BCG 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 conoscentum (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). |
|              | Balanites aegyptiaca(L.) Del.        | Desert date  | Sudan    | Leaf, bark and root: sonication dichloromethane, ethyl acetate and ethanol (10 mg/ml) Branches, leaves and flowers; ethanol extracts 70% |                          | The plant extract exhibited strong activity against Mycobacterium aurum A' (Eldeen and Van Staden, 2008). | Headaché cough (Al-Thubiari 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 African(Lam.) Benth.         | Kigelia     | Sudan    | Leaf, bark: sonication dichloromethane, ethyl acetate and ethanol (10 mg/ml) |                          | The plant parts extract showed 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 Karakus, 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 (Kitesa 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). |
| Plant Family     | Botanical Name            | English Name         | Location     | Part used: Preparation / Active Compound | Mode of Action                                                                 | Local medicinal uses                                                                 |
|------------------|---------------------------|----------------------|--------------|------------------------------------------|--------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| Brassicaceae     | Alyssum fulvescens Sibth. et Sm. var. fulvescens | Sweet alyssum        | 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                                                                                 |
|                  | Cheiranthus cheiri L.     | Wallflower           | Turkey       | Aerial: ethanol extracts 70%              | At 100 µg/ml, the ethanol extract showed activity against H37Rv at 100 µg/ml with 21% inhibition growth (Tosun et al., 2005).                                      | Dry bronchitis (Erum et al., 2017).                                                  |
|                  | Crambe orientalis L.      | Crambe               | Turkey       | Aerial: ethanol extracts 70%              | The crude plant extract showed activity against H37Rv at 100 µg/ml with 3% inhibition of 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, the crude plant extract showed activity against H37Rv strain (Tosun et al., 2005).                                                           | Nil                                                                                 |
|                  | Isatis microcarpa var. Gay ex Boiss. | Violet cabbage      | Egypt        | Whole plant: maceration with 70% methanol | Methanol extracts of whole plant showed activity against M. phieli M. smegmatis and M. tuberculosis H37Rv with MIC 50, 12.5 and 62.5 mg/ml & DIZ 18, 20 and 12 mm, respectively (Safwat et al., 2018). | Nasal infections B cold (Safwat et al., 2018).                                      |
|                  | Lepidium sativum          | Cumin                | Iraq         | Ethanol extract 70%                      | The plant crude extract showed activity against M. phieli M. smegmatis and M. tuberculosis H37Rv with MIC 31.3, 25 and 125 µg/ml & DIZ 15, 25 and 10 mm, respectively (Safwat et al., 2018). | Bacterial infectious (Cushnie and Lamb, 2011).                                      |
|                  | Lepidium vesicarum L.     | Cruciferae           | Turkey       | Aerial: ethanol extracts 70%              | The crude plant extract showed activity against 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 M. phieli M. smegmatis and M. tuberculosis H37Rv with MIC 50, 12.5 and 62.5 mg/ml & DIZ 18, 20 and 12 mm, respectively (Safwat et al., 2018). | Bacterial infectious (Cushnie and Lamb, 2011).                                      |
|                  | Nasturtium officinale (Braun-Blaq) | Moroccon watercress | Egypt        | Aerial part: maceration with 70% methanol | The crude plant extract at concentrations 100 µg/ml showed 19% inhibition of growth against H37Rv strain (Tosun et al., 2005).                                         | Bronchitis (Safwat et al., 2018).                                                   |
|                  | Raphanus raphanistrum L.  | Wild radish          | Turkey       | Aerial: ethanol extracts 70%              | The aerial plant extract showed activity against H37Rv at 100 µg/ml with 3% inhibition of growth (Tosun et al., 2005).                                             | Anti-rheumatic (Kücükboycu et al., 2012).                                           |
| Burseraceae      | Boswellia papyrifera (Del Hochst olibanum) | Olibanum            | Sudan        | Ethanol extract 70%                      | The aerial plant extract at concentrations 100 µg/ml showed 19% inhibition of growth against H37Rv strain (Tosun et al., 2005).                                         | Antibacterial, diarrhoea (Abdoul-latif et al., 2012; Assefa et al., 2012).            |
|                  | Boswellia serrata         | Frankincense         | Iran         | Powder: percolation extraction 80% ethanol | The plant crude extract showed activity against H37Rv strain (Tosun et al., 2005).                                                                       | Anti-inflammatory (Krohn et al., 2001; Poeckel and Werz, 2006).                       |
|                  | Commiphora molmol        | Myrrh                | Iraq         | Ethanol extract 70%                      | The aerial plant extract at concentrations 100 µg/ml showed 19% inhibition of growth against H37Rv strain (Tosun et al., 2005).                                         | Anti-inflammatory (Abdallah et al., 2009).                                           |
| Capparaceae      | Capparis spinosa L.       | Caper                | Iran         | Fruits: methanol extraction              | The aerial plant extract at concentrations 100 µg/ml showed 19% inhibition of growth against H37Rv strain (Tosun et al., 2005).                                         | Anti-inflammatory (Ehsanifar et al., 2012).                                           |

*Note: The table continues on the next page.*
Table 1 (continued)

