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Pure Compounds and Organic Extracts from Mexican Medicinal Plants as a Source of Antimycobacterial or Antitubercular Agentes: Update Review

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Abstract

Tuberculosis is a worldwide health problem and is one of the 10 causes of death caused by a single infectious agent. It mainly affects the economically active population. Currently, there are multidrug-resistant and extended-resistance strains that are difficult to treat. In addition, several factors such as AIDS/HIV, diabetes, cancer and/or arthritis contribute to its persistence, despite having first- and second-line drugs for its treatment. For this reason, it is necessary to contribute to find or search a new treatment alternatives and medicinal plants are an important source of bioactive compounds to be considered.

This manuscript is a review of the publications made from 2014 to date, focused on describing the antimycobacterial activity of extracts and pure compounds obtained from Mexican medicinal plants and their activity against different strains of mycobacteria; as well as its antitubercular evaluation in *in vivo* models.

Keywords: Medicinal Plants; Antimycobacterial Activity; Antitubercular Activity; *Mycobacterium Tuberculosis;* Pure Compound; Extract

Introduction

Epidemiological Data About TB

Tuberculosis (TB) is caused mainly The *Mycobacterium complex includes Mycobacterium tuberculosis (M. tuberculosis), M. bovis, M. africanum, M. avium, M. microti, M. canettii, M. caprae, M. pinnipedii, M. leprae, and M. ulcerans*, among other strains. The World Health Organization (WHO) describes it as one of ten causes of death caused by an infectious agent, surpassing human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), and declared it a global emergency. In addition, they mention that a quarter of the population is infected and at risk of developing TB, above all, patients with HIV/AIDS. During 2018, it was estimated that there were 1.49 million deaths, of which 300,000 were cases of TB/HIV+. In that same year, approximately 10 million new cases were presented, where 90% were adults (>18 years), and 64% of the total cases were males. In regards to resistant TB, in 2017 approximately 558,000 cases presented resistant to rifampicin (RIF-R), and it was deduced that 3.5% of the new cases of TB were multidrugresistant (MDR). Of the total cases of MDR, 8.5% may present extended drugresistant (XDR), and approximately 23% of the world population presents latent TB and may develop the disease at any moment in their lives [1-3].

The presence of MDR-TB or XDR-TB is due to low adherence to current therapies and requires until 20 months of treatment with second-line drugs (capreomicin, kanamicin, amikacin and fluoroquinolones), which are more toxic and scarcely effective [2]. Some factors account for the failure of TB therapy are long and nonadherence treatment, late diagnosis, lack of timely and effective drugs, as well as lower availability of less toxic, cheap and effective drugs.4 MDR cases are mainly cases isoniazide-resistant (ISN-R) and RIF-R and WHO uses five DR-TB categories, being IR-TB, RR-TB, MDR-TB, pre-XDR-TB, and XDR-TB. In the last 10 years, the estimation of new MDR or /RR-TB was about 3-4%, and about 18-21% cases had previously been treated [5].

In America, 282,000 cases of TB were estimated in 2017, 82% being >15 years, and of this total, 30,000 patients were TB/HIV; the rate of incidence for Central America and Mexico is 28 cases/100,000 inhabitants. Death by TB in the continent were 24,000 for 2017, and 6,000 died of TB/HIV. Also, 11,000 cases of MDR were recorded in America, and it is estimated that approximately 6,900 of these patients were undiagnosed MDR without previous treatment. In addition, more than 500 deaths were from this cause. Success in the treatment against TB is 75.4% in America, and of those remaining, 8.3% were not evaluated, 8.6% lacked follow-up, 7.3% died and 0.5% presented treatment failure. In 33% of the new cases of TB, tests were not performed for sensitivity to drugs, which leads to underestimates of cases of MDR. In Mexico, 970 cases of MDR were reported for 2017, and the success of treatment in TB-MDR is only 56%. In addition, during this same year, 121 cases of XPR were reported [6].

In Mexico, during 2018, 16,933 cases of respiratory TB were recorded (including probable cases), of which the majority were male, with a total of 16,700 cases reported. The states with the greatest number of reports in 2017: Veracruz (2,001 cases), Baja California (1,651), Chiapas (1,215), Nuevo Leon (1,065), Guerrero (1,042) and Tamaulipas (1,017).7 Up to June 17, 2019, a total of 13,734 cases were reported (7,536 men and 6,198 women), where Veracruz (872 cases) continues to lead the states with the greatest number of cases, followed by Baja California (709), Nuevo Leon (587), Chiapas (579), Tamaulipas (518) and Guerrero (425).8 However, in 2019 and 2020, these data increased, recording 48,983 and 39,724 cases, respectively. Among the states with the greatest number of cases reported are Guerrero, State of Mexico and Veracruz, and for 2021, 20,075 cases were reported [9].

