Open Access, Peer Reviewed, Referred Research Journal

Print & Online available on https://jbsd.in
ISSN: 2229-3469 (Print); ISSN: 2231-024X (Online)
Research Article

Phytoconstituents: To Eradicate Mycobacterium Tuberculosis

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Article Info

Received: 01-02-2026,
Revised: 10-03-2026,
Accepted: 25-03-2026

Keywords:
Antimycobacterial, Mycobacterium tuberculosis, TB report, Phytoconstituents, Polyherbs

Abstract

TB is the most common infectious disease that kills people worldwide and is typically brought on by Mycobacterium tuberculosis. According to the WHO Global TB Report 2023 and India TB Report 2024, India accounted for 27% and 25% of the world's TB cases and fatalities, respectively, with 2.55 million notified TB cases in 2023 and 331,000 TB deaths in 2022and India's proportion of TB cases and deaths worldwide is 27% and 25%, respectively. The synthetic allopathic therapy for tuberculosis that is currently available includes first- and second-line medications such as rifampin, Isoniazide, ethambutol, pyranzinamide, and streptomycin. These medications are used to treat the disease, but they cause hepatoxicity, increase the number of pills taken, and also cause resistance against the Mycobacterium tuberculosis bacteria, which leads to MDR TB and XDR TB.Medicinal plants with possible antimycobacterial effectiveness against MTB include Acacia, Calotropis, Vasaka, Acalypha, Mint, and Cinnamon. They also have a lower risk of resistance, fewer adverse effects, and less toxicity. In addition to summarizing recent studies on phytochemicals with possible antimycobacterial activity against MTB, this review seeks to highlight the benefits of anti-TB phytocompounds derived from plants. The purpose of this study was to summarize the possible phytoconstituents that could have encouraging effects when used to treat both MDR and XDR TB.

1. INTRODUCTION

TB is a chronic infectious disease, and when a patient has active pulmonary TB, they cough and spread harmful bacteria to healthy people (**Chandra *et al.*, 2022**). The World Health Organization (WHO) estimates that in 2021, mycobacterium tuberculosis (MTB), the causative agent of tuberculosis, infected approximately 25% of the world's population, resulting in 10.6 million cases of illness and 1.5 million fatalities(https://www.whoint/teams/global-tuberculosisprogramme/tbreports/global-tuberculosis-report202. 2021).The main host cells that are engaged in the infection are alveolar macrophages. When MTB enters the respiratory system, it is initially identified by alveolar macrophages, which move to the lung interstitium and create cellular aggregates where the bacteria multiply and infect recruited phagocytes like dendritic cells, neutrophils, monocyte-derived macrophages, and interstitial macrophages. This innate immune response may eradicate the infection (**Ravesloot-Chavez *et al.*, 2021**). Through a variety of processes, including the release of antimicrobial mediators (such as nitric oxide from inducible nitric oxide synthase and reactive oxygen species) and interaction with lysosomesin apoptosis, pyroptosis, and autophagy, macrophages may eliminate invasive pathogens during severe inflammation (**Flynn *et al.*, 2022; Bo *et al.*, 2023**). Immature dendritic cells, meantime, multiply rapidly and move to the lymph nodes that drain. Dendritic cells

develop after absorbing antigen, then deliver the processed antigen to lymphocytes like T and B cells to initiate adaptive immune responses. The activated antigen-specific T and B cells move to the infection site and facilitate the development of granulomas that regulate the infection in conjunction with innate immune cells if the MTB penetrates the innate immunity's defenses (**Chandra *et al.*, 2022; Flynn *et al.*, 2022; Orme *et al.*, 2015; Ernst, 2018**).

