Role of Plant Extracts to Control *Mycobacterium tuberculosis*

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Abstract

Tuberculosis (TB), especially the multidrug-resistant tuberculosis (MDR) and extensively drug-resistant (XDR) forms, is a major global public health threat due to its complexity of treatment regimens as well as the widespread resistance to tuberculosis. The rise of MDR-TB, defined as resistance to isoniazid and rifampicin, was alarming, with over 580,000 new cases recorded in 2015 in regions like India and China. Although treatment for MDR, and to a greater degree XDR-TB, is protracted, often lasting over 20 months with severely toxic second-line drugs, cure rates are as low as 36% and failure rates as high as 50%. Plant extracts could be a feasible solution to combat *M. tuberculosis,* especially given the increasing drug resistance. Bioactive compounds such as alkaloids, flavonoids, terpenoids, and polyphenols have shown potential antimicrobial properties. The diversity in multi-modal actions of these plant-derived molecules, combined with their work to co-deliver with current antibiotics, highlights their potential for use as stand-alone or allied treatments for tuberculosis. It seems that incorporation of plant extracts in therapeutic approaches, therefore, has the potential to increase treatment outcomes and lessen side effects as compared to synthetic drugs. Their potential is supported by data from animals and laboratory research. Certain plant chemicals also lessen the negative effects and increase the effectiveness of current TB medications. Their mechanisms, important substances, experimental results, and possibilities for the future are all covered. When combined with existing medicines, plant-based therapeutics may prove to be effective weapons in the fight against tuberculosis.

Keywords: Tuberculosis, Antimicrobial, Alternatives, Plant extract, Medication

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Introduction

Mycobacterium tuberculosis, the causative agent of TB, is a slow-growing acid-fast bacillus with a complex lipid-rich wall that gives protection against antibiotics and the host's immune response. It was first isolated from infections of the lungs, which can lead to dissemination to different organs, causing extra-pulmonary TB (EPTB). This is a diagnostic and therapeutic challenge (Mohammadnabi et al., 2024). It is transmitted via inhalation of infectious droplets and has a global reservoir of latent TB infections occurring in as one-quarter of the population, which has the potential to reactivate. The prevalence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains further increases the global TB burden, requiring better interventions (Coleman et al., 2022). These include the recent developments of second-line drugs like Bedaquiline, Delamanid, and Pteromalid against resistant strains, as well as drugs with different targets. However, some obstacles persist, especially in low-resource settings where empirical treatment for EPTB is associated with unsatisfactory rates of treatment completion (Jørstad et al., 2019). While molecular diagnostics can revolutionize the diagnosis of TB by providing rapid and accurate detection, they still need to be used alongside experienced personnel and are expensive. There are key needs to understand the evolution and emergence of tuberculosis as a complex set of lineages with multiple host preferences, understanding which will improve mechanisms of infection-based control strategies and guide epidemiologic forecasts (Coleman et al., 2022). As a conclusion, the management of TB needs a multi-pronged approach with rapid detection, timely intervention, and multifaceted management, particularly in disadvantaged socioeconomical populations (Patel et al., 2024).

Tuberculosis (TB) is a major health problem worldwide, and the World Health Organization (WHO) reports approximately 10 million cases, along with more than 1.5 million deaths annually, mainly in low- and middle-income countries of high co-infection with poverty, malnutrition, and HIV impact (Chakaya et al., 2021). The appearance of multidrug-resistant (MDR-TB) and extensively drug-resistant (XDR-TB) strains increases difficulties for controlling it, since these cases usually need longer treatment periods and lead to larger economic burdens, with costs of almost $14,657 in some regions (Cioboata et al., 2025). With the advent of better diagnostic tools and treatment regimens, the challenges like patient non-compliance, individual treatment requirements still stand to be addressed. Wasting, TB treatment outcomes, and

elimination of the disease will not be possible to achieve as a critical determinant of disease progression in TB. Integrated approaches that include multimodal nutritional support, novel therapeutic strategies, and improved healthcare access are indispensable for controlling TB (Naghavi et al., 2019).