Basic Treatment against TB

There are basic treatment strategies recommended by the WHO against sensitive TB that consist in an intensive or initial phase

of 2 months, using four main drugs: INH, RIF, pyrazinamide (PZA) and ethambutol (Etb) or streptomycin (Est), and a phase of continuation of 4 months, where INH and RIF are administered. It should be noted that it is recommended to perform tests of resistance at least for INH and RIF, in order to discard cases of MDR before initiating treatment [2, 10]. The mechanism of action of first-line drugs is: INH inhibits the synthesis of mycolic acid in the mycobacteria wall, RIF inhibits the DNA-dependent RNA polymerase enzyme, suppressing the formation of chains in RNA synthesis, but not their elongation, and Etb inhibits RNA synthesis and inhibits the incorporation of mycolic acid into the mycobacteria wall. In the case of the most important antiTB-drug (PZA), its mechanism of action is not well known; some research indicates that it inhibits the FAS I system in the synthesis of mycolic acid in mycobacteria and alters the pH of the medium [11].

For the treatment of TB-MDR, there are 3 groups of drugs (A-C). From group A levofloxacin or moxifloxacin is administered, in addition to bedaquiline, rifapentine and lineazolid. From group B, cycloserine or terizidone and clofazimine are used, and from group C one might use Etb, delanamide, PZA, imipenem-cilastatin, meropenem, amicacin, Est, etionamide, protionamide and *p*-aminosalicylic acid; these are selected to complement the regimen when A and/or B drugs cannot be used. The duration of this treatment is from 18 to 20 months; however, this treatment (of up to 8 drugs) causes severe secondary effects, including hepatotoxicity (present in between 20 and 30% of patients), nephrotoxicity and ototoxicity. These some factors that favor abandoning the treatment and the appearance of MDR or XPR strains [12, 13]

Advances in the Search for Drugs for the Treatment of TB

Recent studies on the design of new antiTB medications have diversified in regards to mechanisms of action, since before they only focused on bacterial replication. Currently, numerous compounds are in clinical phases of development. Among these, we have TBAJ-587, which is a diarylquinolinain, which is in pre-phase I and inhibits the synthesis of ATP synthase and cellular respiration. Another compound in phase I development is spectinamide 1810, which inhibits protein synthesis; another type are benzotiazonones: BTZ-043 and PBTZ-169, which inhibit the synthesis of arabinogalactane, other compounds with similar action mechanism are TBA-7371 and OPC-167832. The compounds in phases I and II are Q203 (an imidazopyridine), which inhibits cellular respiration, and sutezolide, which inhibits protein synthesis. Among the compounds in phase II, we have two oxazolidinones, AZD5847 and LCB01-0371, which inhibit protein synthesis. Also in phase II, we have levofloxacin, a fluoroquinolone that inhibits the replication of DNA; nitazoxanide, which alters membrane potential and pH. Among the compounds in phase III is bedaquiline, which blocks cellular respiration. This latter compound, according to the latest update from WHO, is widely used in the treatment of TB FMR.7 In this last phase are also two nitroimidazoles: delamanide and pretomanide, which block the synthesis of mycolic and nitric acids; in addition, clofazimine (a riminophenicin) forms reactive oxygen species [14-17]. Despite having first and second line drugs for the treatment of TB, it is necessary to continue exploring various sources for the possible procurement of active compounds against FMR and XPR TB, since recently these cases have increased. It should be noted that there are several reviews which describe the potential of medicinal plant extracts and natural compounds as a source of antitubercular compounds.18-26 Among these reviews, to date only three publications were found that describe the evaluation in vivo (model of pulmonary tuberculosis) of the mixture of two triterpenes (ursolic acid and oleanolic acid) and one neolignan (lycarine A), which were obtained from medicinal plants [18-20]. In addition, recently, silymarin (SLM, a mixture of polyphenols) has been decribed, obtained from the seeds of the plant *Silybum marianum* ("milk thistle") and sibylin (Sb, main component of SLM, have shown antibacterial effects in *in vitro* trials. SLM showed a minimal inhibitory concentration (MIC) = 12.5 μM against M. tuberculosis H37Rv, a MIC = 50 μM against *M. tuberculosis* MDR (CIBIN 99, strain resistant to Est, INH, RIF, Etb and PZA), and Sb also proved active with MIC = 50 and 12.5 μM against H37Rv and against CIBIN 99. These results were confirmed by quantifying the colony-forming units (CFU). SLM and Sb showed synergic effects *in vitro* when combined with first line antiTB drugs (RIF, PZA and INH) against the sensitive strain (H37Rv), and also showed synergy when combined with second line drugs (amikacin, moxifloxacin and ethionamide) against the MDR strain (CIBIN 99). In both trials, a significant reduction was observed in the CFU compared with mycobacteria that only received antiTB. Continuing with the

in vitro trials, in macrophages derived from human monocytes (MDMH) infected with *M. tuberculosis* H37Rv and CIBIN-99, it was observed that the bacillary load diminished in the presence of SLM and Sb at a dose of 50 and 100 μM, showing that Sb had a greater effect against the strain H37Rv, while SLM was more active against CIBIN-99. Given the activity shown in vitro, the evaluation of these substances was performed *in vivo* in the model of progressive pulmonary TB in BALB/c mice infected with *M. tuberculosis* H37Rv. With this trial, it was found that SLM at a dose of 5 mg/kg administered by intragastric via daily, during 30 and 60 days, reduced the CFU in the lungs after 1 and 2 months of treatment; they also found that the combination of SLM with antiTB drugs reduced even more the bacillary load and the percentage of pneumonia in infected animals [27].