A core of caseous necrosis is created at the infection site by the dead phagocytes and toxic by products of the immune response, and this can serve as the resident niche for growing MTB Growth halt of the MTB may result from the harsh and complex milieu seen in granulomas, which includes hypoxia, a lack of vital nutrients, and the presence of respiratory inhibitory chemicals such carbon monoxide and NO (**Chung *et al.*, 2022; Elkington *et al.*, 2022; Prosser *et al.*, 2017; Torrelles *et al.*, 2017; Qualls *et al.*, 2016**). The majority of people who continue to have MTB acquire a latent infection state for the rest of their lives and never get active TB disease. The host faces both advantages and disadvantages from the granuloma. The granuloma walls off the bacteria in a confined area, preventing the infection from spreading. However, it also acts as a reservoir for MTB that survives and is not cleared by host immune responses or anti-TB chemotherapy (**Ramakrishnan, 2012**).The most often used medications in the current chemotherapy regimens for tuberculosis include isoniazid, rifampin, pyrazinamide, and streptomycin (**Assefa *et al.*, 2018**).These medications' drawbacks, however, include poor efficacy, high cost, toxicity, and cross-resistance, which result in lengthy treatment regimens (seven months or longer for drug-resistant TB) and low patient compliance (**Shah *et al.*, 2008; Tweed *et al.*, 2019**).Mutant strains of MTB resistant to these medications have been found, despite the fact that various novel antibiotics, such as bedaquiline, delamanid, linezolid, and pretomanid, have been licensed for the treatment of multidrug-resistant and severely drug-resistant TB in the past ten years (**Ghodousi *et al.*, 2019; Kishor *et al.*, 2015; Gomez-Gonz alez *et al.*, 2021**). Directly Observed Treatment Short Course Chemotherapy, or DOTS, was widely implemented following the National Tuberculosis Program's failure. Short Course Chemotherapy (SCC) is the greatest gift that Dr. Wallace Fox has ever given the world. He is regarded as the founder of clinical trials for TB chemotherapy. Early killings, also known as the initial intensive phase, and sterilizing, also known as the continuing phase, are the two pillars of SCC. As monotherapy isinsignificant and inadequate for the treatment of T.B., multidrug therapy is necessary to prevent drug resistance, eliminate organisms that grow quickly to increase efficiency, deliver the safest, most effective therapy in the shortest amount of time, and guarantee patient adherence to treatment. Numerous studies have been carried out on herbal medicines to assess their applications, and the WHO investigated the safety of widely used but poorly understood herb products in light of the lengthy course of therapy for first-line anti-TB medications and the associated adverse effects.Additionally, WHO has emphasized the importance of herbs that may be useful in circumstances where the safety of current therapy may be insufficient (**Benzie *et al.*, 2011**). Herbs such as Acacia farnesiana, Mentha piperita, Justiciavasica, Calotrpis gigantean, Acalypha indica and Cinnamomum zeylanicum. India has achieved significant strides in the treatment of tuberculosis in recent years. For instance, the nation has adopted a wholly oral, injection-free treatment program for drug-resistant TB (DR-TB). Of the 25.52 lakh TB patients who were diagnosed in 2023, 24.38 lakh (95.5%) received treatment (https://tbcindia.mohfw.gov.in/wpcontent/uploads/2024/10/TB-Report_forWeb_08_10-2024-1.pdf).

The disaggregated treatment success rate of patients notified from the public and private sectors, with the current standard of care for drug susceptible TB i.e. 6-month regimen (two months initiation phase consists of isoniazid [H], rifampicin [R], pyrazinamide[Z], ethambutol[E] followed by four months), are 85% and 87%, respectively (https://tbcindia.gov.in). After the discovery of effective chemotherapy against T.B, it was expected that the disease would be eventually controlled. But then came the scourge of late twentieth century Human Immunodeficiency Virus (HIV). The deadly mix of tuberculosis and HIV infection, as well as inadequate resource allocation, Poverty and antibiotic resistance to tuberculosis bacteria fueled the TB epidemic (**Narasimhan *et al.*, 2013**). The situation has become much more complex due to the issue of multidrug resistance (MDR). MDR-TB affects 20% of patients with a history of prior therapy and 3.8% of newly diagnosed TB patients worldwide Treatment for MDR-TB is more costly, time-consuming, toxic, and challenging (**Seung *et al.*, 2015**).

1.1 Current Antibiotic Treatments in Action

1.1.1 ***Various Antibiotics Used to Treat TB*:** First-line drugs for six months are advised for the treatment of TB, and this schedule has an 85% success rate (two months of isoniazid, rifampicin,

