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# Potential of plant extracts against *Mycobacterium tuberculosis*: an integrative review

## Potencial de extratos vegetais contra o *Mycobacterium tuberculosis*: uma revisão integrativa

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### ABSTRACT

*Mycobacterium tuberculosis* (MTB) is the main cause of tuberculosis. For decades, new forms of treatment and new ways of dealing with the growing resistance acquired by this bacterium to first-line drugs have been studied. Medicinal plants are a source of new bioactive compounds with antimicrobial potential. **Objective**: to investigate which plant species have already been tested and which main secondary metabolites are active against MTB. **Methodology**: an integrative review that included in vitro experimental studies, carried out around the world, that used medicinal plant extracts to evaluate the antimycobacterial activity by microdilution, with identification of major compounds, against MTB, between 2011 and 2021, the Web of Science and PubMed were used and the descriptors “medicinal plants AND against AND MTB”. **Results**: 20 species of plants with antimycobacterial activities were found. Four stood out with MIC<10 μg/mL. The variety of secondary metabolites was determinant for antimycobacterial activity, highlighting alkaloids, terpenes and phenolic compounds. **Conclusion**: the number of secondary metabolites obtained in the extraction is decisive in the antimycobacterial activity.

**Keywords:** Medicinal Plants; tuberculosis; microbiology;

### RESUMO

*Mycobacterium tuberculosis* (MTB) é a principal causa de tuberculose. Há décadas se estudam novas formas de tratamento e de lidar com a crescente resistência dessa bactéria aos medicamentos de primeira linha. As plantas medicinais são uma fonte de novos compostos bioativos com potencial antimicrobiano. **Objetivo**: investigar quais espécies vegetais já foram testadas e quais principais metabólitos secundários são ativos contra o MTB. **Metodologia**: revisão integrativa com estudos experimentais *in vitro*, realizados em todo o mundo, que utilizaram extratos de plantas medicinais para avaliar a atividade antimicobacteriana por microdiluição, com identificação de compostos majoritários, contra MTB, entre 2011 e 2021, foram utilizados Web of Science e o PubMed e os descritores “plantas medicinais AND against AND MTB”. **Resultados**: Foram encontradas 20 espécies de plantas com atividade antimicobacteriana. Quatro se destacaram com MIC<10 μg/mL. A variedade de metabólitos secundários foi determinante para a atividade antimicobacteriana, destacando-se alcaloides, terpenos e compostos fenólicos. **Conclusão**: o número de metabólitos secundários é decisivo na atividade antimicobacteriana.

**Palavras-chave:** Plantas Medicinais; tuberculose; microbiologia;

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## INTRODUÇÃO

Tuberculosis (TB), after the COVID-19 pandemic, is the second infectious disease that causes the most deaths in the world, with about 10.6 million infected and 1.6 million victims in 2021(WHO, 2022). Predominantly caused by *Mycobacterium tuberculosis* (MTB), cases are concentrated in 30 countries and account for 87% of all notifications, including Brazil (STEPHANIE; SARAGIH; TAMBUNAN, 2021).

First-line treatment is performed with a combination of antimicrobial agents such as isoniazid, rifampicin, pyrazinamide and ethambutol, and has a 95% cure rate if performed correctly. Treatment time consists of six months, with the first two months being the attack phase and the subsequent four months being the maintenance phase (RABAHI et al., 2017).

Long TB treatment ends up being one of the factors for the high rate of bacterial resistance to first-line antimicrobials, when not performed correctly. Other factors are also identified as guiding the progression of resistance, such as co-infection with the human immunodeficiency virus (HIV), interruption of treatment and genetic factors of the host (KHAWBUNG; NATH; CHAKRABORTY, 2021), in addition to late diagnosis and natural evolution of bacterial strains (SINGH et al., 2020). These factors corroborate that around 166,000 individuals were diagnosed with multidrug-resistant TB (MDR-TB) in the year 2021 worldwide. In the same year, around 60% of cases diagnosed with MDR-TB were treated and had a cure outcome (WHO, 2022). The fact that the therapy has been the same since 1952, with few modifications, is also an important factor related to resistance. Only after the introduction of linezolid in 2000 and bedaquiline in 2009 did the World Health Organization (WHO) recommend new therapeutic strategies to treat cases of MDRTB (SHARIFI-RAD et al., 2020).