| Plant Family       | Botanical Name                           | English name | Location   | Part used: Preparation Extract / Active Compound | Mode of Action                                                                 | Local medicinal uses                                                                 |
|--------------------|------------------------------------------|--------------|------------|------------------------------------------------|--------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| Capparidaceae      | Capparis decidua (Forssk.) Edgew.        | Karira       | Sudan      | Twigs and root: Sonication dichloromethane, ethyl acetate and ethanol (10 mg/ml) | seven clinical samples & H37Rv strain (Ehsanifar et al., 2017). The plant extract exhibited activity against Mycobacterium aurum A’ with (MIC) values | Asthma (Singh et al., 2011).                                                                 |
|                    |                                          |              |            |                                                 | Twigs extract 12.5, 25 & 6.25 mg/ml Root extract 25, na & 6.25 mg/ml (Eldeen and Van Staden, 2008). At 100 µg/ml, the plant extract showed activity against H37Rv with 24% Inhibition of growth (Tosun et al., 2005). | Nil                                                                                     |
|                    | Calystegia silvatica                     |              |            |                                                 |                                                                                | Antimicrobial &antifungal (Mamadalieva et al., 2014).                                                                                      |
| Caryophyllaceae    | Silene arguta Fenzl.                     | Givisganotu  | 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). | Cold & cough (Chandra and Rawat, 2015).                                                                                                        |
|                    |                                          |              |            |                                                 | Ethanol extract at 100 µg/ml concentrations showed activity 42% Inhibition of growth against H37Rv strain (Tosun et al., 2005). |                                                                                      |
|                    | Silene chlorofolia Sm.                   | Nil          | 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). | Antimicrobial (Safwat et al., 2018).                                                                                                         |
|                    |                                          |              |            |                                                 | 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).                                                                                                          |
|                    | Silene dichotoma Ehrl. subsp. sibthorpiana | Forked catchfly | 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). | Antiinfective, antifungal (Chandra and Rawat, 2015).                                                                                         |
|                    | (Reichb.) Rech                          |              |            |                                                 |                                                                                      |                                                                                      |
|                    | Silene vulgaris (Moench) Garcke var. commutata (Guss.) Coode et Cullen | Bladder campion | 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). |                                                                                      |
|                    |                                          |              |            |                                                 |                                                                                      |                                                                                      |
| Chenopodiaceae     | Spinacia oleracea L.                     | Spinach      | Turkey     | Leaves: ethanol extracts 70%                   | The plant parts extract exhibited activity against Mycobacterium aurum A’ at different concentration (Eldeen and Van Staden, 2008). | Nil                                                                                   |
|                    |                                          |              |            |                                                 |                                                                                      |                                                                                      |
| Cistaceae          | Cistus laurfoilius L.                    | Laurel-leaf  | Turkey     | Aerial: ethanol extracts 70%                    | Antimicrobial, antitubercular (Eldeen et al., 2008). | Nil                                                                                   |
|                    |                                          | cistus       |            |                                                 | Asiatiche (Gambo and Da'u, 2014).                                                                                           |
|                    |                                          |              |            |                                                 |                                                                                      |                                                                                      |
| Combretaceae       | Combretum hartmannianum Schweinf.         | Nil          | Sudan      | Leaf, bark and root: Sonication dichloromethane, ethyl acetate and ethanol (10 mg/ml) | The extract at concentration of 100 µg/ml exhibited anti-TB activity against growth H37Rv with 15% Inhibition of growth (Tosun et al., 2005). | Ashima & expectorant (Iseri et al., 2014).                                                                                                     |
| Convolvulaceae     | Calystegia silvatica (Kit.) Griseb.      | Giant bindweed | Turkey    | Aerial: ethanol extracts 70%                    | At 100 µg/ml, the plant extract showed activity against H37Rv with 65% 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).                                                                                                         |
|                    |                                          |              |            |                                                 |                                                                                      |                                                                                      |
| Cruciferae         | 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). | Ashima & 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 (Gaikwad et al., 2010).                                                                                                         |
|                    |                                          |              |            |                                                 |                                                                                      |                                                                                      |
| Elaeagnaceae       | Elaeagnus angustifolius 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 with Petroleum ether, Chloroform, Ethyl acetate, Methanol and 70% 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 (Salwat et al., 2018). | Treat asthma, bronchitis. Used as expectorant (Salwat et al., 2018).                                                                         |
| Plant Family | Botanical Name | English Name | Location | Part used: Preparation | Extract / Active Compound | Mode of Action / Local medicinal uses |
|--------------|----------------|--------------|----------|-------------------------|---------------------------|---------------------------------------|
| **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                                    |
|              |                |              |          |                         |                           |                                       |
|              | *Geranium asphodeloides* |            |          | 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** | *Crocus ancyrensis* |              |          | Aerial: ethanol extracts 70% | At 100 µg/ml, the ethanol extract of plant showed 12% inhibition of growth against H37Rv strain (Tosun et al., 2005). | Cooked with vegetables (Kızılarslan, 2012). |
|              | *Geranium divaricatum* | Rose-scented geranium | Turkey | Aerial: ethanol extracts 70% | The extract at concentrations 100 µg/ml exhibited activity against H37Rv with 19% inhibition of growth (Tosun et al., 2005). | Anti-hyperglycaemiant (Ferreira et al., 2010). |
|              | *Geranium robertianum* | Herb Robertian | 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). | Nil                                    |
| **Hypericaceae** | *Hypericum trifolium* | Turkish | Turkey | Aerial: ethanol extracts 70% | At 100 µg/ml, the ethanol extract of plant showed activity against *M. tuberculosis* H37Rv (Tosun et al., 2004). | Snake bite, antimicrobial (Asgarpanah, 2012; Shirvastava and Dwivedi, 2015). Analgesic (Moraga et al., 2013). |
|              | *Hypericum perforatum* | St. John’s wort | Iran | Aqueous extracts | The extract showed inhibitory cell growth activity at 1 mg/ml concentration by time kill 95% in 1 week and 60 mm inhibition zone by disk diffusion method (Ajemian-Zadeh et al., 2016). | Nil                                    |
| **Iridaceae** | *Crocus ancyrensis* (Herbert) | Ankara crocus | Turkey | Flowers: ethanol extracts 70% | The extract at concentration of 100 µg/ml exhibited activity against H37Rv with 30% inhibition of growth (Tosun et al., 2005). | Asthma (Taha and Al-wadaan, 2011). |
| **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). | Cold (El-Shamy et al., 2015). |
| **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). | Antimicrobial (Borrás-Linares et al., 2014). |
| **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 (Pitarokili et al., 2013). Colds & antifungal (Pitarokili et al., 2003). |
| **Lamiaceae** | *Salvia tomentosa* Mill. | Mint | Turkey | Aerial part: methanol extract 98% | 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 (Askun et al., 2009a). | Colds & antifungal (Pitarokili et al., 2003). |
|              | *Salvia fruticosa* Mill. | Greek sage | Turkey | Aerial part: methanol extract 98% | Methanol extract and selected bioactive compound (1, 2, 3 and 4) showed activity against H37Ra at MIC 392 µg/ml by MGIT fluorometric test tube (Askun et al., 2010). | Colds & antifungal (Pitarokili et al., 2003). |
|              | *Salvia aucheri* Bentham subsp. aucheri | Turkish | Turkey | Aerial part: Hydro- | 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 (Askun et al., 2010). | Nil                                    |