ethambutol, and pyrazinamide, and four months of isoniazid and rifampicin) (WHO: Geneva, Switzerland, 2019; 284).First-Line Treatment: Around the 1950s, ethambutol, pyrazinamide, and streptomycin significantly decreased the number of TB cases, particularly in industrialized countries. For drug-susceptible pulmonary Antibiotics 2023, 12, 541 4 of 18 TB (DS-TB), the WHO recommends either a 6-month course of isoniazid and rifampicin with pyrazinamide and ethambutol in the first two months or a 4-month regimen consisting of rifapentine, moxifloxacin, isoniazid, and pyranzinamide (WHO:Geneva, Switzerland, 2022; 68). Second-Line Treatment: MDR and XDR-TB are treated with a combination of first- and second-line medications (subject to antibiotic susceptibility testing). Streptomycin, rifampicin, pyrazinamide, ethambutol, cycloserine, ethionamide, kanamycin, and thioacetazone are the second-line medications (SLDs). Compared to the DS-TB regimen, treatment for MDR and XDR-TB is typically longer, less successful, less pleasant, and more costly and involves injectable medications.Even after receiving directly monitored treatment, the percentage of MDR-TB patients who were cured in a retrospective cohort analysis was not higher than 69% (**Maus *et al*., 2005**).

To treat drug-resistant TB, new medications with a unique mechanism or fewer side effects must be investigated (**Muniyan *et al*., 2017**).A pathogen faces harsh circumstances including an acidic pH, free radicals, hypoxia, and nutritional shortages once it penetrates the host. It has been demonstrated that MTB has three βcarbonic anhydrases (β-CAs), which are necessary for the bacteria to survive in the hostile host environment. It is generally known that CAs play a part in maintaining pH homeostasis and the bicarbonate transport necessary for cellular metabolism (**Aspatwar *et al*., 2022; Supuran, 2008**).The β-CAs are known to be essential for the formation of biofilms and the synthesis of virulence factors in mycobacteria, which in turn promote antibiotic tolerance and survival (**Aspatwar *et al*., 2018; Aspatwar *et al*., 2019**).An attempt has been made to create anti-TB small molecules that target the β-CAs of mycobacterium (**Supuran, 2008; Aspatwar *et al*., 2018; Aspatwar *et al*., 2019**).It's interesting to note that humans only have α-CAs and no β-CAs, hence theAnti-TB drugs that target MTB's β-CAs have little adverse effects and may be able to cure Sand, which stops mycobacterium growth in the zebrafish model both in vitro and in vivo (**Aspatwar *et al.*, 2017**).It has been demonstrated that certain plant-derived substances called coumarins (Table 1), in addition to chemically produced CA inhibitors, have antibacterial and anti-tubercular properties (**Giovannuzz *et al*., 2022**). Coumarins suppress the action of carbonic anhydrases and prevent the synthesis of proteinsRecent research has demonstrated the role of coumarins in biofilm development and microbial quorum sensing (**Giovannuzz *et al.*, 2022; Basile *et al*., 2009; Reen *et al*., 2018**).

Table 1. Anti-TB drugs and their mechanism of action (WHO: Geneva, Switzerland, 2019284).

Drugs	**Mode of Action**
Streptomycine	Reductional in the production of ribosomal protein.
Isoniazid	Cellular, lipid, carbohydrate and metabolism inhibition.
Pyrazinamide	Membrane transport disruption and energy exhaustion.
Rifampin	Inhibiting the synthesis of RNA.
Cycloserine	Reduction in the production of mycolic acid.
Kanamycine	Decrease in protein synthesis.
Ethambutol	Inhibiting the synthesis of RNA.
Quinolones	Inhibition of transcription replication and DNA replication.
CA inhibitors	Inhibit the activity of carbonic anhydrase needed for PH regulation.
Coumarins	Inhibit protein synthesis and activity of carbonic anhydrase.

1.2 Diagnostic tests

Above tests are used to detect TB: Nucleic acid amplification test, sputum culture, chest radiography, sputum smear microscopy, and tuberculin skin test. In this review, we concentrated on a number of herbal plants that exhibited superior antimycobacterial activity. We can overcome toxicity by using natural medications to combat MTB as well as adverse effects and drug resistance with the existing medication regimen. Additionally, reducing the number of pills can increase patient compliance.

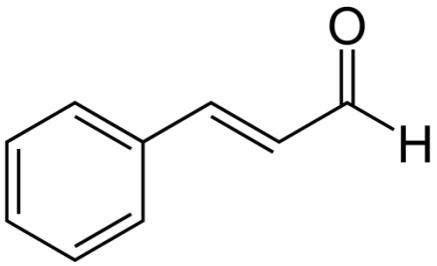
2. METHODOLOGY

The current review was conducted using a complete and organized search of the available literature on the medicinal plants. The searches where performed using various databases, including PubMed, Pubchem, Google Scholar, Science Direct, Scopus, Research gate etc.

