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Current Status from Mexican Medicinal Plants as Source of Antimycobacterial and Antituberculosis Compounds

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Abstract

Tuberculosis (TB) is a worldwide health problem, being among the 10 causes of death by a single infectious agent. This infection mainly impacts the economically active population, and it is aggravated by the presence of MDR and XDR strains. This scenario makes the research for new alternatives of treatment imperative. Medicinal plants have proved to be a source of useful pharmaceutical molecules for lots of diseases, including TB. 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 *in vitro* and in vivo activity against different strains of mycobacteria.

The most active extracts against *M. tuberculosis* H37Rv were CH_2Cl_2, EtOAc and EtOH from *Bidens odorata*, and the EtOAc extract from *Musa spp*. The Hex extract from *Trixis angustifolia* (MIC=12.5 µg/mL) and the Hex and EtOAc extracts of *Musa spp* were active against *M. tuberculosis* MDR (CIBIN 99) with MIC=12.5 and 6.25 µg/mL, respectively. From the EtOH extract of *B. odorata*, an active glycoside against *M. tuberculosis* H37Rv (MIC=3.125 µg/mL) was isolated. Fractions 4 and 5 of *T. angustifolia* showed a MIC=12.5 and 6.25 µg/mL against *M. tuberculosis* H37Rv and against *M. tuberculosis* R-INH and the INS-4 clinical isolate. To date, in vivo evaluation with the pulmonary TB model in BALB/c mice of silymarin has been only reported. The compound reduced the bacillary load and lung pneumonia percentage. Extracts and/or pure bioactive compounds might improve and/or reduce the complex treatment scheme against TB. Therefore, it is important that this type of research be carried out given the problem that TB represents.

Keywords: Medicinal plants; Antimycobacterial activity; Antitubercular activity; *Mycobacterium tuberculosis*

Epidemiology of TB

Tuberculosis (TB) is mainly caused by *Mycobacterium tuberculosis* (*M. tuberculosis*). The World Health Organization (WHO) includes it among the ten causes of deaths by a single infectious agent, surpassing Human Immunodeficiency Virus (HIV). An estimated 1.3 million deaths occurred in 2007, of which 300,000 were TB/VIH+cases. In that same year, approximately 10 million new cases were diagnosed; 90% were adults (>15 years), and 64% of the total cases were men. 23% of the world's population has latent TB, and they may develop the disease at any time in their life.

Drug resistance is a common inconvenience. In 2017, approximately 558,000 cases resistant to rifampin (RR-TB) were reported, and it was surmised that 82% of these presented multi-drug resistance (MDR). In addition, 3.5% of new TB cases were MDR, and around 18% of previously treated cases became MDR. Worse, TB with Extended Resistance (XDR) will be developed in 8.3% of MDR cases [1].

The Pan-American Health Organization (PAHO) reported 282,000 cases of TB for the Americas region. Of these, 82% were in people older than 15 years, and 30,000 were TB/HIV confected. The incidence rate for Central America and Mexico was 28 cases/100,000 inhabitants. Likewise, roughly 24,000 deaths occurred in 2017 due to TB, and 6,000 people died from TB/HIV. Nearly 11,000 MDR cases were registered in Americas´ region. Sadly, around 6,900 of these patients had not been diagnosed or had not received treatment. In addition, about 500 deaths have been attributed to this condition.

The TB treatment success in the Americas region is around 75.4%. The remaining amount has the follow distribution: 8.3% were not evaluated, 8.6% had no follow-up, 7.3% died and 0.5% presented treatment failure. In 33% of new TB cases, drug sensitivity tests are not performed, leading to underestimates of cases of MDR. In Mexico, the success of treatment in TB-MDR is only 56%, and 970 MDR cases were reported at 2017. In addition, during this same year, 121 cases of XDR were registered [2].

In Mexico, during 2018 there were registered 16,933 cases of respiratory TB (including probable cases). Most of them were in men (16,700). The states with the major number of cases reported in 2017 were: Veracruz (2,001 cases), Baja California (1,651), Chiapas (1,215), Nuevo León (1,065), Guerrero (1,042) and Tamaulipas (1,017) [3].Until June 17, 2019, a total of 13,734 cases (7,536 men and 6,198 women) had been reported; Veracruz (872 cases) continues leading the list of states with the highest number of cases, followed by Baja California (709), Nuevo León (587), Chiapas (579), Tamaulipas (518) and Guerrero (425) [4].