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Table 1 (continued)

| Plant Family | Botanical Name | English Name | Location | Part used: Preparation | Mode of Action | Local medicinal uses |
|--------------|----------------|--------------|----------|------------------------|----------------|---------------------|
| Salvia verticillata L. subsp. amasisica | Hooked<br>bristlegrass | Turkey | Aerial part: Hydro-distillation | The essential oil extract with bioactive compounds (1 and 2) was active against M. tuberculosis H37Rv at MIC 196 µg/mL by MGIT fluorometric test tube (Askun et al., 2010). | Cold, antibacterial | (Askun et al., 2010; Soliman and Badeea, 2002). |
| Salvia. kronenburgii Rech. | Nil | Turkey | Aerial: ethanol extracts 70% | At 100 µg/ml, the ethanol extract of plant showed activity against M. tuberculosis H37Rv (Tosun et al., 2004). | Nil | |
| Sideritis albiflora | Mountain tea | Turkey | Aerial part: methanol extract 98% | The whole plant extract with active compound showed activity against H37Rv 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% | The methanol extract showed activity against H37Rv 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 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 | Zarriingah | Iran | Leaves: maceration methanol 70% | The methanol extract exhibited activity against H37Rv at 640 µg/mL concentration (Asghari et al., 2015). | Nil | |
| 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 | (Umecu 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 | (Balkali et al., 2008; Ozcan, 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). | Antimicrobial, antifungal | (Millezi et al., 2012; Pourazar Dizaji et al., 2012). |
| Thymus vulgaris | Garden Thyme | Iran | Leaves: hydro-distillation process | The essential oil showed strong activity against clinical isolate M. tuberculosis and H37Rv 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; |
| Plant Family | Botanical Name | English Name | Location | Part used: Preparation / Active Compound | Mode of Action | Local medicinal uses |
|-------------|----------------|-------------|----------|------------------------------------------|----------------|---------------------|
| Micromeria juliana (L.) Benth. ex Reich | Meris | Turkey | Aerial part: maceration by petroleum ether, ethyl acetate, methanol and fraction: 1) Rosmarinic acid 2) Naringenin 3) Hesperidin 4) Rutin hydrate 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. | |
| 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) Rutin hydrate 4) Caffeic acid | 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 H37Rv and H37Ra with MIC 392 µg/ml concentration by MGIT indicator tubes (Askun et al., 2009b). | Antimicrobial (Dadalıoğlu 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 lacinia (L.) Bunge | Bunge | Turkey | Aerial: ethanol extracts 70% | The plant extraction showed inhibition of growth H37Rv at concentrations 100 µg/ml with 9% (Tosun et al., 2005). | Headaches (Hadipour et al., 2016). |
| Lamium purpureum L. | Red deadnettle | 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). | Fracture (Yalçin and Kaya, 2006). |
| Lavandula stoechas L. subsp. cariensis (Boiss.) Rozetria | French lavender | Turkey | Aerial: ethanol extracts 70% | The ethanolic 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 extract showed 48% inhibition against H37Rv (Tosun et al., 2005). | Nil |
| Mentha 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 (Mikali et al., 2013). |
| Phlomis lunaris Sm. | Jerusalem sage | Turkey | Aerial: ethanol extracts 70% | The extract at concentrations 100 µg/ml showed 66% inhibition of growth against H37Rv strain (Tosun et al., 2005). | Nil |
| Rosmarinus officinalis L. | Nil | Turkey | Leave and flower: ethanol extracts 70% | The ethanolic extract showed activity against H37Rv at concentrations 100 µg/ml with 4% inhibition of growth (Tosun et al., 2005). | Nil |
| Sideritis libanoria 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 3% inhibition (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 (Türkoglu et al., 2010). |

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| Plant Family | Botanical Name | English Name | Location | Part used: Preparation | Mode of Action | Local medicinal uses |
|--------------|----------------|-------------|----------|------------------------|---------------|---------------------|
| Origanum onites | Pot marjoram | Turkey | Aerial: ethanol extracts (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 acuridens[Hand.-Mazz.]  | letswaart. | 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 sylpleum 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 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). | Antispasmodic & antibacterial (Rasper, 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). | Antimicrobical, 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 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). | Antimicrobical, 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 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). | 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 H37Ra with MIC 0.4 mg/mL in chloroform extract (Askun et al., 2012). | Antimicrobical, 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 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). | Nil |
| Stachys byzantinae 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). | Antimicrobical, common cold, throat infections (Ribeiro 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 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). | Antimicrobical, common cold, throat infections (Ribeiro et al., 2010; Takayama et al., 2011). |
| Stachys cretica subsp. smyrneae 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 0.8 mg/mL in chloroform extract (Askun et al., 2012). | Antimicrobical, common cold, throat infections (Ribeiro 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 0.8 mg/mL in chloroform extract (Askun et al., 2012). | Antimicrobical, common cold, throat infections (Ribeiro et al., 2010; Takayama et al., 2011). |
| Plant Family | Botanical Name | Englishname | Location | Part used: Preparation | Extract / Active Compound | Mode of Action | Local medicinal uses |
|-------------|----------------|-------------|----------|------------------------|---------------------------|---------------|----------------------|
| Mimosaceae  | Acacia seyal   | Fig         | Iraq     | Ethanol extract 70%     | Rosmarinic acid, Rutin hydrate | Antimicrobial, common cold, throat infections (Loizzo et al., 2010; Takayama et al., 2011). | |
| Moraceae    | Ficus carica    | Fig         | Turkey   | Ethanol extract 70%     | Rosmarinic acid, Rutin hydrate | Antimicrobial, common cold, throat infections (Loizzo et al., 2010; Takayama et al., 2011). | |
| Lamiaceae   | Phlomis fruticosa | Jerusalem sage | Egypt | Leaves, young stems, and flowers: hydrodistillation process | 1) Trans-caryophyllene 2) β-phellandrene 3) α-pinene | Pain (Abuzeid et al., 2014). | |
| Rosmarinus officinalis | 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). | Bacterial infections (Cushnie and Lamb, 2011). | |
| Lamiaceae   | Phlomis fruticosa | Jerusalem sage | Egypt | Leaves: maceration with 70% 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). | Nil | |
| Lauraceae   | Camphora | Cubeb | Iraq | Ethanol extract 70% | The ethanolic extract showed activity at 200 mg/ml against growth MTB and 18 colonies in 4 week incubation time (Abbas, 2011). | Antimicrobial (Caputo et al., 2017). | |
| 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). | Nil | |
| 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 100 μg/ml with 95% Inhibition of growth. The chloroform fraction 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). | |
| Malvaceae   | Hibiscus syriacus L. | Hibiscus | Turkey | Axial: ethanol extracts 70% | The extract showed activity against H37Rv strain at 100 μg/ml with 77% inhibition (Tosun et al., 2005). | Nil | |
| Meliaceae   | Khaya senegalensis(Dess.) 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) leaves: ethanol extracts 70% | 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 | Ethanol extract 70% | The extract at concentration of 100 μg/ml showed 1% inhibition | Asthma and cough (Badgujar et al., 2008). | |