Over the last three decades, 162 new compounds have been obtained with the intention of fighting bacterial infections. Of these, 11 compounds are derived from natural products and 78 are semi-synthetic products manipulated from natural compounds (NEWMAN; CRAGG, 2020). Despite the increased demand regarding bacterial resistance and the number of compounds acquired from natural products, the industry has increasingly invested in fully synthetic products (HARVEY; EDRADA-EBEL; QUINN, 2015).

Medicinal plants have been used in treating diseases such as TB, throughout history, since ancient times, as a traditional treatment in the fight against TB, empirically through infusions and teas. However, with the advancement of research using plant matrices, extracts based on medicinal plants have emerged as important sources of potential agents in TB treatment (KOIRALA et al., 2021; SHARIFI-RAD et al., 2020).

One of the determining factors for the activity of medicinal plants against infections are compounds known as secondary metabolites (SM), present in several species. Some of these compounds, such as terpenoids, alkaloids and polyphenols are responsible for antimicrobial responses (KUMAR et al., 2021). The production of these SM depends directly on the way of planting, harvesting and mainly extracting these compounds, since polarity, temperature and form of exposure of the solvents directly affect the type of substance that will be obtained (IDRIS; NADZIR, 2021).

Based on the problem of MTB resistance and plant extract antimycobacterial potential, this work aims to investigate which plant species have already been tested and which main secondary metabolites act against MTB.

## METHODS

An integrative review was carried out with the following guiding questions to guide this study: which are the plant species that have already shown potential antimycobacterial activity against MTB? And which groups of secondary metabolites stood out among the investigated species as possible antimycobacterial agents?

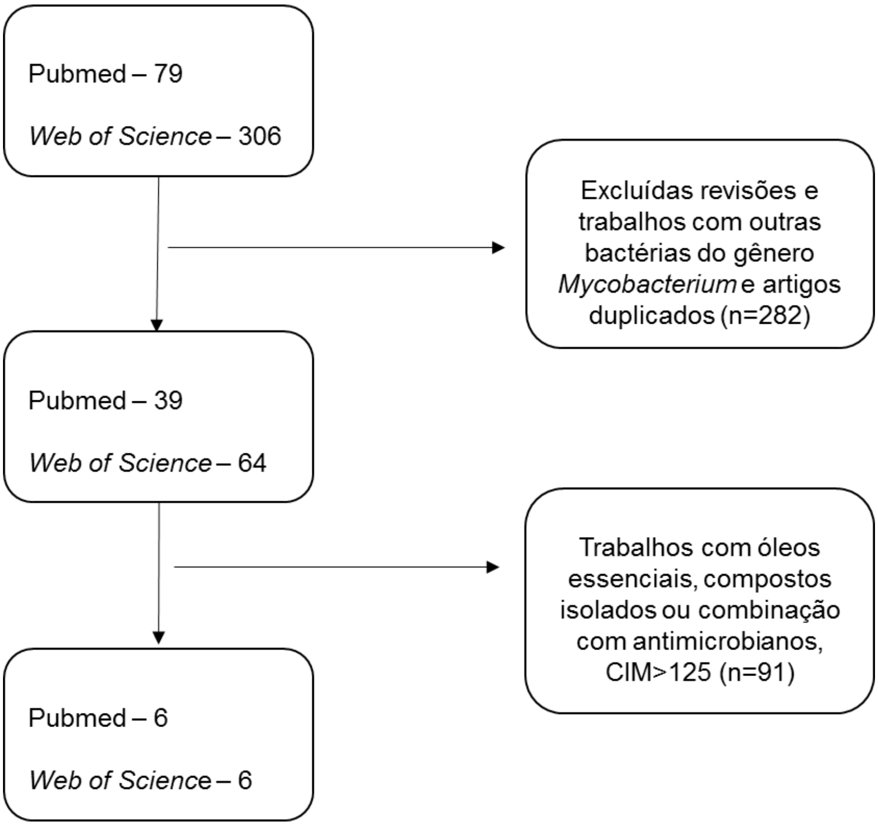
The works included in this review were in vitro experimental studies, carried out around the world, which used medicinal plant extracts in order to assess in vitro antimycobacterial activity by microdilution method, with identification of major compounds, against MTB, published between 2011 and 2021, open access and in Portuguese and English. For the research, the electronic Web of Science and PubMed databases were used. The search was performed using the descriptors “medicinal plants AND against AND Mycobacterium tuberculosis”, which are part of the Health Sciences Descriptors (DeCS) and Medical Subject Headings (MeSH) (WHITTEMORE; KNAFL, 2005).