One of the main adverse effects of conventional treatment against TB is hepatotoxicity, being one of the main causes of treatment abandonment; [28-29] therefore, the use of medicinal plant extracts also represents a great alternative to counteract the hepatotoxic effect [30, 31].

Methods

The object of the present work was to review bibliographic sources in English (PUBMED, Web of Science, SciFinder, Springer, Science Direct, Google Scholar and Scopus) from 2015 to 2022 on advances in the search for medicinal plant extracts and pure compounds, and their antimycobacterial and/or antitubercular activity. Included are only articles that describe the research performed on extracts and pure compounds obtained from medicinal plants in Mexico with antimycobacterial and antitubercular activity. It should be stressed that in the absence of effective therapies and lower secondary effects to treat TB, medicinal plants are an important source of active components due to the chemical biodiversity that biosynthesizes them, which have been scarcely explored and have been used since ancestral times. In addition, it should be noted that approximately 80% of the population in developing countries employ medicinal plants to treat their various conditions, among them tuberculosis. The main data extracted from each article reviewed were: authors, year of publication, scientific name for the medicinal plant, site of collection, type of extract evaluated, name of the compounds extracted and evaluated, biological assay used, mycobacterial strains employed, and the MIC obtained.

Results and Discussion

This review includes 17 articles, the majority written in English, that describe the antimycobacterial activity of extracts from medicinal plants and the pure compounds isolated from them. Each article was reviewed carefully and filed for saving. Then, each of the articles was described in the corresponding section: integral extracts with antimycobacterial activity, pure compounds obtained from medicinal plants with antimycobacterial and/or antitubercular activity. It is worth noting that the WHO indicates that approximately 80% of the world population uses medicinal plants to treat their main health problems, among them, TB. The country of Mexico has a wide variety of medicinal plants, ranking fourth in biodiversity worldwide, coupled with the fact that the various ethnic groups (68 groups) have developed their own traditional medicine to treat their main health problems.32 Continuing with the exploration of the biological potential of several plant species as a potential source of anti-TB substances, this review summarizes the research published since 2015 on Mexican medicinal plant. It should be noted that we have previously published a review until 2015 [18-20].

Antimycobacterial Mexican Medicinal Plant Extracts

Bidens odorata is a medicinal plant commonly known as "beggarticks, black jack, burr marigolds, cobbler's pegs, Spanish needles, stickseeds, tickseeds and tickseed sunflowers", which was collected in Calpulalpan, Mexico, in June, 2016. First, the extract was prepared with hexane (Hex), dichloromethane (CH_2Cl_2), ethyl acetate (EtOAc), ethanol (EtOH) and water, which resulted active when evaluated *in vitro* against *M. tuberculosis* H37Rv and *M. smegmatis* mc^2155 by the Alamar blue colorimeter method

(MABA). The MIC values were the following: Hex extract showed MIC = 100 μg/mL; extracts CH_2Cl_2, EtOAc and EtOH showed MIC = 12.5 μg/mL against *M. tuberculosis*, and only Hex extracts (MIC = 50 μg/mL) and CH_2Cl_2 (MIC= 100 μg/mL) showed moderate activity against *M. smegmatis* [33]. The same authors reported that the EtOH extract of *B. odorata* showed hypolipemiant activity in obese mice (induced with diet and tritonWR-1339) at doses of 100 and 1000 mg/kg, and also reported a DL_{50} < 2 g/kg. In addition, this extract (EOH) had anticonvulsive and sedative activity, and the combination of this extract with paracetamol (1:1) or naproxen (1:1) showed synergic antinociceptive activity using the model of acetic acid and formalin *in vivo*. It also has antiinflammatory activity in the model of topical inflammation (TPA) and a DL_{50} >5 g/kg administered by oral via [34, 35]. Chloroform extract ($CHCl_3$) reduced diarrhea induced with castor oil [36]. To date, this specie has not been studied for its antibacterial potential.

Another medical species under investigation was *Salvia coccinea* ("blood sage, scarlet sage, Texas sage, or tropical sage") and *Teucrium bicolor* ("oreganillo") collected in Nuevo Leon, Mexico, during the summer of 2011, also showed to be active against *M. tuberculosis* H37Rv, when evaluated by MABA assay. The methanol (MeOH) extract of both species showed moderate antimycobacterial activity, with MIC= 1 25 μg/mL;[37] however, the authors did not describe the active compounds of this species.

It has been reported that the aqueous extract of the species *S. coccinea* showed antioxidant and antidiabetic activity in diabetic Wistar rats, when administered orally. It was observed that this extract favored the activity of superoxide dismutase (SOD), catalase and peroxidase glutatión [38].The MeOH extract of *S. coccinea* showed activity against (*C. albicans, C. parapsilosos, C. tropicalis, C. krusei and C. glabrata*) with MIC < 31.25 μg/mL [37].To date, the specie *Teucrium bicolor* does not has additional study.