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Table 1 (continued)

| Plant Family | Botanical Name | English name | Location | Part used: Preparation Extract / Active Compound | Mode of Action | Local medicinal uses |
|--------------|----------------|--------------|----------|--------------------------------------------------|---------------|---------------------|
| Moraceae     | Morus alba L.  | White mulberry | Turkey   | leaves: ethanol extracts 70%                     | against H37Rv (Tosun et al., 2005). 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). |
| Moraceae     | 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 Saglam, 2014; Katooli et al., 2011). |
| Myrtaceae    | Eucalyptus camaldulensis | River red gum | Sudan | hydro-distillation / 2) p-Cymene 16.710 3) β-Phellandrene 3.990 | The oils extract showed activity at 15 µg/ml against nine clinical isolates and H37Rv of tuberculosis (Elhassan et al., 2017). | Antifungal (Fathi and Shakarami, 2014; Katooli et al., 2011). |
| Nyctaginacea | Bougainvillea glabra | 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 | Glochicium 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.). |
| 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 A1. 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% | The plant extract and fraction with petroleum ether, chloroform, methanol and water inhibited the growth at 50 µg/ml with 5% inhibition (Tosun et al., 2004). | Nil |
| Pinaceae     | Pinus brutia Ten. | Nil | Turkey | Oleoresin: ethanol extracts 70% and fraction with petroleum ether, chloroform, methanol and water 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 |
| Pinaceae     | Pinus nigra Arn.ssp. pallassiana (Lamb.) Holmblae | 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). | Oral abscesses (Safwat et al., 2018). |
| Piperaceae   | 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). | Nil |
### Table 1 (continued)

| Plant Family | Botanical Name               | Englishname | location | Part used: Preparation | Mode of Action | Local medicinal uses |
|--------------|------------------------------|-------------|----------|-------------------------|----------------|----------------------|
| Poaceae      | Cymbopogen citratus leaves  | Lemon grass | Sudan    | Leaves: hydro-distilled | Ethanol extract showed activity at 200 mg/ml concentration against growth MTB and 4 colonies in 4 week incubation (Abbas, 2011). Anti-TB activity of essential oils at 15 µl/ml against nine clinical isolated M. tuberculosis strains and H37Rv (Elhassan et al., 2016). | Oral abscesses (Safwat et al., 2018). Antifungal, antibacterial (Matasyoh et al., 2011; Millezi et al., 2012; Uraku et al., 2012). |  |
|              | Cymbopogen nervatus          | Lemon grass | Sudan    | Leaves: hydro-distilled | 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 | 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 (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). The plant extracts showed Activity at H37Rv 100 µg/ml with 4% & 36% Inhibition, respectively (Tosun et al., 2005). | Muscle spasms (Samad et al., 2011). Anti-inflammatory (Mohammed et al., 2018). |  |
| Primulaceae  | Cyclamen hederifolium Aiton  | Sowbread    | Turkey   | Aerial & Tuber: ethanol  | The plant extracts showed Activity against H37Rv 100 µg/ml with 4% & 36% Inhibition, respectively (Tosun et al., 2005). | Anti-bacterial cold, flu (Ghaemi et al., 2011; Jahanpour et al., 2015). |  |
| Primula vulgaris Huds. subsp. sibthorpi | Primrose | Turkey | Leaves & Flower: ethanol extraction 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 extraction 70% | At 100 µg/ml, the ethanol extract of both leaves and flower showed 36% inhibition of growth against H37Rv (Tosun et al., 2005). 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) |  |
| Punica granatum L. | Anar | Egypt | Fruit: methanol extract | | |  |
| Ranunculaceae| Adonis dentat                | Delile      | Egypt    | Aerial part: maceration 70% | 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). Cough, asthma & cold (Hussain and Hassan, 2015). |  |
|             | Nigella sativa seeds         | Black cumin | Sudan    | Hydro-distillation | The oils extract exhibited anti-TB at 15 µl/ml against nine clinical isolates and H37Rv of tuberculosis (Elhassan et al., 2017). | |  |
|             | Ziziphus spina-christi(L.)   | 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); Citral b against sensitive (non MDR; non multi drug resistant) strains of M. tuberculosis (Jahanpour et al., 2015). | |  |
| 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) |  |
| Plant Family | Botanical Name | Englishname | location | Part used: Preparation | Extract / Active Compound | Mode of Action | Local medicinal uses |
|-------------|---------------|-------------|----------|------------------------|---------------------------|---------------|---------------------|
| Scrophulariaceae | Digitalis. Sp. | Angoshtane | Iran | Leaf: maceration method by 70% ethanol | | | Antipyretic |
| | | | | | | | |
| Salicaceae | Salix babylonica L. | Weeping willow | Egypt | Leaf: methanol extract | | | Antipyretic |
| | | | | | | | |
| Sapindaceae | Koelreuteria paniculata | Goldenrain tree | Turkey | Leaf: ethanol extracts | | | Nil |
| | | | | | | | |
| Sapotaceae | Argania spinosa L | Argan | Iraq | Mixture of argan oil: 1.5% H2O at six different concentrations. | | | Antibacterial |
| | | | | | | | |
| Solanaceae | Atropa belladonna L. | Belladonna | Turkey | Aerial & fruit : ethanol extracts 70% | | | Analgesic |
| | | | | | | | |
| Scrophulariaceae | Haplophyllum schelkovnikovii Grossh. | Nil | Turkey | Aerial: ethanol extracts 70% | activity against M. smegmatis strain at 4 mg/ml with 27 mm inhibition zone (Ghaemi et al., 2011). Ethanol extract showed activity against H37Rv at concentrations 100 µg/ml with 24% inhibition (Tosun et al., 2005). The plant extract was active against M. bovis BCG at MIC > 500 µg/ml (Abou El Seoud et al., 2003). Methanol plant extract showed activity against M. bovis BCG at MIC > 500 µg/ml (Abou El Seoud et al., 2003). | | | Antibacterial (Tekin and Eraygur, 2016). Anti-mycobacterial (Dizaye and Abdulqadir, 2008). Antimicrobial (Hussain et al., 2011). |
| | | | | | | | |
| Ulmaceae | Ulmus glabra Hudson | Nil | Turkey | Leaves: ethanol extracts 70% and fraction with petroleum ether, chloroform, methanol and water | | | Antibacterial agent (Salwat et al., 2018). |
| | | | | | | | |
| Urticaceae | Urtica dioica L. | Nil | Turkey | Aerial: ethanol extracts 70% and fraction with petroleum ether, chloroform, methanol and water | | | | |
| | | | | | | | |
| Usneaceae | Usnea barbata (L.) Mott | Beard lichen | Turkey | Whole plant: maceration by ethanol extracts 70%, fractionation by with | | | |
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 bioassay-guided drug discovery 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.**