Anti-tuberculosis (TB) first-line drugs, isoniazid, rifampicin, ethambutol, and pyrazinamide, must be incorporated into a treatment minimum of six months; however, treatment is complicated by resistance due to TB mostly being drug resistant, including MDR and XDR. MDR-TB treatment can last 18–24 months and consists of stronger and less effective second-line drugs that are more toxic (Liu et al., 2023). Unfortunate absence of a safe and effective vaccine for adults, with BCG providing marginal protection (Iqbal et al., 2025).

Drug-resistant tuberculosis (TB) is on the rise, and new treatment options are needed to overcome the rapidly expanding problem; natural plant-based products represent a biologically safe and promising source of these therapeutic leads (Tiberi et al., 2022; Abbas et al., 2024; Naz et al., 2025). Ancient traditional medicine had been extensively using medicinal plants to treat respiratory infections, which are vital in modern healthcare. The multi-target mechanisms of phytochemicals (particularly bioflavonoids) can interfere with the survival pathways of *Mycobacterium tuberculosis*, which was predicted to inhibit resistance development and possibly reduce the treatment period (Gautam et al., 2023; Ali et al., 2024). These anti-TB high-affinity compounds synergize with the current drugs used for this disease and have anti-inflammatory properties that may reduce tissue damage from the disease. Additionally, Incorporation of plant-based therapeutics as adjuvant therapy has the potential to dramatically benefit treatment success, further underscoring the necessity for collaborations across multiple disciplines in order to exploit their extraordinary range of functionality (Maiolini et al., 2020).

Plants are the primary producers of secondary metabolites such as alkaloids, flavonoids, terpenoids, and polyphenols that show high antimicrobial potential and, in many cases, against TB with promising in vitro and even a few *in vivo* data. Plant-derived molecules can also compound the action of current antibiotics by acting on the bacterial machinery that drug resistance often targets, such as efflux pumps, antimicrobial resistance (AMR) (Othman et al., 2019). The traditional plant extracts may show synergistic action with presently used antibiotics and thus enhance their efficacy against multidrug-resistant strains (Sajid et al., 2025). Moreover, some natural products may affect the host immune responses, which could provide additional tools for TB control with more efficient treatment potential. This chapter highlights the need for assimilation of phytochemicals in advanced therapeutic strategies to tackle AMR and improve clinical results.

Mycobacterium tuberculosis: Pathogenesis and Drug Resistance

Mechanism of Infection and Disease Progression

M. tuberculosis, an incredibly transmissible pathogen that enters the human body by inhaling droplet-borne infection and disseminates to the alveolar space, where it is subsequently phagocytosed by alveolar macrophages (Asghar et al., 2024). It differs from the great majority of pathogens as it has been documented to maintain itself within macrophages by the inhibition of phagosome-lysosome fusion. It relies on lipoarabinomannan in its cell wall to prevent fusion, as well as acidification and reactive oxygen species production, thereby allowing it to persist, lurking inside granulomas (Howard et al., 2024). However, these granulomas may also rupture and are a means for active TB, where bacilli are disseminated through the bloodstream to infect distant organs with symptoms including coughing, weight loss, fevers, and night sweats (Verma et al., 2024). Despite having successful containment, the immune system in latent TB fails to eliminate the bacteria, and reactivation occurs when immunity is compromised. *M. tuberculosis* survives by hijacking macrophage bioenergetics. This translates into a relationship between glycolytic suppression/oxidative phosphorylation elevation, macrophage phenotype, and drug-tolerant *M.*TB populations (Verma et al., 2022). Moreover, during prolonged chronic infection, *M. tuberculosis* can decisively live in a lysosome in rare-poor monocyte-derived lung cells based on the impaired lysosomal activity of these cells (Mpande et al., 2021). Boosting macrophage bactericidal function or blocking *M. tuberculosis* entry (e.g., metabolic rewiring, lysosome biogenesis) represent attractive approaches to treat tuberculosis. Strategies to understand mechanisms are essential for designing potent and efficacious therapy and vaccines against TB (Leukes, 2022).