3. DESCRIPTION

3.1 Cinnamon:

Fig. 1. i. Cinnamon Bark



ii. Cinnamaldehyde structure

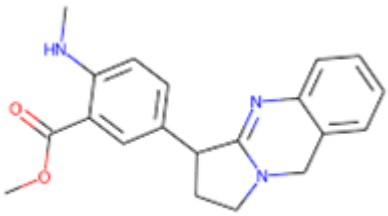
Biological Source: Cinnamon cassia, or dried bark of Cinnamomum zeylanicum, is a member of the Lauraceae family.

Chemical Constituents: Cinnamaldehyde (65-80% in bark), Eugenol (5-10% in bark), Campor (60% inroot),Terpenehydrocarbon (78%inbud),Trans-cinnamylacetate (42-54%infruit), Eucalyptol, Caryophyllene Oxide, Linalol, Caryophyllene, Alpha Pinene, Benzaldehyde, Limonene, Isoborneol, Cinnamyl ester, Alpha humulene, Delta Cadinene, Benzyl Benzoate, P-Chymene (**Jayaprakasha *et al.*, 2002**).

Uses: Antioxident, Anti-inflammatory, Antidiabetic, Antimicrobial, Anticancer, Lipid lowering and cardiovascular disease lowering compound, also have activities against Neurological disorders such as Parkinson's and Alzheimer's diseases.

3.2 Vasaka:

Fig. 2. i. Vasaka leaves



ii. Adhatodine

Biological Source: Vasaka consists of either freash or dried leaves of Adhatoda Vasica belongs to Acanthaceae family **Chemical Constituents:** Arachidic (3.1% in seeds), Linoleic (12.3% in seeds), Oleic (49.9% in seeds), Sitosterol (2.6% in seesd), Vasicinone, Adhatodine, Vasicinol, Anisotine, Vasicoline (7.5% in Leaves), Kaempferol, Quercetin, B-sitoterol, Deoxyvasicine, Epitaraxerol, Carotene, 2-4-dihydrochalcone-4-glucoside, Bglucoside-galactose, peganidine.

Uses: Anti-microbial activity, Antioxidant, Expectorant, Myocardial infraction, Anti-cancer, Anti-inflammatory, Anti-feedant properties against pests, Anti-diabetic (**Singh *et al.*, 2017; Roy *et al.*, 2013**).

3.3 Acalypha indica:

Biological Source: is the dried portion of Acalypha indica's roots and leaves, which are members of the Euphorbiaceae family.

Chemical constituents: Cysteine, kaempferol, lupeol benzoicacid, n-hexadecanoicacid, strychnine, penbutolol, quinine, evoxine, Anandamide, mimosine.

Uses: Antimicrobial, anti-inflammatory, antiulcer activity, analgesic activity, cytotoxic activity, lipid lowering activity, antihelmintic activity, anticonvulsant activity (**Rajkumar *et al.*, 2022; Madhavan , 2021**).

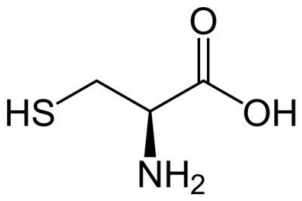


Fig. 3. i. Acalypha indica leaves **ii. Cysteine Structure**

3.4 Calotropis Gigantea:

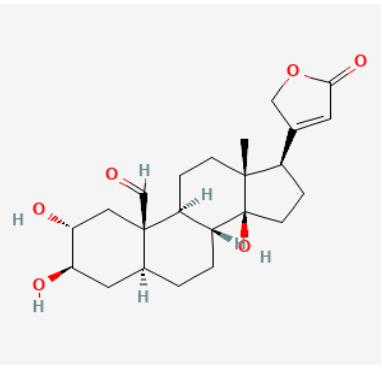


Fig. 4. i. Calotropis Gigantea **ii.Calotropogenin Structure**

Biological Source: The entire Asclepiadaceae family, which includes Calatropis gigantean.**Chemical Constituents:** Calacitin, calotropogenin, Calotropin, Frugoside, Calotoxin, Uscharin (**Fakim , 2006; Sureshkumar *et al.*, 2012; Dulloo , 2019; Patil*et al.*, 2022; Yadav *et al.*, 2021**).

Uses: Anti-inflammatory, Anti-microbial, Anti-cancer, Anti-diabetic (**Setty *et al.*, 2007**).