TB Treatment

The basic treatment recommended by WHO against sensitive TB consists of an initial phase of two months, using the mixture of four drugs: Isoniazid (INH), Rifampicin (RIF), Pyrazinamide (PZA) and Ethambutol (Etb) or Streptomycin (Est). The next phase includes four months with INH and RIF. INH and RIF resistance tests must be done, at least to rule out cases of MDR before beginning treatment [5].

For the treatment of TB-MDR, we have 3 groups of drugs (A-C). Group A considers the administration of levofloxacin or moxifloxacin plus bedaquiline and lineazolide. From group B, cycloserine or terizidone and clofazimine are administered; and for group C: Etb,

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delanamide, PZA, imipenem-cilastatin, meropenem, amikacin, Est, ethionamide, protionamide and *p-aminosalicylic* acid can be used. These last are chosen to complement the regimen when drugs of A and/or B group cannot be used. The duration of this treatment ranges from 18 to 20 months [6].

Advances in TB Treatment

Current designs of new anti-TB drugs have diversified in terms of the mechanisms of action, since previous research was focused on bacterial replication. Several compounds are in clinical stages of development. In pre-phase I, we have TBAJ-587, a diarylquiniline which inhibits the synthesis of ATP synthase and cellular respiration. In phase I of development is spectinamide 1810 that inhibits protein synthesis. The benzothiazonones BTZ-043 and PBTZ-169 offer a novelty mechanism of action: inhibiting the synthesis of arabinogalactan. Other molecules with similar mechanisms of action are TBA-7371 and OPC-167832. The compounds that are between phase I and II are Q203 (an imidazopyridine that inhibits cellular respiration) and sutezolide (that inhibits protein synthesis). Among the compounds in phase II we have two oxazolidinones: AZD5847 and LCB01-0371, that inhibit protein synthesis.

Also, in phase II we have levofloxacin, a fluoroquinolone that inhibits DNA replication. Likewise, Nitazoxanide, that makes over membrane potential and pH. Among the compounds in phase III research are bedaquiline that blocks cellular respiration. According to a recent WHO update, this last is widely used in TBMDR treatment (WHO, 2018b). Another phase III compounds are two nitroimidazoles (delamanide and pretomanide), that block the synthesis of mycolic acids and nitric acid (NO), and clofazimine (a riminophenicin) that forms Reactive Oxygen Species (ROS) [7-9].

Research of New Anti TB Drugs in Medicinal Plants

Despite having first-and second-line drugs for TB treatment, the search for possible active compounds against MDR and XDR TB is still mandatory. Regarding this, extensive reviews describing the potential of medicinal plants and natural compounds evaluated *in vitro* or *in vivo* against diverse mycobacteria strains, have been published [10-16].

In additional to these papers, it has recently been described that Silymarin (SM), a mixture of polyphenols, obtained from the seeds of the *Silybum marianum* plant ("milk thistle") and Silibinin (Sb), the main component of silymarin, presented antimycobacterial effects in *in vitro* assays. SM showed a minimum inhibitory concentration (MIC)=12.5 μM against *M. tuberculosis* H37Rv, an MIC=50 μM against *M. tuberculosis* MDR (CIBIN 99, strain resistant to Est, INH, RIF, Etb and PZA). On the other hand, Sb was active with MIC=50 μM against H37Rv and MIC=12.5 μM against CIBIN 99. The results were confirmed quantifying the Colony Forming Units (CFU). Additionally, SM and Sb showed a synergistic effect *in vitro* with first-line anti TB (RIF, PZA and INH) against the sensitive strain (H37Rv). Synergy was also shown with second-line drugs (amikacin, moxifloxacin and ethionamide) against MDR strain (CIBIN 99).

Other *in vitro* assays were made in macrophages derived from human monocytes (MDMH) infected with *M. tuberculosis* H37Rv and CIBIN-99. The results indicate that the bacillary load decreased in the presence of SM and Sb at a dose of 50 and 100 μM, showing that Sb had a better effect against the drug sensible strain H37Rv, while SM was more active against CIBIN-99. Due to the promissory activity of SM shown *in vitro*, the *in vivo* evaluation was performed in the progressive pulmonary TB model in BALB/c mice infected with *M. tuberculosis* H37Rv. In this trial, they found that SM, at the dose of 5 mg/kg (administered by intragastric *via* dayly, from day 30 to day 60) reduced CFU in the lungs after 1 and 2 months of treatment. It was even noted that the combination of SM with anti-TB drugs further reduced the bacillary load and the percentage of pneumonia in infected animals [17].