### Table 1 (continued)

| Plant Family | Botanical Name | English Name | Location | Part used: Preparation / Active Compound | Mode of Action | Local medicinal uses |
|--------------|----------------|--------------|----------|------------------------------------------|---------------|---------------------|
| Verbenaceae  | Vitex agnus-castus L. | Chaste tree | Turkey | Leaves & fruit; ethanol extracts 70% | 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). 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). Respiratory diseases (Jahanpour et al., 2015). |
| 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). | Antibacterial (Santhosh and Suriyanarayanan, 2014). Respiratory diseases (Jahanpour et al., 2015). |

**Fig. 1. Research Process.**

Fig. 1. Research Process.

Identification step

“Middle East (n=327) and North African” (n=199)

Screening step

Anti-mycobacterium tuberculosis, in vitro and in vivo (n=43)

Included step

Selected articles assessed for eligibility (n=26)

n refers to number of articles

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...
and catalase (Gautam et al., 2007). The sample to be tested can be added to 7H11 agar media, which comprise oleic acid, albumin, dextrose for many fastidious organisms, most mycobacterial strains, such as MTB isolates and the H37RV strain with a mean inhibitory zone of 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 bioprocess is that approximately a minimum of 18 days is needed for the visible growth of Mycobacterium colonies (Gautam et al., 2007; Nguta et al., 2015).

### 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, 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 tubercle 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...
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 253 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 (Manjunath 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., *Centaura depressa* Bieb., *Cerinthe minor* L. auriculata (Ten.) Domac., *Cheiranthus cheiri* L., *Cistus laurifolius* L., *Clinopodium vulgare* L. subsp. arunadanum (Boiss.) Nyman., *Crocus ancyrensis* (Herbert) Maw., *Cryptomeria japonica* (L. fil.) D. Don., *Elaeagnus angustifolia* L., *Echinops pungens* Trautv., *Echium plantagineum* L., *Echiochlorus angustifolium* L., *Eremostachys lacinuataiata* (L.) Bunge., *Erysimus cuspidatum* (Bieb.) DC., *Ficus carica* L. subsp. carica, *Geranium asphodeloides* Burm. Fil., *Geranium divaricatum* Ehtr., *Geranium robertianum* L., *Glaucium leucocarpum 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. turcoracemos, *Inula peacockiana* (Aitch. et Hemsl.) Krovin., *Inula peacockiana* (Aitch. et Hemsl) Krovin., *Jasminum officinale* L., *Juglans regia* L., *Koelreuteria paniculata* Laxm., *Laurus purpureum* L., *Laurus nobilis* L., *Lavandula stoechas* L. subsp. cariensis (Boiss.) Rozeira., *Lepidium vesicarium* L., *Liriophyllum tulipifera* L., *Magnolia grandiflora* L., *Malonine 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.) Holmbar., *Primula vulgaris* Huds. subsp. sibthorpi (Hoffmanns.) W. W. Sm. et Forrest., *Punica granatum* L., *Raphanus raphanistrum* L., *Rosmarinus officinalis* L., *Salvia* *kronbergii* Rech., *Scrophularia.* *Cryptophila* Boiss. & Heldr., *Sedum stoloniferum* Gmel., *Sideritis linabatis* Labill. subsp. linearis (Benthorm) Bornm., *Silene arguta* Fenzl., *Silene chlorolda* Sm., *Silene dichotoma* Ehtr. subsp. sibthorpi (Reichb.) Rech., *Silene vulgaris* (Moench) Garcke var. commutata (Guss.) Coode et Cullen., *Spinacia oleracea* L., *Tripleurospermum concolinis* (Boiss. et Ball) Hayek., *Teucrium parviflorium* Schreber., *Usnea barbata* (L.) Mott., *Veratrum album* L., *Vitex agnus-castus* L and *Vitis vinifera* L.

*Boswellia papyrifera* (Del) Hochst olibanum, *Chelidonium majus* L., *Cymbopogon citratus* L., *Cymbopogon nervosus* inflorescences, *Cymbopogon proximus* L., *Eucalyptus camaldulensis* Inula helenium L. subsp. *tucoracemosama*, *Khaya senegalensis* Micromeria juliana, *Nigella sativa* Pinus brutia Ten. Premna odorata, Rosmarinus officinalis Nalisalis, *Salvia aethiopis* *L*, *Nigella sativa* (L.), *Silene arguta* Fenzl., *Silene chiorolda* Sm., *Silene dichotoma* Ehtr. subsp. sibthorpi (Reichb.) Rech., *Silene vulgaris* (Moench) Garcke var. commutata (Guss.) Coode et Cullen., *Spinacia oleracea* L., *Tripleurospermum concolinis* (Boiss. et Ball) Hayek., *Teucrium parviflorium* Schreber., *Usnea barbata* (L.) Mott., *Veratrum album* L., *Vitex agnus-castus* L and *Vitis vinifera* L.

The oil extracts of *B. papyrifera* (Del) Hochst olibanum contained octyl acetate, octyl formate, verticill-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 against *M. tubercu-losis* H37Ra. Essential oils and fractions containing citral b, citral a and b-pinene from *C. citratus* leaves show anti-TB activity with the MIC of 15 µl/ml. α-Verbenol (20%), transpincarveol, trans-p-menthene-2,8-dien-ol and d-limonene have been isolated from the essential oil of *C. nervosus* inflorescences and presented activity against MTB strain with the MIC of 15 µl/ml. The active compounds isolated from *C. proximus* leaves are piperitnone, elemol, 4-carene and b-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 (Buono-Sánchez et al., 2009; Koroch et al., 2007).