3.5 Acacia farnesiana:

Biological Source: It Consists of Acacia Farnesiana bush as and tiny trees also known as Vachellia Farnesiana belongs to Leguminosae family.

Chemical constituents: Methyl Salicylate (47.5%), Anisaldehyde917.3%), Geraniol (9.8%), Benzaldehyde (6%), Benzyl Alcohol (0.5%), Myrecene (0.5%), Linalol (0.4%), Geranyl Acetate Stigmasterol (51.08%), Linoleic Acid (40.50%),Oleic Acid (30.73%), Stearic Acid (8.01%), Palmitic Acid (13.05%) in pods and seeds (**Deshmukh *et al.*, 2011**).

Uses: Anti-bacterial, Anti-oxidant, Anti-microbial, Anti-inflammatory, Analgesic (**Abrantes *et al.*, 2013**).

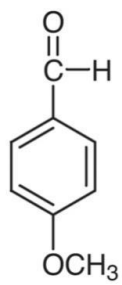
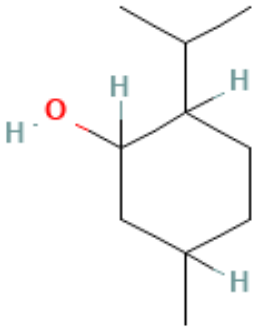


Fig. 5. i. Acacia farnesiana **ii. Anisaldehyde Structure**

3.6 Mint:

Fig. 6. i. Mint leaves



ii. Menthol Structure

Biological source: The labiatae family includes the monoterpene alcohol menthol, which is extracted from the oils of Mentha piperta var vulgares (black peppermint) and Mentha piperita var officinalis (white peppermint).

Chemical constituents: Menthol 70%, l Limonene, Pinene, Camphene .

Uses: Antibacterial activity, Antioxidant, Anti-inflammaatory, Antimicrobial activity (**Fit *et al*., 2007**).

4. Discussion:

Cinnamon causing the bacterial cell membrane to become unstable and stop working, which results in cell death.Vasaka substances like vasicine acetate and 2-acetyl benzylamine, it can prevent the growth of Mycobacterium tuberculosis. It can also help expel mucus and modulate the inflammatory response. Acalypha indica provides bronchodilation by stabilizing mast cells, blocking inflammatory pathways such as NF-kB, and blocking histamine and acetylcholine. Calotropis gigantea in the lab, its extracts may have anti-tuberculosis properties, but they work by compromising the integrity of the bacterial cell wall or membrane, inhibiting enzymes, and reducing or inducing oxidative stress.Acaciafarnesiana involves methyl gallate and other phenolic chemicals that can alter pH, membrane potential, and ATP levels in Mycobacterium tuberculosis by compromising the integrity of the cell membrane. Mint involves breaking down the bacterial cell membrane, which causes leakage and depolarization of the cell. Additionally, it lowers ATP synthesis, destroys membrane proteins, and modifies the pH gradient across the membrane.

5. Conclusion:

In these review we conclude that medicinal plants like “Acacia, Calotropis, Vasaka, Acalypha indica , Mint, Cinnamon” are good alternatives to currently available allopathic medicine with fever toxicity, less side effects and less pill count .One crucial step in improving TB management is the hunt for phytodrugs. We come to the conclusion that employing plants and plant-based products to treat tuberculosis presents a promising chance to create novel formulations, therapies, and cures for health management. When treating XDR and MDR TB, antimycobacterial activity against MTB was more advantageous and effective. New researchers will benefit from this summary. As an adjuvant medication, phytochemicals may strengthen immune cells and present a viable substitute for conventional antibiotics, opening the door for the development of environmentally friendly and sustainable therapies..More study must be done to determine the effectiveness of all this herbal phytochemicals. In future this phytoconsitutents may offer promising results in the treatment of MDRas well as XDR tuberculosis.

Author Declaration

We certify that each of the listed authors has read and approved the article, and that no other persons meet the requirements to be included as authors. We also certify that we have all approved the order of authors as stated in the manuscript.

Acknowledgements

Authors are thankful to the Management of TPCT’ College of Engineering, Dharashiv, Maharashtra India for the support.

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Cite this article

Aishwarya K. Dhengle, Kalyani A. Shinde, Ankita Y. Kshirsagar, Rajesh B. Nanaware. 2026. Phytoconstituents: To Eradicate Mycobacterium Tuberculosis. *Bioscience Discovery*, **17**(2):98-106.