Drug Resistance in *M. tuberculosis* (MDR-TB, XDR-TB)

M. tuberculosis is inhaled into the body and found in alveoli where they are taken up by alveolar macrophages. Nonetheless, *M. tuberculosis* avoids clearance as it does not undergo phagosome-lysosome fusion, which is a mandatory process for pathogen neutralization and allows it to survive within macrophages, as arrest within those cells is seen through the generation of granulomas, a hallmark of TB (Scordo et al., 2019). Eventually, this forms macrophages into granulomas that harden, allowing for the incubation of active TB where bacteria are disseminated through the bloodstream to other organs, and subsequent symptoms like cough, weight loss, persistent fever, and night sweats appear (Ashenafi & Brighenti, 2022). The latent TB allows the immune system to control an infection, but not eliminate it, and reactivation can happen after immunity declines. A few recent works have now proposed that reprogramming macrophage metabolism may improve their capacity to combat *M. tuberculosis*, which might reduce drug tolerance and treatment response (Chandra et al., 2022).

Drug resistance arises due to various sources, which are sub-standard treatment, incomplete prescriptions, poor quality drugs, and bacterial genetic mutations. Poor treatment adherence, especially with antiretroviral therapy (ART), will result in increased risk of drug-resistant infections, projecting that if adherence drops, the impact on treatment wider scale can be offset (Akpobolokemi et al., 2022). Inaccurate and non-prescription use render treatment ineffective, thus pathogens survive, evade elimination, and evolve, whereas a further augmentation of this issue through the presence of sub-standard or falsified products by failing to act therapeutically (Ugoala, 2023). Bacterial genetic mutations that shift drug targets or increase efflux also contribute substantially to resistance, and the emergence of resistance, for which previously curable infections become more difficult. In conclusion, there is an acute requirement for multi-pronged approaches to combat drug resistance in the healthcare setting (Ahmad et al., 2025).

Multifaceted bacterial resistance to antibiotics involves several important mechanisms are involved in the issue of antibiotic resistance. RND superfamily resistance-related drug efflux pumps, in particular, are key players in actively pumping antibiotics out from bacterial cells and thus are a major contributor to multi-drug resistance (Huang et al., 2022). Enzymes KatG mutation giving rise to isoniazid resistance and target site modifications for example, in RNA polymerase variant rifampicin resistance allow bacteria to inactivate drugs as well as preventing

effective drug binding respectively (Marney et al., 2018). Enzymatic modifications in biofilm therefore make it easier for bacteria to survive and achieve resistance simultaneously, but also render therapeutic intervention more difficult (Azeem et al., 2025). Together, these mechanisms and their interactions with environmental factors and the overuse of antibiotics highlight a critical requirement for innovation in therapeutic approaches to combat a worsening antibiotic resistance crisis (Muteeb et al., 2023).

Challenges in TB Treatment and Control

The challenges of the treatment for MDR-TB and XDR-TB are peculiar due to the long duration and toxicity of the drugs that are required. Standard TB usually takes six months of treatment, MDR-TB and XDR-TB regimens can last up to 2 years on average, which also means there is an increased risk of adverse event (AEs) like GI disturbances, arthralgia, psychiatric symptoms, for a large part of patients or even ALL (9–50%) (Pontali et al., 2019). The type of regimen and the duration of therapy were associated with increased severity of adverse drug reactions (ADRs) with the longer treatment having higher potency of all ADRs (Geer et al., 2016). Newer developments have also brought forth shorter 6-9 months all-oral regimens for MDR-TB that may be able to decrease treatment duration compared with the more frequent adverse effects of prolonged therapy (Pontali et al., 2019).

Still, long treatment durations are common in co-morbidities (e.g., hepatitis B or recent cancer therapy), known to be associated with a higher risk of drug adverse effects and treatment interruption. The updated guidelines of the World Health Organization advise shorter treatment regimens with combinations such as BPaLM for MDR-TB in particular situations, thus aiming at better treatment results and less following ADRs (Sandmann et al., 2019). Despite this progress, the toxicity of TB drugs is still a big issue; some second-line drugs cause severe adverse side effects, including drug-induced hearing loss from aminoglycosides, which may affect the management of TB, as some healthcare access in resource-constrained settings is poor (Prasad et al., 2021).