Another Mexican species with antimycobacterial activity is *Cnidoscolus chayamansa*, known as "Mayan spinach", and was collected in Hidalgo, Mexico in 2107. The $CHCl_3$:MeOH extract (1:1) of the leaves was active (MIC = 50 μg/mL) against *M. tuberculosis* H37Rv, against 4 strains monoresistant to Est, Etb, RIF and INH, and against two clinical MDR isolates (SIN 4, resistant to first-line drugs and MMDO, resistant to INH and Etb), when evaluated by MABA [39].For the species *C. chayamansa,* various biological activities have been reported: cardioprotective, hypocholesterolemiant, antidiabetic, cytotoxic, anticancerous, antioxidant *in vitro* and *in vivo*, anti-inflammatory activity in various models *in vivo*, hepatoprotector activity before various hepatotoxic substances, antiprotozoan, and antitubercular, among other activities [40-44].

Research into three medicinal plants: *Rhynchosia precatoria, Euphorbia albomarginata* and *Helianthus annuus* (known as "rosary snoutbean", "rattlesnake weed" and "sunflower", respectively), collected between September, 2012 and January, 2015 in the cities of Alamos, Navajoa, Etchojoa and Huatabampo, in the state of Sonora, presented important activity against *M. tuberculosis* H37Rv and scant activity against *M. smegmatis,* when was evaluated by MABA. Extracts of de Hex, CH_2Cl_2 and EtOAc of *R. precatoria* (root) showed MIC = 15.6, 31.25 and 125 μg/mL, respectively, and the minimum bacteriostatic concentration (MBC, minimum concentration of the extract that does not produce a change in reincubated cultures in a fresh medium) were 31.25, 62.5 and 125 μg/mL for the three extracts, these being the ones that presented the most activity against *M. tuberculosis* H37Rv. Hex extract from the buds of *E. albomarginata* showed MIC and MBC = 250 μg/mL, and the CH_2Cl_2 extract from the stem of *H. annuus* proved inactive (MIC = 500 μg/mL). For the case of *M. smegmatis*, only the CH_2Cl_2 and EtOAc extracts of *R. precatoria* presented scant activity with MIC = 250 μg/mL and MBC = 500 μg/m [45]. *Rhynchosia precatoria* and *Euphorbia albomarginata* are medicinal species that do not have additional studies. To date, only the antioxidant and antidiabetic activity has been reported for the species *Helianthus annuus* [46-48].

Also reported is the antimycobacterial effect of some medicinal plants used by native groups from Hermosillo, Sonora, México, which are used to treat symptoms related to TB. The species were collected and evaluated by MABA against *M. tuberculosis*

H37Rv and against some clinical isolates of *M. tuberculosis*. $CHCl_3$, CH_2Cl_2, EtOAc and MeOH extracts of *Ambrosia confertiflora* (mugwort) showed MIC = 90, 120, 160 and 200 μg/mL, respectively, and the MeOH extracts of *Guaiacum coulteri* (guajacum) and of *Ambrosia ambrosoides* ("chicura") was inactive, with MIC = 790 and 1000 μg/mL, respectively [49].

The ethylic ether extract of *A. confertiflora* inhibited the growth of larva of *Aedes aegypti* (dengue mosquito, CI_{50} <400 mg/mL), and was toxic against Vero cells [50], and EtOH extract also inhibited the growth of *Helicobacter pilori* with MIC <400 mg/mL. To date, only the MeOH and EtOH extracts of *A. confertiflora* have been reported, showing antifungal activity against *Penicillum expansum, Fusarium poae* and *F. moniliforme* [51]. However, their activity against gram positive and/or negative bacteria remains unknown. For the species *Guaiacum coulteri*, it has been reported that the aqueous extract shows hypoglycemic activity in diabetic rabbits and mice [52-53]. The MeOH extract of this species has activity against *Helicobacter pilori* [54].

In a recent study, the antimicrobial activity was reported for extracts of *Musa* spp ("apple tree"), collected in June, 2017. The most active extract against *M. tuberculosis* H37Rv was EtOAc (MIC = 12.5 μg/mL) and against clinical isolate CIBIM 99 (MIC = 6.25 μg/mL). Meanwhile, the Hex extract presented MIC = 25 μg/mL against the sensitive strain (H37Rv) and MIC = 12.5 μg/mL against the MDR strain. The least active extract was MeOH, with MIC = 50 μg/mL against H37Rv and MIC = 25 μg/mL against the MDR strain. In this case, only the antimycobacterial effect of the extracts was reported, without describing the active compounds [55]. Various extracts (organic and aqueous) of *Musa* spp. have antidiabetic activity in various biological models (mice, rats or rabbits), and only one clinical study was performed with the aqueous extract of flowers of Musa spp in patients with diabetes, where it demonstrated antidiabetic activity [56]. On the other hand, antiviral and cytotoxic activity has been reported against the virus for Chikungunya, enterovirus 71 and against the yellow fever virus for Hex, acetonic, ethanolic and aqueous extracts of the leaves, pseudostems and upper body of Musa spp. The results indicated that only the acetonic extract was the most active (CI_{50} < 50 μg/mL) against the Chikungunya virus, and acetonic, EtOH and Hex extracts were more active against the yellow fever virus (CI_{50} < 76.5 μg/mL). Qualitative phytochemical analysis reported that the extracts contain flavonoids, saponins and terpenoids [57].