Mexican Medicinal Plants With *In Vitro* Antimycobacterial Properties

Organic extracts (hexanic [Hex], dichloromethane [CH_2Cl_2], ethyl acetate [EtOAc], ethanolic [EtOH] and aqueous) from *Bidens odorata*, known as "white mozote, olives, acahual or mozoquelite", and the glycosides isolated from the EtOH extract and the 3-5 dihydrobenzoic acid (isolated from the aqueous extract) were active *in vitro* against *M. tuberculosis* H37Rv and *M. smegmatis* mc2155. The MIC, obtained by the Alamar blue colorimetric micrometer (MABA), was as follows: Hex extracts showed MIC=100 μg/mL; CH_2Cl_2, EtOAc and EtOH extracts showed a MIC=12.5 μg/mL against *M. tuberculosis*. Only, Hex extracts (MIC=50 μg/mL) and CH_2Cl_2 (MIC=100 μg/mL) showed moderate activity against *M. smegmatis*. The pure compounds were only active against *M. tuberculosis* H37Rv, the glycosidic compound showed a MIC=3,125 μg/mL and 3, 5 dihydroxybenzoic acid showed a MIC=50 μg/mL [18].

The medicinal species *Salvia coccinea* ("Jericho flower or hummingbird flower") and *Teucrium bicolor* ("oreganillo") were active against H37Rv. The MeOH extract of both species showed moderate antimycobacterial activity, with MIC=125 μg/mL [19]; however, this work does not describe the active compounds of this assayed species.

Another Mexican species with antimycobacterial activity is *Cnidoscolus chayamansa*, known as "Chaya". The $CHCl_3$: MeOH extract (1:1) was active against: *M. tuberculosis* H37Rv, four monoresistant strains (resistant to Est, Etb, RIF and INH) and two MDR clinical isolates (SIN 4, resistant to first-line drugs and MMDO resistant to INH and Etb). The MIC was 50 μg/mL in all cases. From the active extract, moretenol, moretenyl acetate, kaempferol-3,7-dimethyl ether and 5-hydroxy-7,3',4'-trimethoxyflavonone were isolated by chemical fractionation. Moretenol and moretenyl acetate were the most active compounds against *M. tuberculosis* H37Rv (MIC=25 μg/mL), while the other compounds were inactive [20].

In another study carried out with three medicinal plants: *Rhynchosia precatoria* (the Mexican sauco), *Euphabia albomarginata* (cuépari) and *Helianthus annuus* (sunflower) collected in the northern state of Sonora, it was found that these species showed a significant activity against *M. tuberculosis* H37Rv, and poor activity against *M. smegmatis*. The Hex, CH_2Cl_2 and EtOAc extracts from *R. precatoria* root had a MIC=15.6, 31.25 and 125 μg/mL, respectively, against *M. tuberculosis* H37Rv. The minimum bacteriostatic concentration (MBC) was 31.25, 62.5 and 125 μg/mL, respectively, for the three extracts. The Hex extract from *E. albomarginata* sprouts showed a MIC and MBC=250 μg/mL and 500 μg/mL, respectively; meanwhile, the CH_2Cl_2 extract of the *H. annuus* stem was inactive (MIC=500 μg/mL) against *M. tuberculosis* H37Rv. For *M. smegmatis*, only the CH_2Cl_2 and EtOAc extracts from *R. precatoria* showed scarce activity with MIC and MBC=250 and 500 μg/mL, respectively [21,22]. From this last species, five isoflavonoids with activity against *M. tuberculosis* H37Rv were isolated. These isogflavonoids were identified as precatorin A, precatorin B, precatorin C, lupinifoline and cajanone. All the compounds had a MIC=62.5 μg/mL, with exception of lupinifoline, which displayed an MIC=31.25 μg/mL.

Some medicinal plants used by indigenous groups in Sonora, México, to treat symptoms related to TB, were collected and evaluated

against *M. tuberculosis* H37Rv and against some clinical isolates of *M. tuberculosis*. The $CHCl_3$, CH_2Cl_2, EtOAc and MeOH extracts of *Ambrosia confertiflora* (estafiate) showed an MIC=90, 120, 160 and 200 µg/mL, respectively, while the MeOH extract of *Guaiacum coulteri* (guayacán) and *Ambrosia ambrosoides* (chicura) showed an MIC=790 and 1000 µg/mL [23]. From the most active extract ($CHCl_3$) of *A. confertiflora*, two active compounds, reinosa and santamarina, were isolated. Reinosa showed an MIC=64 µg/mL and CMB=128 µg/mL against *M. tuberculosis* H37Rv; MIC and MBC=128 µg/mL against the clinical isolate 366-2009; MIC=64 µg/mL and MBC=128 µg/mL against the clinical isolate 104-2010, and MIC=128 µg/mL against the clinical isolate 430-2010. Santamarina presented an MIC and MBC=128 µg/mL against *M. tuberculosis* H37Rv, clinical isolate 366-2009, and against the clinical isolate 104-2010 [24].