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

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material exhibits activity against H37Rv with the MIC of 15 µg/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 *L. helenium* L. subsp. *tucoracemos* 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 MBT 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 quantity 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 water and caffeic acid were investigated as active compound. *P. odorata* L. ethanol extraction and fraction by petroleum ether exhibited MIC value at 12.5–100 µg/ml and the petroleum ether fractions against *M. tuberculosis* H37Rv with MIC of 15 µg/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, p-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 (38.60%) (Esquivel-Ferrito 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. ethanolation 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 quantity of phenolic compound such as rosmarinic acid, naringin, 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. sipthoorpii* 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 stamder strain at MIC value ≤40 µg/ml. Carvacol compound is considered 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 solvable 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 (Yesilada, 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 mechanisms 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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References

Abarca-Vargas, R., Petricevich, V.L., 2018. Bougainvillea genus: a review on phytochemistry, pharmacology, and toxicology. Evidence-Based Complement. Altern. Med. 2018, 2474–2478

Abbas, M.S., 2011. Study the effect of some plants extracts on growth of *Mycobacterium tuberculosis* in Comparison with Ethambutol. *Iraqi J. Vet. Med.* 35, 129–134.
Azaizeh, H., Fulder, S., Khalil, K., Said, O., 2003. Ethnobotanical knowledge of local
people to medicinal plants in Sido, South Lebanon. J. Ethnopharmacol. 86, 127–130.
Askun, T., Tumen, G., Satil, F., Modanlioglu, S., Yalcin, O., 2012. Antimycobacterial
activity of ethanolic extracts of Foeniculum vulgare (common fennel) in vitro. J. Ethnopharmacol. 139, 370–378.
Abu-Zeid, O., Khalil, A., 2012. Biopreparations of essential oils of Rosmarinus officinalis
(L.) for the production of new antimycobacterial agents. J. Med. Microbiol. 61, 1208–1212.
Abd-El-Hamid, M.M., 2011. Antimicrobial activity of some Tunisian medicinal plants
against Mycobacterium tuberculosis. Res. J. Pharmacogn. Phytochem. 5, 19–22.
Adaskappan, P., Kannapiran, M., Anthonisamy, A., 2012. Antimycobacterial activity of
various extracts of Aegle marmelos (jack fruit). Food Sci. Biotechnol. 21, 1178–1183.
Abdallah, T.M., Ali, A.A., 2017. Antimicrobial activity of some plants against Mycobacterium
(tuberculosis) in vitro. J. Basic. Microbiol. 57, 822–828.
Azaizeh, H., Fulder, S., Khalil, K., Said, O., 2003. Ethnobotanical knowledge of local
people to medicinal plants in Sido, South Lebanon. J. Ethnopharmacol. 86, 127–130.
Askun, T., Tumen, G., Satil, F., Modanlioglu, S., Yalcin, O., 2012. Antimycobacterial
activity of ethanolic extracts of Foeniculum vulgare (common fennel) in vitro. J. Ethnopharmacol. 139, 370–378.
Abu-Zeid, O., Khalil, A., 2012. Biopreparations of essential oils of Rosmarinus officinalis
(L.) for the production of new antimycobacterial agents. J. Med. Microbiol. 61, 1208–1212.
Abd-El-Hamid, M.M., 2011. Antimicrobial activity of some Tunisian medicinal plants
against Mycobacterium tuberculosis. Res. J. Pharmacogn. Phytochem. 5, 19–22.
Adaskappan, P., Kannapiran, M., Anthonisamy, A., 2012. Antimycobacterial activity of
various extracts of Aegle marmelos (jack fruit). Food Sci. Biotechnol. 21, 1178–1183.
Abdallah, T.M., Ali, A.A., 2017. Antimicrobial activity of some plants against Mycobacterium
(tuberculosis) in vitro. J. Basic. Microbiol. 57, 822–828.
Elmadomy, A.H., Mohyeldin, M.M., Ibrahim, M.M., Hassan, H.M., Amin, E., Rateb, M.E., Hetta, M.H., El Sayed, K.A., 2017. Acylated iridoids and rhaponticosides from premon odorata (lamiaceae) as novel menschymal-epithelial transition factor receptor inhibitors for the control of breast cancer. Phytomer. Res. 31, 1546–1556.
El-Shamy, A.I., Abdel-Razek, A.F., Nassar, M.L., 2015. Phytochemical review of juncus gynandra. J. Indian Soc. Anim. Sci. 88, 1–7.
Erum, A., Azam, M., Jafri, M.A., Ahmed, M., Younis, A.W., 2017. Phytochemical and ethnomedical review of “Tudr-i surkh” (Cheiranthus cheiri). World J. Pharm. Res. 6, 352–359.
Esquivel-Ferreño, P.C., Cerecedo-Sorte, A.F., Ramírez-Cabriles, M.Y., Garza-González, E., Álvarez, L., Camacho-Corona, M. del r., 2014. Volatile constituents identified in hexane extract of Citrus sinensis peel and antimycobacterial tuberculosis activity of some of its constituents. J. Mex. Chem. Soc. 58, 1–14.
Fadipe, V.O., Mongalo, N.L., Oporu, A.R., Dikohoa, M.P., Makihuafo, T.J., 2017. Isolation of anti-mycobacterial compounds from Curtisia dentata (Burm.f.) C.A. Sm (Curtisiaceae). BMC Complement. Altern. Med. 17, 106. https://doi.org/10.1186/s12906-017-1818-9.
Fulazi, K., Zha, Z., Pan, D., Liu, H., Hongmanee, P., Franzblau, S.G., 2005. In vitro and in vivo activities of macrodile derivatives against Mycobacterium tuberculosis. Antimicrob. Agents Chemother. 49, 1447–1454.
Fathi, A., Shakarami, J., 2014. Larvicidal effects of essential oils of five species of Eucalyptus against Tribolium confusum (du Val) and T. castaneum (Herbert). Int. J. Agric Crop Sci. 7, 220.