Hernández-García et al. reported the antimycobacterial activity of fruits of *Acacia farnesiana*, known as "huizache", collected in Acatlán de Osorio, Puebla, Mexico, evaluated by MABA. They obtained Hex, $CHCl_3$, MeOH and aqueous extracts; these four extracts inhibited the growth of *M. tuberculosis* H37Rv with MIC = 200 μg/mL; while the Hex and aqueous extracts showed activity against clinical isolate MDR G122 (with resistance to INH, RIF and Etb) with MIC = 100 μg/mL [58]. Additionally, the hydroalcoholic extract of *A. farnesiana* has antihelmintic activity *in vivo*, specifically against eggs and larva *Haemonchus contortus* (gastrointestinal nematode in cattle). From the active extract, the compounds gallic acid, methyl gallate, ethyl gallate, naringin, naringenin 7-O-(4″, 6″-digalloylglucoside), naringenin 7-O-(6″-galloylgluco-side) and naringenin were isolated [57, 58] In addition, the aqueous extract showed antiparasitary activity (Haemonchus contortus) in trials in vitro and in vivo [59, 60]. Also, the MeOH extract at 80% showed antioxidant activity *in vitro* (determined by colorimetric method of ABTS and DPPH, and on the cellular line pig kidney cells LLC-PK1) and *in vivo* (evaluated in gerbils) [61]. On the other hand, only the MeOH extract of *A. farnesiana* has activity against *Vibrio cholerae*, whose MBC (minimum bariostatic concentration) was 0.5 y 0.9 mg/mL against strains 1837 and 569-B, respectively [62], and was also active against *Campylobacter jejuni* and *C. coli,* with MBC = 0.3 mg/mL [63].

Another plant studied is *Trixis angustifolia* ("threefolds"), which was collected in Durango, Mexico. From the aerial parts, Hex, $CHCl_3$ and EtOAc extracts were obtained. The Hex and $CHCl_3$ extracts showed activity against *M. tuberculosis* H37Rv (MIC = 25 μg/mL), and the EtOAc extract was less active (MIC = 50 μg/mL) [64].On the other hand, the EtOH extract of *T. angustifolia* showed antinociceptive activity (model of contortions induced with acetic acid). The authors concluded that this medicinal species has a strong potential for compounds with peripheral antinociceptive effect [65].

The anthracycline identified as steffimycin B, is isolated from the endophytic fungus (*Streptomyces scabrisporus*) located in the medicinal species *Amphipterygium adstringens.* It presents activity against *M. tuberculosis* H37Rv (MIC = 7.8 μg/mL) and against *M tuberculosis* resistant to RIF (Mtb-209) with MIC = 3.9 mg/mL [66]. Goméz-Cansino [67] describes the antimycobacterial evaluation of the CH_2Cl_2:MeOH (1:1) extract from leaves and bark of five species of *Amphipterygium* (*amplifolia, molle, adstringens, glaucum* and *simplicifolium*), collected in Guadalajara and Michoacan. Another five species evaluated were *Vismia mexicana, V. baccifera, Clusia guatemalensis, C. lundellii* and *Calophyllum brasiliense,* whose CH_2Cl_2:MeOH (1:1) extract was prepared from leaves collected in Veracruz and Oaxaca. Of these ten species, evaluated by MABA assay, only the species *A. glaucum* (IC_{50} = 1.87 μg/mL), *A. molle,* (IC_{50} = 2.27 μg/mL), *A. simplicifolium* (IC_{50} = 2.35 μg/mL), *Calophyllum brasiliense* (IC_{50} = 3.02 μg/mL), *Vismia mexicana* (IC_{50} = 3.64 μg/mL), *V. baccifera* (IC_{50} = 3.82 μg/mL), were active against *M. tuberculosis* H37Rv. The authors reported that the active species of *Amphipterygium* contains masticadienoicacid and α- y β-hydromasticadienoic acid; however, these compounds were not evaluated against contra *M. tuberculosis*. These species were also active against HIV-Reverse Transcriptase, with values of IC_{50} were between 26.24-97.83 μg/mL [67].

Compounds with Antimycobacterial Properties *in vitro* Isolated from Mexican Medicinal Plants

The compounds (glycosides, 1) isolated from EtOH extract of *Bidens odorata* and ácido 3,5-dihydrobenzoic acid (**2**, isolated from aqueous extract) were active when evaluated *in vitro* against *M. tuberculosis* H37Rv and *M. smegmatis* mc^2155 by MABA. The glycosidic compound (1) showed MIC = 3.125 μg/mL and the 3,5- dihydroxybenzoic acid showed MIC = 50 μg/mL [33].

From the active extract of *C. chayamansa,* moretenol, bruisette acetate, kaempferol-3,7-dimetil ether and 5-hydroxy-7,3',4'-trimetoxiflavonone were obtained by chemical fractioning and were evaluated against some mycobacteria strain tetsted by MABA assay. Moretenol (3) and moretenil acetate (4) were the most active compounds against *M. tuberculosis* H37Rv, with MIC = 25 μg/mL; both compounds also inhibited the growth of *Entamoeba histolytica* and *Giardia lamblia* (IC_{50} < 71.70 mg/mL) and showed significant topical (TPA model) and systemic (carragenine model) anti-inflammatory activity [39].