Works that carried out experiments with isolated compounds or essential oils and combination of extracts with antimicrobials already used in TB treatment were not selected for the study. Studies that presented active plant extracts against MTB with a minimum inhibitory concentration (MIC) greater than 125 µg/mL were also excluded from that research. Repeated articles in more than one database were counted only once, linked to the database with the highest number of accepted publications.

## RESULTS AND DISCUSSION

After conducting a search in the databases and reading the articles, 12 were selected for review, six found in PubMed and six in Web of Science (Figure 1).

**Figure 1** – Flowchart of selection of studies for the study




**Source:** Elaborated by the authors

Among the 12 articles selected for the work, antimycobacterial activities of 20 plant species were reported, as well as the parts of each mentioned plant, the most used solvents, and the way they are prepared. The MIC was also analyzed for each studied extract and its major compounds.

### Extraction forms, solvents and pharmacogens researched

When evaluating the pharmacogens used, it was observed that aerial parts (36%), leaves (36%), roots (7%) and flowers (7%) represent 86% of the total plant parts used to obtain the extracts, other parts such as seeds, bulbs and calluses (14%) were also analyzed to a lesser extent in the evaluated studies. SM are distributed in the different organs of plants, since they act for different purposes: from providing pigment to fruits to even acting as antimicrobials. Compounds with this activity are normally found in the leaves' vascular veins, as they need to be quickly distributed throughout the plant in case of any infection (GÓRNIAK; BARTOSZEWSKI; KRÓLICZEWSKI, 2019). When it comes to the number of SM, the roots and stems are the organs that store the largest amount of these products, which are directly dependent on the environment, since these compounds are obtained through the metabolic processes of plants (LI et al., 2020).

In the selected studies a total of 20 different plants were analyzed. The method used to obtain the extracts in all studies was maceration. Maceration consists of depositing the chosen part of a plant in a container with the addition of an extraction solvent and maintaining this mixture for a period of at least three days, with the advantages of low investment in addition to not requiring specific equipment (ABUBAKAR; HAQUE, 2020).

The type of solvent is a determining factor for the quality in obtaining the extract, being directly linked to the type of compound that will be obtained in the process (ALAWI; HOSSAIN; ABUSHAM, 2018; TIAN et al., 2009). The authors reported the use of six different types of solvents to carry out these preparations: methanol (25%), ethyl acetate (21%), hexane (18%), dichloromethane (18%), ethanol (14%) and chloroform (4%). Using more polar solvents such as methanol and ethanol enables a more efficient extraction of polar compounds such as phenolic compounds, tannins, flavonoids and quinones. Using more nonpolar compounds, such as ethyl acetate, dichloromethane, chloroform and hexane, improves the obtainment of SM with nonpolar properties such as terpenes and alkaloids (ABUBAKAR; HAQUE, 2020).

## Antimycobacterial potential of investigated plants

Table 1 shows the potential of the extracts studied as well as the solvents used and the major compounds of each plant. They were arranged in increasing order of MIC in order to compare extract active concentration with the compounds assessed in each plant.