Plant Extracts as Potential Anti-TB Agents

Historical Perspective on Medicinal Plants for TB

Medicinal plants used in some ancient healing systems like Ayurveda, Traditional Chinese Medicine (TCM), and African herbal medicine have been used historically to treat tuberculosis (TB) similar respiratory tract infection in antiquity that continue today (Singh et al., 2024) Ethnobotanical surveys have revealed many plants used in traditional medicine with antimicrobial potential, such as several most documented ones like *Artemisia annua*, *Azadirachta indica* (Neem) *Curcuma longa* (Turmeric) and *Allium sativum* (Garlic) that have been used as folklore remedy against TB-like illnesses (Chew et al., 2022; Izah et al., 2023). Contemporary studies have reaffirmed this folk wisdom by identifying the bioactive compounds from amongst these plants. Plants found to possess potent anti-TB activities as an alternative for synthetic antibiotics were considered (Singh et al., 2024). The *Fabaceae* family, for example, has shown great potential for TB eradication with several flavonoids and alkaloids as the most common bioactive compounds (Nyambo et al., 2023). These antibacterial compounds of plant origin directly show their antiviral activity and immunomodulatory efficacy against *M. tuberculosis*. Thereby improve natural defenses and inflammation reduction (Sarangi et al., 2021). Integrating traditional herbal therapy as part of the modern treatment for TB is likely to bring safer and sustainable therapeutic alternatives to the management of both efficacy and safety challenges associated within current TB drugs (Gautam et al., 2023).

Mechanisms of Antibacterial Action of Plant Extracts

Cell Wall Disruption

Key challenges to the treatment of *M. tuberculosis* are the distinctive cell wall rich in mycolic acids, abound from the perspective of antimicrobials because both aspects confer protective properties and resistance mechanisms (Abrahams & Besra, 2018). Approaches with existing approved drugs target cell wall biosynthetic pathways, such as enzymes for mycosublin acids, peptidoglycans, and other arabinogalactans. Approved drugs like isoniazid and ethambutol address specific pathways, whereas novel agents in clinical trials endeavor to target additional targets such as DprE1 and MmpL3 (Abrahams & Besra, 2018). Apart from that, some plant-derived small molecules such as flavonoids and tannins showed the ability to breach the lipid bilayer in the cell wall of *M. tuberculosis*; therefore, suspect these antibiotics. This two-pronged strategy of harnessing both synthetic and natural compounds might be a better way for fighting resilient strains of TB (Gautam et al., 2023).

Enzyme Inhibition

The survival of bacteria is largely attributed to key enzymes, i.e. DNA gyrase essential for DNA replication and central to its overall metabolic process. Plant-derived constituents, especially alkaloids such as berberine, have extremely promising anti-bacterial potential to inhibit such enzymes and therefore provide a mechanism for bacterial growth inhibition by mediators derived from plants (Mittal & Jaitak, 2019). Antimicrobial activity of berberine, an isoquinoline alkaloid present in many medicinal plants, including the inhibition of DNA gyrase, which is indispensable for bacterial life. Researchers revealed that berberine binds more strongly with the active sites of bacterial replication enzymes, thereby demonstrating monomeric nature and recognizing it as one of the effective natural antimicrobials (Liu et al., 2019). Additionally, research into other plant-derived inhibitors of DNA gyrase and other replication enzymes is essential in finding new approaches for overcoming antibiotic resistance and emphasizes the role of phytochemicals in contemporary medicinal practices (AlSheikh et al., 2020).

Bioactive Compounds in Plant Extracts with Anti-TB Potential

Alkaloids, including berberine and piperine, are nitrogenous compounds with a powerful antimicrobial activity as they are potent inhibitors of bacterial DNA replication/protein synthesis. Berberine isoquinoline alkaloid isolated from various medicinal plants, has been found to be able to inhibit the growth of *M. tuberculosis in vitro*, as mentioned in Table 1, by targeting bacterial enzymes and disturbing the mycobacterial membranes, thus sensitizing drugs (Thawabteh et al., 2019). Along with this, berberine presents a more diversified

pharmacological profile as an anticancer, antidiabetic, and antimicrobial agent, so it could be a promising therapeutic agent. The nutritional piperine, also known as alkaloid piperine, found in *Piper nigrum,* boosts bioavailability of anti-tuberculosis drugs and hinders bacterial efflux pumps, leading to minimal drug resistance (Rauf et al., 2021). Advanced chromatographic and spectroscopic methods have been employed for the isolation and purification of alkaloids such as piperine to retain their purity and feasibility in pharmaceutics (Nadeem et al., 2025). In addition, other microbial alkaloids (e.g., berberine) are considered a possible means of cost-effective production due to the superior capabilities of transformation systems in microorganisms over conventional plant-derived methods. Together, these results bring the therapeutic promise of alkaloids in disease therapy and elucidate the ongoing endeavors to perfect their activity and clinical use (Quijia & Chorilli, 2020).