Coronado-Aceves et al. [68] reported activity against *M. tuberculosis* H37Rv of six isoflavonoids obtained from the roots of *Rhynchosia precatoria* (collected in Etchojo, Sonora, Mexico during July, 2015); these compounds were isolated from the CH_2Cl_2 extract by chemical fractionation. The compounds were identified as precatorin A (5), precatorin B (6), precatorin C (7), lupinifolinain (8), cajanone (9) and lupinifolinol (10). Compounds 5-9 were active against *M. tuberculosis,* with values of MIC = 31.25 μg/mL, and compounds 5, 6 and 8 showed slight activity against *M. smegmatis* (MIC 125 μg/mL). The combination 1:2 of lupinifolinain (8) and cajanone (9) showed synergic effect against both strains of Mycobacterias. In addition, five of these isoflavones (5-9) were cytotoxic on murine macrophages (RAW 264.7), with values of IC_{50} between 13.3-46.98 μM.

From the most active extract ($CHCl_3$ extract) of *A. confertiflora,* two sesquiterpenic lactones were isolated, identified as reynosin (11) and santamarine (12), with antimycobacterial activity. Reynosin showed MIC = 64 μg/mL and MBC = 128 μg/mL against *M. tuberculosis* H37Rv; MIC and MBC = 128 μg/mL for *M. tuberculosis* isolated 366-2009; MIC = 64 μg/mL and MBC = 128 μg/mL against the isolate 104-2010, and isolate 430-2010 showed MIC = 128 μg/mL. Santamarine presented MIC and MBC = 128 μg/mL against *M. tuberculosis* H37Rv; the isolate 366-2009 showed MIC = 128 μg/mL and the MIC and MBC was 128 μg/mL against the isolate 104-2010 [69]. Santamarine (12) showed anticancer activity *in vitro* against the cellular lines of human lung adenocarcinoma (A549 and NCI-H1650) and against the cellular line of normal lung (NL-20) by inhibiting oxidative stress, while inhibiting NF-kB, protein module Bcl-2 and active caspase-3, inducing mitochondrial apoptosis of these cellular lines [70]. They also reported the anticancer activity of compound 12 on the HeLa cellular line by inhibiting thioredoxin reductase, causing alteration in the cellular redox system,[71] and against murine L1210 leukemia cells by inhibiting phase G(2)/M of the cellular cycle [72]. It had the same effect on the hepatocellular line HepG2, with IC_{50} ~70 μM [73].This compound (12) at 100 μM showed anti-inflammatory activity *in vitro*, by reducing levels of IL-6, IL-1β, TNF-α, prostaglandins (PGE2), lipooxyge-

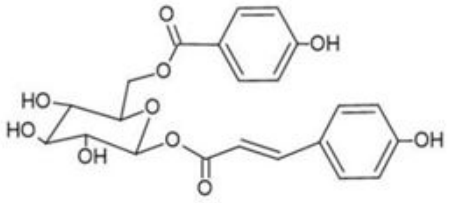
nase-5 and COX-2 [74, 75]. An additional work, the anti-inflammatory effect of santamarine on macrophages RAW264.7 stimulated with lipopolysaccharide and in macrophages of murine peritoneum by inhibiting the production of inducible nitric oxide synthetase (iNOS), COX-2, and PGE2, as well as reducing levels of TNF-α and IL-1β was reported [75, 76].

Reynosin (11, isolated from *Laurus nobilis*) showed hepatoprotector effect in culture of primary hepatocytes of damaged rats with thioacetamide (200 mg/kg) and in rats. This compound inhibited apoptosis and damage to the DNA of hepatocytes [77].

From aqueous and MeOH extracts of *Acacia farnesiana* methyl gallate (13) was obtained; this compound showed activity against the sensitive strain (MIC = 50 μg/mL), while its acetylated derivative (triacetyl methyl gallate) demonstrated greater antimycobacterial activity (MIC = 25 μg/mL) [58]. The reynosin (11) was one of the compounds responsible for activity against the parasite *Haemonchus contortus* [60].