**Table 1-** Description of plant species assessed against Mycobacterium tuberculosis.

| Species | MIC µg/mL | Solvent | Alka loids | Terpe noids | Ter pe nes | Phenols | Tannins | Flavonoids |
|---|---|---|---|---|---|---|---|---|
| *Artemisia abyssinica* | 6.25 | Methanol | * | - | - | * | * | * |
| *Duroia macrophylla* Huber | 6.25 | Dichloromethane | - | - | * | * | - | - |
| *Uvaria rufa* | 8 | Chloroform | - | * | - | * | - | - |
| *Bridelia micrantha* (Berth) | 8.25 | Ethyl acetate | - | - | * | * | - | - |
| *Croton macrostachyus* | 12.5 | Methanol | * | - | - | * | * | * |
| *Satureja aintabensis P.H.* | 12.5 | Ethyl acetate | - | - | - | * | * | * |
| *Thymus sipthorpii Benth* | 12.5 | Ethyl acetate | - | - | - | * | * | * |
| *Satyrium nepalense* | 15.7 | Hexane | * | * | - | - | * | - |
| *Duroia macrophylla* Huber | 25 | Dichloromethane | * | - | * | * | - | - |
| *Duroia saccifera* | 25 | Ethyl acetate | - | * | - | - | - | - |
| *Eucalyptus camaldulensis* | 25 | Methanol | * | - | - | * | * | * |
| *Ocimum basilicum* | 25 | Methanol | * | - | - | * | * | * |
| *Struthanthus concinnus* | 25 | Ethyl acetate | - | * | - | - | - | - |
| *Dioscorea bulbifera* | 32 | Methanol | - | - | * | - | - | - |
| *Gymnosporia senegalensis* | 36.8 | Dichloromethane | * | - | * | * | - | - |
| *Calpurnia aurea* | 37.5 | Methanol | * | - | - | * | * | * |
| *Struthanthus concinnus* | 50 | Dichloromethane | - | * | - | - | - | - |
| *Struthanthus concinnus* | 50 | Hexane | - | * | - | - | - | - |
| *Rhynchostylis retusa* | 62.5 | Ethanol | * | * | - | - | - | - |
| *Costus speciosus* | 100 | Hexane | * | - | - | * | - | - |

**Source:** Elaborated by the authors. "-" absence; "*" presence

One way to assess an extract's antimicrobial activity is to assess its MIC, which is based on the lowest concentration of a compound capable of inhibiting the growth of a pathogen (ELOFF, 2019). The plate microdilution method is recommended by the WHO for MTB assessment (WHO, 2021). An extract that demonstrates a MIC ≤125 µg/mL is considered active against MTB (LUO et al., 2011; MOLINA-SALINAS et al., 2007).

Among the plants that showed greater activity is Artemisia abyssinica, analyzed in the work by Gemechu et al. (2013) where Ethiopian plants normally used to treat TB caused by both MTB and Mycobacterium bovis were evaluated. For assessing antimycobacterial activity, the methanolic extract of different plants was prepared. Among the species tested, Artemisia abyssinica leaves stood out, which showed the highest amount of SM such as alkaloids, tannins, phenols and flavonoids and the lowest MIC among all the plants in the study (6.25 µg/mL). Another species in this study with a high SM content and with good results against MTB were Croton macrostachyus leaves (12.5 µg/mL). Other plants assessed in this study had activity against MTB strains (GEMECHU et al., 2013)

Martins et al. (2013) carried out two different extractions of Duroia macrophylla Huber, an Amazonian species of the family Rubiaceae, which in the dichloromethane fraction of its leaves presented MIC of 6.25 µg/mL against MTB, presenting mostly terpenes and phenolic compounds in this pharmacogen. From the branches of the plant, in the fraction that used the same solvent, alkaloids and tannins were isolated, having a MIC lower than 25 µg/mL (MARTINS et al., 2013)

Chloroform fraction of Uvaria rufa leaf extract demonstrated MIC of 8 µg/mL against MTB and terpenoids and phenolic compounds were isolated from this extract (MACABEO et al., 2012). The juice of the stem of this species is commonly used by Amazonian indigenous peoples to cure papa-din, a condition of "weakness" that can have an infectious bias (REIS et al., 2016).