Table 1: Some active compounds in the plant extract used to treat *Mycobacterium tuberculosis*

Plant name	Common name	Active compounds	Mode of Action	References
Allium sativum	Garlic	Allicin	Inhibits cell wall synthesis	(Teixeira et al., 2023)
Azadirachta indica	Neem	Nimbin, Nimbidin	Disrupts membrane integrity	(Joshi & Prabhakar, 2021)
Curcuma longa	Turmeric	Curcumin	Inhibits bacterial enzymes and signaling	(Jyotirmayee & Mahalik, 2022)
Ocimum sanctum	Tulsi	Eugenol, Ursolic acid	Antioxidant, immunomodulatory effects	(Arya et al., 2024)
Withania somnifera	Ashwagandha	Withanolides	Enhances host immunity, anti-inflammatory	(Alanazi & Elfaki, 2023)
Moringa oleifera	sohanjana	Quercetin, Kaempferol	Disrupts bacterial cell processes	(El-Sherbiny et al., 2024)
Tinospora cordifolia	Guduchi	Tinosporide, Berberine	Boosts macrophage activity, inhibits growth	(Rachana et al., 2022)
Adhatoda vasica	Vasaka	Vasicine, Vasicinone	Inhibits protein synthesis in *M. tuberculosis*	(Shoaib, 2021)

Evidence from Experimental Studies

In Vitro* Studies against *M. tuberculosis

The antiamine activity of different plant extracts against *M. tuberculosis* has been indicated in vitro studies with the potential to affect bacterial growth by disrupting cell wall integrity, for instance, and inducing oxidative stress (Kumar et al., 2021). *Curcuma longa* (curcumin) is known to have an inhibitory effect on biofilm formation. *Azadirachta indica* (neem) breaks up bacterial cell walls, and *Allium sativum* (bell peppers) is a bactericidal against multi-drug-resistant strains (Shastri et al., 2018). Also, in another research study, 20 Asteraceae plants with antibacterial recorded against *M. tuberculosis* were reported. This calls for the investigation of these plant-derived compounds as novel agents that can be used in place of conventional treatment, as most of the drugs are losing their efficacy due to a high level of drug resistance and the requirement for new therapeutic options (Chassagne et al., 2021).

***In Vivo* Studies and Animal Models**

Animal models, especially mice and guinea pigs, are essential for testing the efficacy of plant extracts in TB, mainly for the reduction of bacterial load in lungs and other organs through efficacy studies. *In vivo* studies of medicinal interest have previously been successful with respect to curcumin treatment in mice, greatly ameliorating TB-driven lung inflammation; upon berberine treatment, TB-infected rodents significantly increased survival rates. It is further noted that artemisinin suppresses the bacterial count as well as augments immune responses. The plant extract *Centella asiatica,* favors immune-modulatory properties, enhancing phagocytic ability of macrophages with the secretion of proinflammatory mediators, particularly TNF-α, and IFNγ, all required to combat TB. Moreover, the extracts such as that of *Tussilago farfara* decrease the levels of inflammatory cytokines and neutrophil infiltration, which prevents lung tissue damage (Tian et al., 2025).