From the Hex extract of *Trixis angustifolia,* five fractions were obtained, which were also subjected to MABA assays against *M. tuberculosis* H37Rv, the most active being fraction 5 with MIC = 6.25 μg/mL, followed by fraction 4 with MIC = 12.5 μg/mL; from these fractions, two flavones (pebrella -14- and salvigenine) were obtained. The active fractions (4 and 5) were subjected to a following fractioning and 12 sub-fractions were obtained, whose antimycobacterial activity was also determined against *M. tuberculosis* H37Rv, sub-fractions 1-8 being the most active (MIC = 12.5 μg/mL). From sub-fraction 7, a mixture of aliphatic compounds was obtained, which were not characterized, and this fraction was called active fraction (AF). The Hex extract, AF and pebrella were again subjected to MABA assay, where it was tested against *M. tuberculosis* H37Rv, two monoresistant strains (resistant Est, RIF and INH) and against three clinical MDR isolates: SIN-4 (resistant to various drugs), MTY 147 (resistant to INH, RIF, Etb and ethionamide), and MMDO (resistant to INH and Etb). The Hex extract showed MIC = 12.5 μg/mL against the strains *M. tuberculosis* R-INH and against the isolate SIN-4 with mIC = 25 μg/mL against the strains R-RIF, MTY 147 and MMDO; while for the strain R-Est it showed MIC = 50 μg/mL. The AF sub-fraction showed MIC =12.5 μg/mL against all the strains evaluated, and pebrella alone was inactive; however, the combination of AF with pebrella (14) showed synergic effect against H37RV, MIC = 6.25 μg/mL for pebrella and 0.78 μg/mL for the strains of *M. tuberculosis* monoresistant to INH and Est, and against the MDR strain MMDO, and in the case of the strain monoresistant to RIF and for the MDR strain MTY, the value was MIC = 12.5 μg/mL [64].

Three alkaloids were identified as ibogaine (15), voacangine (16), and voacamine (17), which were isolated from the hexaic extract of the root and bark of *Tabernaemontana alba* and *T. arborea.* Of these three alkaloids, voacamine (17) was 15 times more active against *M. tuberculosis* H37Rv (MIC = 15.6 μg/mL), than the other two alkaloids (250 μg/mL), but was less active than the original extract, which showed MIC = 7.8 μg/mL. However, these alkaloids were very cytotoxic against the Vero cells, with a poor selectivity index (<1.42) [78].The chemical structures of the compounds mentioned in this section are shown in Figure 1. It is important to mention that the chemical structure of the compounds isolated from medicinal plants from Mexico have no structural relationship with any anti-TB drug.



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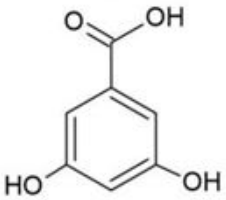

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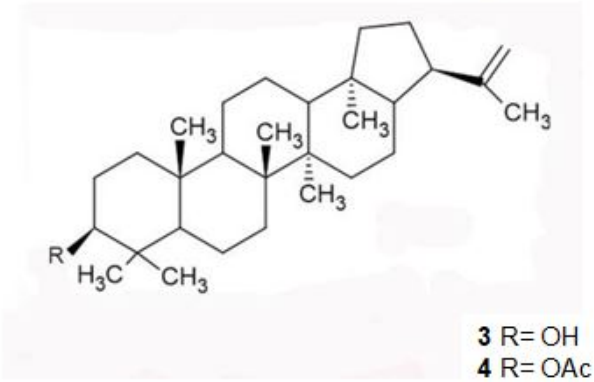
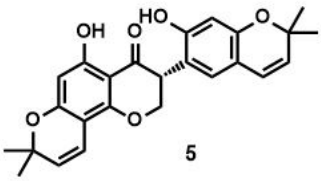


3 R= OH
4 R= OAc



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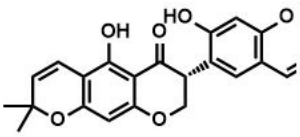

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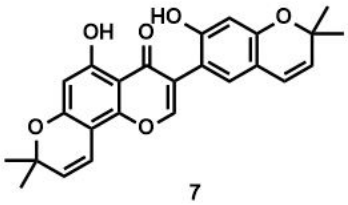

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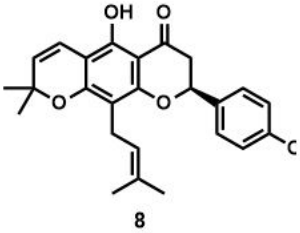

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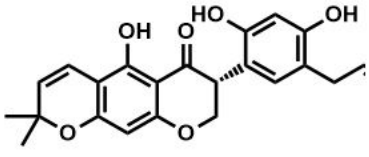

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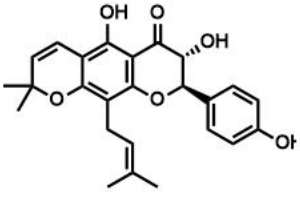