Ferreira, F.M., Peixoto, F., Nunes, E., Sena, C., Sequeira, R., Sanchez Santos, M., 2010. “Microbial” Genus Geosporus L. decociones decrease blood glucose and improve liver mitochondrial oxidative phosphorylation in diabetic Goto-Kakizaki rats. Acta Biochim. Pol. 57, 399.
Franzblau, S.G., DeGroot, M.A., Cho, S.H., Andries, K., Nuermberger, E., Orme, I.M., McDaniel, M., 2011. Anti-Tuberculosis Activity of Amplicorn, L. Dick, T., Dartois, V., 2012. Comprehensive analysis of methods used for the evaluation of compounds against Mycobacterium tuberculosis. Tuberculosis 92, 453–488.
Freiberg, C., Brötz-Oesterhelt, H., Labischinski, H., 2004. The impact of Mycobacterium tuberculosis. Tuberculosis 92, 453–488.
Garaniya, N., Bapodra, A., 2014. Ethno botanical and Phytopharmacological potential of ethnomedicinal herbs: a review. Adv. Med. Plant Res. 4, 27–57.
Ibekwe, N.N., Amez, S.J., 2014. Plant natural products research in tuberculosis drug discovery and development: a situation report with focus on Nigerian biodiversity. African J. Biotechnol., 13.
Iki, A., Oni, D., Oni, O.J., 2011. Antimycobacterial activity of plumericin and isoplumericin against MDR Mycobacterium smegmatis. Molecules 15, 1546–1556.
Jahanpour, S., Ghazisaií, K., Davoodi, H., Mazandarani, M., Samet, M., Jahanpour, N., Ghaemi, E.A., 2015. Antimicrobial effects of folk medicinal plants from the North of Iran against Mycobacterium tuberculosis. Arch. Pediatr. Infect. Dis., 3.
Jalil, A., Azri, M., Shuid, A.N., Muhammad, N., 2012. Role of medicinal plants and natural products on osteoporoic fracture healing. Evidence-Based Complement. Altern. Med. 2012.
Jin, Z., Zhang, Y.-J., Guo, N., Sun, H., Li, L., Liang, J.-C., Wang, X.-L., Liu, Y., Liu, M.-Y., Wu, X.-P., 2010. Farnesol, a potential efflux pump inhibitor in Mycobacterium smegmatis. Molecules 15, 7750–7762.
Kareem, P.G., Keriño, J.M., Kenji, G.M., Cachanana, A.N., 2010. Anti-termite and antimicrobial properties of paint made from Theteva peruviana (Perr.) Schum. oil extract. African J. Pharm. Pharmacol. 4, 87–89.
Karunamoorthi, K., Theshaey, E., 2012. Ethnomedical knowledge, belief and self-reported practice of local inhabitants on traditional antimalarial plants and phytotherapy. J. Ethnopharmacol. 143, 143–150.
Katooli, N., Maghsodlo, R., Razavi, S.E., 2011. Evaluation of eucalyptus essential oil against some plant pathogenic fungi. J. Ethnopharmacol. 141, 143–150.
Kızılarslan, Ç., 2012. An ethnobotanical study of the useful and edible plants of Izmit. J. Ethnopharmacol. 146, 113–126.
Kumar, A., 2010. Antileprotic potential of ethnomedicinal herbs: a review. Adv. Med. Plant Res. 4, 27–57.
Kume, M., Akay, N., Harada, S., Kubo, T., 2012. Comparative genotoxicity analysis of methods used for the evaluation of compounds against Mycobacterium tuberculosis. Tuberculosis 92, 453–488.
Koroch, A.R., Juliani, H.R., Zygadlo, J.A., 2007. Bioactivity of essential oils and their components in biological activities: implications for plant pathogens. J. Biol. Act. Prod. Nat. 4, 19–28.
Krohn, K., Rao, M.S., Raman, N.V., Khalilullah, M., 2001. High-performance thin layer chromatographic analysis of methods used for the evaluation of compounds against Mycobacterium tuberculosis. Aust. J. Chem. 54, 721–728.
Krzysko, K., Ganiy, A., 2012. Tiger nut (Cyperus esculentus): composition, products, and synthetic agents: pyrrolodiquinolines and vermelhotin as anti-mycobacterial Tuberculosis. Tuberculosis 92, 453–488.
Kızmaz, M., Karakus, O., 2007. An ethnobotanical study of the useful and edible plants of Izmit. J. Ethnopharmacol. 105, 360–367.
Kızılarslan, Ç., 2012. An ethnobotanical study of the useful and edible plants of Izmit. J. Ethnopharmacol. 105, 360–367.
Kumar, V., Goyal, B.M., Singh, R., Gupta, V., Gupta, A., Mishra, A.K., Bansal, S., 2009. Indian medicinal plants as a source of natural products on osteoporoic fracture healing. Evidence-Based Complement. Altern. Med. 2012.
Kuroch, A.R., Juliana, H.R., Zygaldo, J.A., 2007. Bioactivity of essential oils and their components. In: Flavours and Fragrances. Springer, pp. 87–115.
Krohn, K., Rao, M.S., Raman, N.V., Khalilullah, M., 2001. High-performance thin layer chromatographic analysis of anti-inflammatory triterpenoids from Boswellia serrata Roxb. Phytochem. Anal. An Int J. Plant Chem. Biochem. Tech. 12, 374–377.
Kuşçüboyacı, N., Güven, A., Turan, N.N., Aydin, A., 2012. Antioxidant activity and total phenolic content of aqueous extract from Raphanus raphanistrum L. Turkish J. Pharm. Sci. 9.
Kumar, D., Sharma, D., Sharma, P., Katech, V.M., Venkatesan, K., Bish, D., 2013. Protoxenic extract of Mycobacterium tuberculosis isolates resistant to kanamycin and amikacin. J. Proteomics 94, 68–77.
Kuroch, A.R., Singh, D., Shahid, M.P., Singh, S., 2013b. Anti-mycobacterial activity of plumericin and isoplumericin against MDR Mycobacterium tuberculosis. Pulm. Pharmacol. Ther. 26, 332–335.
Kuzuruzum-Uz, A., Suleyman, H., Cadirci, E., Guvenalp, Z., Demizerie, L.O., 2012. Investigation on anti-inflammatory and antitumor activities of Anchusa azurea extracts and their major constituent rosomaranic acid. Zeitschrift für Naturforsch. C 67, 360–366.
Lawal, T.O., Adeniyi, B.A., Adegoke, A.O., Franzblau, S.G., Mahady, C.B., 2012. In vitro susceptibility of Mycobacterium tuberculosis to extracts of Eucalyptus...
Poeckel, D., Werz, O., 2006. Boswellic acids: biological actions and molecular effects. J. Ethnopharmacol. 105, 342–343.

Randhawa, M.A., 2011. In vitro antibacterial activity of thymoquinone, an active principle of Nigella sativa. J. Ayub Med. Coll. Abbottabad 23, 78–81.

Razavi, S.M., Nejad-Ebrahim, S., 2009. Chemical composition, allelopathic and cytotoxic effects of essential oils of flowering tops and leaves of Crambe orientalis L. from Iran. Nat. Prod. Res. 23, 1492–1498.