The species Bridelia micrantha (Berth) is a medicinal plant from South Africa used for various purposes in traditional medicine. The plant was tested against MTB by Green et al. (2011), demonstrating antimycobacterial activity when extracted with ethyl acetate with MIC of 8.25 µg/mL and presenting monoterpenes, diterpenes and phenols in the composition (GREEN et al., 2011).

Askun et al., in 2013 in Turkey, tested three plant species against MTB, Thymus sipthorpii Benth, Micromeria juliana (L.) Benth and Satureja aintabensis P.H. The aerial parts were used to obtain the extracts, all of which had polyphenolic compounds such as rutin, quercetin and caffeic acid such as SM. Ethyl acetate extraction from S. aintabensis leaves stood out, which showed a higher amount of rosmarinic acid as its main constituent and MIC of 12.5 µg/mL, the same result of ethyl acetate extraction from T. sipthorpii. M. juliana and S. aintabensis methanolic fractions have a MIC of 100 µg/mL (ASKUN et al., 2013). S. aintabensis belongs to the family Lamiaceae, where several ornamental and edible plants rich in SM can be found (TRIVELLINI et al., 2016).

Some orchid species are popularly used in India for treating symptoms of asthma and common flu. When tested against MTB, these plants showed antimycobacterial activity, like the Satyrium nepalense species, which presented in its hexane extract alkaloids, terpenoids and tannins as major SM with a MIC of 15.7 µg/mL. The species Rhynchostylis retusa in its ethanolic fraction showed alkaloids and terpenes and a MIC of 62.5 µg/mL (BHATNAGAR et al., 2017).

Ethyl acetate extract from Duroia saccifera calluses, another Amazonian species of the family Rubiaceae, presented a MIC of 25 µg/mL against MTB, being verified the existence of triterpenoids as major SM in this plant presentation (LOZANO et al., 2020).

The mistletoe Struthanthus concinnus and Struthanthus marginatus were assessed and presented triterpenoids in their composition, with the fraction of Ethyl acetate of S. concinnus, demonstrating MIC of 25 µg/mL, containing terpenes and phenols, the other fractions being also considered effective with MIC between 50 and 100 µg/mL against MTB (LEITÃO et al., 2013)

Dioscorea bulbifera is used in traditional African medicine as a natural antibiotic; its bulbs are consumed as a form of treatment; the methanolic extract of their bulbs detected the presence of diterpenes and had a MIC of 32 µg/mL against MTB (KUETE et al., 2012).

The species Costus speciosus Sm and Tabernaemontana coronaria L. are shrubs from Asia, and their flowers and leaves are used as medicine in the region for the treatment of various diseases. Hexane extracts from C. speciosus flowers and T. coronaria leaves had a MIC of 100 µg/mL against MTB, differing in SM. The existence of alkaloids was verified in C. speciosus flowers, while in Tabernaemontana coronaria L. flowers, terpenes and phenols were detected as major SM (MOHAMAD et al., 2018).

Gymnosporia senegalensis is a plant endemic to northern Africa and used in folk medicine as a treatment for various diseases, being tested for MTB. When tested by Makgatho et al., the crude extract of this shrub's leaves was shown to have alkaloids, terpenes and phenols as major SM and this extract obtained a MIC of 36.8 µg/mL (MAKGATHO; NXUMALO; RAPHOKO, 2018)

## Plant secondary metabolites with potential antimycobacterial activity

Among the main SM assessed in this study, phenolic compounds, alkaloids and terpenes stood out, the extracts that contained more than one of these combined classes presented the lowest MIC when compared to the less effective extracts.