Synergistic Effects with Conventional Anti-TB Drugs

The synergy between plant extracts and existing anti-TB drugs is also encouraging, because it helps to not only ameliorate *M. tuberculosis* treatment but also oppose the emergence/re-emergence of drug resistance. Well, this goes to no better evidence that combination extracts from *Zanthoxylum leprieurii* and *Rubia cordifolia* showed substantial inhibition with some of the standard anti-TB drugs, more especially towards multidrug-resistant (Ayodele et al., 2023). Moreover, piperine as an efflux pump inhibitor suppresses the efflux and likely increases the retention of rifampicin, isoniazid. In addition, essential oils eugenol and thymol have been reported for the inhibition of bacterial adaptation, thus preventing the emergence of resistance (da Silva et al., 2023). TB treatment is associated with oxidative stress and liver toxicity. Plant antioxidants such as phenols and resveratrol need to be mentioned. In brief, these combinations not only have better therapeutic results nonetheless also tackle a requirement for TB treatment drug resistance (Jubilee et al., 2024).

Plant extracts are consistent and efficacy dependent; variability of plant composition greatly influences bioactivity, and standardization as well as quality control in plant extracts must be applied to ensure that the active compounds are therapeutically effective (Heinrich et al., 2022). These differences arise from the heterogeneity in the growing environment, extraction techniques, in addition to the manner of storage, making it difficult for comparisons among studies to be made. Lack of well-defined protocols only adds to these, causing inferior herbal products that could be unsafe/ineffective (Câmara et al., 2022). Some of the possible solutions are preparing strict guidelines on plant cultivation and extraction processes, as well as profiling chemicals to be able to have uniform concentrations of bioactive compounds. In addition, enforcement of GMP is imperative to ensure quality is maintained on a batch-by-batch level throughout production, as required to meet regulatory needs for heavy metal contamination and batch-to-batch variability has to be dealt which gives (Da Silva et al., 2022).

The safety and toxicity of plant bioactives, particularly in herbal medicines, is somewhat of concern because high-dose potent cytotoxins and possible drug interactions of plant compounds with short-acting antituberculosis (TB) medications (KhokharVoytas et al., 2023). Preliminary studies suggest that ~150,000 plant species are toxic, thus, well-documented animal pre-clinical toxicity studies are needed to identify the dose range finding and look at long-term effects on liver/kidney (Tripathi et al., 2018). Changes are underway in current botanical safety evaluation approaches, with e.g., the Botanical Safety Consortium promoting alternative strategies for assessment that incorporate traditional knowledge and modern toxicological practices (Mitchell et al., 2022). Concomitant to this, thorough safety

assessment is needed for herbal products used in biopharmaceuticals to meet legal requirements and to mitigate potential risks from long term use ensuring herbal product safety and compliance for biopharmaceutical use, A full-driven safety evaluation, in combination of human studies on adverse effects delivers a paradigm for consumer protection and enhancement of the efficacy of the potential herbal treatment (Gupta et al., 2024).

Plant-based anti-TB therapy development is hampered by numerous bottlenecks, including slow progress from in vitro assays to clinical trials and funding shortfalls/regulatory holdups throughout the drug development process. Although plant medicines have shown promise with antimicrobial and immunomodulatory properties, many have remained untested in the rigorous clinical space, as witnessed by the continuing validation of novel TB vaccines and drugs (Sieniawska et al., 2020). The standard phases preclinical, Phase I–III of a clinical trial are an important necessity before these treatments can ever offer any efficacy and safety (Cook et al., 2015; Iftikhar et al., 2023). Research should focus on collaborative pathways of researchers, pharmaceutical corporations, and policymakers to integrate plant-derived therapies into modern drug discovery pipelines and normative settings for herbal medicines. This three-pronged strategy might benefit the generation of new and effective TB treatments, especially against the backdrop of mounting drug resistance (Chaachouay & Zidane, 2024).

Conclusion

Despite the global threat, *M. tuberculosis* continues to be a significant burden on health due to the developing drug resistance, and as current treatments are often associated with toxicity, long duration. Tuberculosis, a major global menace with escalating drug resistance, is further complicated by our current treatments, which include severe toxicity or long duration. Plants containing bioactive compounds with anti-TB potential are the focus of recent studies. For example, several medicinal plants *Zanthoxylum leprieurii*, *Rubia cordifolia,* and others, in *in vitro* studies have shown notable activity against both drug-susceptible and resistant strains of the *M. tuberculosis*. Yet some plant compounds have been shown to increase the bioactivity of conventional TB medications, and their use could eventually temper drug resistance. Yet important hurdles to effective natural therapies in their own right include bioavailability, standardization, safety, and regulatory approval.

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