Rennie, C.E., Pai, I., Selvadurai, D., 2011. Tuberculosis presenting as bilateral vocal fold palsy: case report and review of otolaryngological manifestations of tuberculosis. J. Laryngol. Otol. 125, 559–562.

Reynolds, T.O., 2004. Aloe chemistry. Alos. CRC Press, 57–92.

Ribeiro, V.L.S., dos Santos, J.C., Bordin, G.A.L., Apel, M.A., Henriques, A.T., von Poser, G.L., 2010. Acaricidal properties of the essential oil from Hesperoyziago ringens (Lamiaceae) on the cattle tick Rhipicephalus (Boophilus) microplus. Bioresour. Technol. 101, 2506–2509.

Riccardi, G., Pasca, M.R., 2014. Trends in discovery of new drugs for tuberculosis therapy. J. Antimicrob. Chemother. 69, 655–658.

Roy, A., 2015. Pharmacological activities of Indian Heliotrope (Heliotropium indicum L.); a review. J. Pharmacogn Phytoremed. 4.

Sahran, S.F., Mohamed, M., Baker, A., Fadzelly, M., 2016. Ethnomedical knowledge of plants used for the treatment of tuberculosis in Johor, Malaysia. Evidence-Based Complement. Altern. Med. 2016, 1–10.

Saeidnia, S., Gohari, A.R., Ito, M., Kuchi, F., Honda, G., 2005. Bioactive constituents from Dracaena cinnabari subsp. (O. Kuntze) Lipsky. Zeitschrift für Naturforsch. C 60, 22–24.

Salati, N.A., Kazhev, M.T., R.K., A.K., F.K., R.M.A., 2016. Quercetin 3-C-glucoside recovered from the wild Egyptian Sahara plant, Euphorbia paralias L., inhibits glucose synthetase and has antibacterial activity. Tuberculosis 108, 106–113.

Saini, S., Kaur, H., Verma, B., Singh, S.K., 2009. Kigelia africana (Lam.)—an overview.

Samae, A., Ayajakumar, P.V., Panda, S., Gupta, M.K., Somkuwar, B.G., 2011. Characterisation of phytoplasma (16S rRNA) associated with little leaf disease of Portulaca grandiflora—An in silico analysis. Arch. Phytopathol. Plant Prot. 44, 1447–1455.

Santhosh, R.S., Suryanarayanan, B., 2014. Plants: a source for new antitubercular drugs. J. Herb. Drug. Res. 8, 9–21.

Sanusi, S.B., Baker, A., Fadzelly, M., Mohamed, M., Sahran, S.F., Mainassara, M.M., 2017. Southeast Asian medicinal plants as a potential source of antibacterial agent. Evidence-Based Complement. Altern. Med. 2017.

Sekericioglu, C.H., Anderson, S., Alcyon, E., Bilgin, R., Can, O.E., Semiz, G., Tasvanoglu, C., Yokes, M.B., Soyument, A., Ipekdeli, K., 2011. Turkey’s globally important biodiversity in crisis. Biol. Conserv. 144, 2752–2769.

Selm, S.A., 2011. Chemical composition, antioxidant and antimicrobial activity of the essential oil of Opuntia ficus indica f.NPC of the Egyptian lemongrass Cymbopogon proximus Stapf. Grasas y aceites 62, 55–61.

Servo, H., Uyel, Y.Y., Polatoglu, K., 2018. Composition and Acetylcholinesterase inhibition properties of Triploespernum inodorum (L.) Sch. Bip. Essential Oil from Turkey. J. Essential Oil Res. 30, 239–243.

Sharif-Rad, J., Salehi, B., Stoianovici-Radiciuc, Z.Z., Fokou, P.V.T., Sharif-Rad, Marzieh, Mahady, G.B., Sharif-Rad, Majed, Masjedi, M.-R., Lawal, T.O., Ayatollahi, S.A., 2017. Medicinal plants used in the treatment of tuberculosis-Ethnobotanical and ethnopharmacological approaches. Biotechnol. Adv. 1447–1455.

Sharma, S., Sharma, M., Bose, M., 2009. Mycobacterium tuberculosis infection of human monocyte-derived macrophages leads to apoptosis of T cells. Immunol. Cell Biol. 87, 226–234.

Shashidhar, M., Sandhya, M.S., Panik, P., Suhasini, B., 2015. Herbal drugs as anti-tuberculosis agents. Int. J. Ayurvedic Herb. Med. 4, 1895–1900.

Shrivastava, M., Dwivedi, L., 2013. Therapeutic potential of Hypericum Perforatum: a review. Int. J. Pharm. Sci. Res. 4, 4982–4988.

Singh, S., Kumar, J.K., Saisik, D., Shanker, K., Thukur, J.P., Negi, A.S., Banerjee, S., 2010. A bioactive labdane diterpenoid from Curcuma amada and its semisynthetic analogues as antibacterial agents. Eur. J. Med. Chem. 45, 1447–1455.

Singh, P., Mishra, G., Srivastava, S., Jha, K.K., Khose, R.L., 2011. Traditional uses, phytotoxic and pharmacological properties of Capparis decidua: an overview. Der Pharm. Lett. 3, 71–82.

Soliman, R.M., Badea, R., 2002. Effect of oil extracted from some medicinal plants on different mycobacterial pathogenicity. CML. J. Agric. Food Chem. 50, 669–1675.

Son, S., Sahu, K.R., Dagonaw, S., Son, Y., Kati, S., 2009. Medicinal value of [Morus alba] mulberry plant. Int. J. Res. 2, 449–450.

Soytossav, A., Soyal, S., Kumar, S., 2011. Antimicrobial activities of the essential oils of various plants against tomato late blight disease agent Phytophthora infestans. Mycopathologia 161, 119–128.

Taha, N.A., Al-wadaan, M.A., 2011. Utility and importance of walnut, Juglans regia L. Al-Qattib. Int. Res. J. 2, 449–450.

Taha, N.A., Al-wadaan, M.A., 2011. Utility and importance of walnut, Juglans regia L. Al-Qattib. Int. Res. J. 2, 449–450.

Tomlins, K., Da, F.F.M., De-Almeida, A.A.C., Rehen, C.S., Dender, R.J., Socca, E.A., Manzo, L.P., Rozza, A.L., Salvador, M.J., Pelizzon, C.H., 2011. Gastroprotective and ulcer healing effects of essential oil from Hyptis spicigera Lam. (Lamiaceae). J. Ethnopharmacol. 135, 147–155.