Hernández-García et al. [25] reported the antimycobacterial activity of the organic extracts from *Acacia farnesiana* (huizache) fruits. The Hex, $CHCl_3$, MeOH and aqueous extracts inhibited the growth of *M. tuberculosis* H37Rv with an MIC=200 µg/mL, while the Hex and aqueous extracts displayed activity against the MDR G122 clinical isolate (resistant to INH, RIF and Etb) with MIC=100 µg/mL. From the aqueous and MeOH extracts, methyl gallate was isolated, which showed activity against the sensitive strain H37Rv (MIC=50 µg/mL), while their acetylated derivative (triacetyl methyl gallate) was more active against both strains with MIC=25 µg/mL.

Another plant studied was *Trixis angustifolia* ("grass of the air"). From the aerial parts, three organic (Hex, $CHCl_3$ and EtOAc) extracts were obtained. 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). From the Hex extract, they obtained five fractions, which were also subjected by MABA against *M. tuberculosis* H37Rv. Fraction 4 and 5 were the most active, with MIC=12.5 µg/mL and 6.25 µg/mL, respectively. From them, two flavones (pebrelline and salvigenin) were obtained. The active fractions (4 and 5) were subjected to a subsequent fractionation, and 12 sub-fractions were obtained and these were submitted antimycobacteail activity against *M. tuberculosis* H37Rv. Here, sub-fractions 1-8 were the most active (MIC=12.5 µg/mL). From sub-fraction 7 (renamed Active Fraction-AF), a mixture of aliphatic compounds was obtained, although it has not been characterized. Hex extract, AF and pebrelline were again subjected by MABA assay against *M. tuberculosis* H37Rv, two monoresistant strains (resistant Est, RIF and INH) and against clinical isolates: SIN-4 (resistant to different drugs), MTY 147 (resistant to INH, RIF, Etb and ethionamide), and MMDO (resistant to INH and Etb). The Hex extract showed an MIC=12.5 µg/mL on the *M. tuberculosis* R-INH strains and against on the SIN-4 isolate, and an MIC=25 µg/mL against the R-RIF strain, MTY 147 and MMDO, while against the R-Est strain, it showed an MIC=50 µg/mL. The FA sub-fraction display an MIC=12.5 µg/mL against all the strains evaluated, and pebrelline was inactive. However, the combination of AF with pebrelline showed a synergistic effect against H37RV (MIC=6.25 µg/mL); against the resistant strains to INH and Est, and the MDR MMDO, MIC=0.78 µg/mL. For the case of the RIF monoresistant strain and for the MDR MTY strain, the MIC=12.5 µg/mL was obtained [26].

In a recent study, the antimycobacterial activity of *Musa spp* (apple banana) extracts were reported. The most active extract against *M. tuberculosis* H37Rv was EtOAc (MIC=12.5 µg/mL), and against the clinical isolate CIBIM 99 (MIC=6.25 µg/mL). Meanwhile, the Hex extract showed an MIC=25 µg/mL against the sensitive strain and MIC=12.5 µg/mL against the MDR strain [27]. In this case, only the antimycobacterial effect of the extracts was reported, without describing the active compounds.

It should be noted that none of the extracts of these medicinal species and/or pure bioactive compounds have been evaluated in vivo, so their anti-TB potential is unknown.

Conclusion

Although TB is a global health problem, being one of the leading causes of death worldwide, few changes have been made concerning its treatment. This has favored the rising of MDR and XDR strains, which implies long and complicated treatments, with high dropout rates.

Plants are an important source of countless therapeutic compounds that can give rise to alternatives to current treatments for various diseases, including TB. Mexico has a large number of medicinal plants that have been used since pre-Hispanic times and whose properties have been described in ancient documents, such as the Libellus de Medicinalibus Indorum Herbis, also known as Codex De la Cruz-Badiano. Several studies have focused on demonstrating the antimycobacterial properties of compounds obtained from Mexican native plants, some of them traditionally used to treat airway problems, which can lead to an improvement in current TB treatment.

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