The number of SM is directly linked to the antimicrobial effect of medicinal plant extracts, including against multi-drug resistant strains (KEBEDE; GADISA; TUFA, 2021), being a natural evolutionary process of plants that deal with the infections that affect them with several compounds acting in a synergistic or antagonistic way with each other (CAESAR; CECH, 2019). Using different extracts synergistically to increase the number and variability of compounds in a sample decreases the MIC against other bacteria that cause skin disease such as Staphylococcus aureus (ARCHANA; GEETHA BOSE, 2022). Research with plant extracts and assessment of their SM is a way to find new molecules that may be useful in obtaining responses to resistant infections (NEWMAN; CRAGG, 2020).

The resistance of the MTB occurs in two ways: acquired and intrinsic. Acquired is due to the modification of binding sites in the cell membrane, through the modification of target proteins. Intrinsic comes from actions such as changes in the efflux pump, caused by environmental exposure to antibiotics, poorly conducted treatment, among others (MAZLUN et al., 2019; SCAINI et al., 2019).

Some phenolic compounds have already shown antimycobacterial effect, inhibiting mechanisms of action of the MTB cell envelope (KOIRALA et al., 2021). Another form of activity of phenolic compounds is mycolic acid synthesis inhibition, which are fundamental in MTB structure, responsible for the low permeability of these bacteria, being determinant in their resistance (MAZLUN et al., 2019). Another way to control MTB growth is to produce adenosine triphosphate (ATP), the molecule responsible for cellular energy, by inhibiting the enzyme ATP synthetase, since some phenols bind to this enzyme, inhibiting its functioning (MAPARI et al., 2022).

Anthraquinones are compounds capable of affecting the complexation of DNA-gyrase at its binding site, which prevents this enzyme from performing its functions in the MTB cell, thus preventing replication and transcription of the genetic material of this bacterium (AMORIM et al., 2022). Another mechanism of action of anthraquinones is inhibition of enzymes that synthesize mycolic acids, the main constituent of the membrane of the genus Mycobacterium and responsible for the impermeability of the membrane of these bacteria (HAFEZ GHORAN et al., 2022).

Alkaloids, present in most of the plants with activity against MTB, have a mechanism of action like isoniazid and pyrazinamide in MTB cell membrane, acting as efflux pump inhibitors, which hinders one of the main resistance mechanisms of MTB (AMENGOR et al., 2022). Some of these compounds have already gone to advanced stages of testing, such as thiliacorinin, nortiliacorinin and thiliacorin, which showed low MIC values such as 3.1 µg/mL, demonstrating that this class of compounds has great antimycobacterial potential (BOSE et al., 2021).

Terpenes and terpenoids antimicrobial activity have already been assessed against resistant strains of Gram-negative and Gram-positive bacteria, demonstrating that some terpenes have antibacterial activities at low concentrations (GUIMARÃES et al., 2019). Recently it was discovered that MTB produces the enzyme tuberculosinol phosphatase, which binds to a specific site on the membrane responsible for increasing virulence. This site is the binding target of some terpenes, thus favoring antimycobacterial activity (KATAEV et al., 2018). Although many compounds of this type have already been tested, none has evolved into a drug. Even so, natural products derived from medicinal plants continue to be a source of understanding of various mechanisms and may indeed be a way out of multidrug-resistant diseases (JAGATAP; AHMAD; PATEL, 2022).

## CONCLUSION

It was evident that most of studied plants come from traditional medicine, being used for different therapeutic purposes in different parts of the planet. Pharmacogens were also the most diverse, such as roots, leaves, flowers, among others. Among the 20 plants that showed antimycobacterial activity, four of them stood out with MIC<10 µg/mL, they were Artemisia abyssinica, Duroia macrophylla Huber, Uvaria rufa, Bridelia micrantha (Berth). These plants showed SM variability and demonstrated therapeutic potential against MTB.

SM were determinant in extract activity quality. The extractions that obtained the greatest variety of SM showed the best in vitro results in MTB inhibition, with combinations of alkaloids and phenolic compounds or terpenes and phenolic compounds being the most effective when compared to extracts that had only one of these classes.

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