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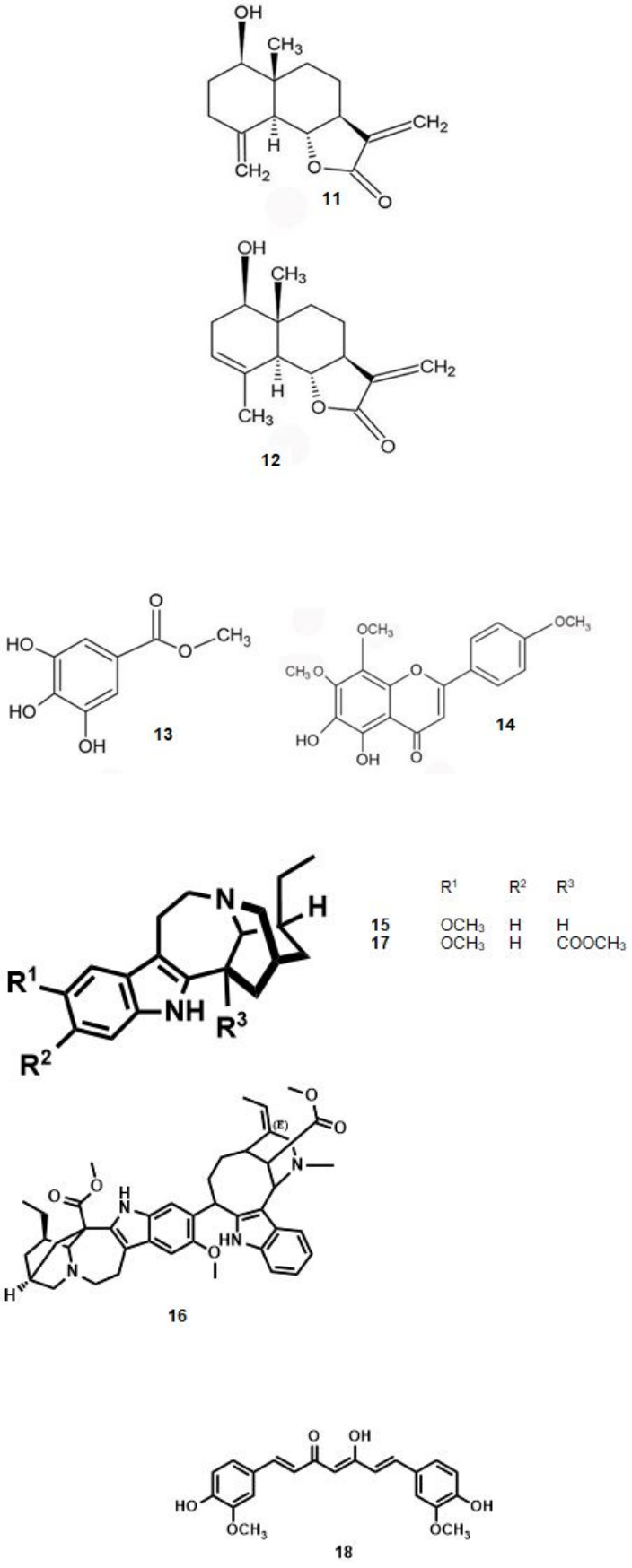

Figure 1: Chemical structure of compounds with antimycobacterial activity

Compounds with Antitubercular Potential *in vivo* Obtained From Medicinal Plants

To date, only curcumin (CUR, 18, Sigma) a natural product with antioxidant, anti-inflammatory and antibacterial activitie, isolated mainly from *Curcuma longa*, has been reported to show antitubercular effect. This compound was dissolved in DMSO and was administered at a dose of 32 and 16 μg/mL by intraperitoneal via for 21 days, at day 14 the infection was introduced. The experiment was performed in male Balb/C mice infected with the strain *M. tuberculosis* H32Rv by intratracheal route. This compound reduced the bacillary load in the lungs and reduced pneumonia in the infected animals. It should be noted that the better effect was observed at a low dose (16 μg/mL) than at high dose. In addition, they reported a reduction in neuroinflammation (reduced expression of TNF-α, IFN and IL12) in these animals.79 Notably, this compound has various biological activities, especially the anti-inflammatory, antiarthritic, antioxidant, anticancer and hepatoprotector activities, among others.80 It is important to highlight that to date few compounds such as ursolic acid, oleanolic acid, lycarin A, silymarin and silybin (obtained from medicinal plants) have been evaluated in in vivo model of progressive pulmonary TB in Balb/C.18-20,27

Conclusions

In spite of the fact that TB is a global health problem, being one of the main causes of death, to date few changes have been made in its treatment, generating MDR and XPR strains of *M. tuberculosis*. The basic treatment is a mixture of four drugs and, in cases of MDR, up to eight, in addition to being each time more prolonged and with severe secondary effects, causing abandonment of the treatment.

The most active extracts *in vitro,* with MIC ≤ 12.5 μg/mL against *M. tuberculosis* H37Rv were CH_2Cl_2, EtOAc and EtOH from *Bidens odorata,* EtOAc extract from *Musa* spp., Hex extract from *Trixis angustifolia* and Hex extract from *Tabernaemontana alba* and *T. arborea.* The Hex and EtOAc extracts of *Musa* spp were active against MDR *M. tuberculosis* (CIBIN 99) with MIC = 12.5 and 6.25 μg/mL, respectively. From the EtOH extract of *B. odorata* a glycoside was isolated, which was very active against *M. tuberculosis* H37Rv (MIC = 3.125 μg/mL). The alkaloid voacamine, isolated from *T. alba* and *T. arborea,* showed MIC = 15.6 μg/mL against *M. tuberculosis* H37Rv. Recently, *in vivo* evaluation (BALB/c mouse pulmonary tuberculosis model) of curcumin has been reported; this compound reduced the bacillary load and reduced the percentage of lung pneumonia presented in cases of pulmonary TB, as well as reducing neuroinflammation in the mice. The extracts and/or pure bioactive compounds can help improve and/or reduce the complex scheme of treatment against TB; therefore, it is important to continue performing this type of research, given the problem this disease represents and the need to find novel substances that contribute to treatment.

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