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Current and Future Prospective in Management of Tuberculosis

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ABSTRACT: Tuberculosis is chronic airborne bacterial infection caused by Mycobacterium tuberculosis, characterized by respiratory illness, impaired immune systems and is one of the leading causes of mortality in the world. The significant harmful side effects of the conventional synthetic therapeutic approaches and the development of cross- or multidrug resistance, which makes medication more challenging, have a detrimental impact on people health. Unsatisfactory diagnostics and treatment, multidrug-resistant tuberculosis (MDRTB), the Short Course (DOTS) programme, unregulated private health care leading to widespread irrational use of first- and second-line anti-TB drugs, and HIV coinfection are some of the main causes of the ongoing challenges in TB control. Natural products have been and will be a prominent source of novel medications for a wide range of disease. Antituberculotic medicinal plants provide an innovative clinical management, enabling the discovery of new molecules to prevent infection. The rising prevalence of multidrug-resistant, MTB strains and the adverse consequences of first- and second-line antitubercular agents have led to the growing interest in natural products in the search for novel antitubercular leads. Previous research has demonstrated that ayurvedic treatments significantly lower TB patients' mortality rates. Due to its low toxicity and safety as compared to allopathic therapies, ayurvedic medicine is become most popular.

Many medicinal plants have shown potential for the development of drug-hit candidates and many other drugs are currently in different phases of clinical trials. New drug delivery systems are currently being studied for the effective delivery of drugs to increase efficacy and reduce the chances of toxicity with the delivery of the drugs to the targeted site. The present review provides In-depth features of antituberculosis plants, chemical constituents, anti-tubercular characteristics and their ability of impacting the early stages of drug discovery with which they can be used as future novel treatment option in management of TB.

Keywords: Tuberculosis, management of TB, natural products, recent approved anti-tubercular agents, novel treatment for TB, Ayurveda in TB.

INTRODUCTION

Tuberculosis (TB) is a leading infectious disease that caused the deaths of a total of 1.6 million people in 2021 and is one of the top causes of mortality worldwide. India is the country with the highest TB burden. Over 1.9 million TB cases were diagnosed globally in 2021 which is 19% more from 2020 (Chakaya *et al.*, 2022). TB is chronic airborne bacterial infection caused by mycobacterium tuberculosis (Mtb), characterised by respiratory illness, impaired immune systems and is one of the leading causes of mortality in the world (Tufariello *et al.*, 2003). Mtb is a non-motile aerobic bacillus that causes respiratory infection when an infected person, during coughing or sneezing, releases the droplets with droplet nuclei of 1-5 microns containing viable Mtb, and these droplets are inhaled and reach the respiratory alveolar units. With the phagocytic efforts of the host's innate immune cells which includes primarily alveolar macrophages, dendritic cells, monocytes, and neutrophils, Mtb is still able to persist in the host and results in the formation of granulomas. It is difficult to treat because its cell wall contains mycolic acids. This unusual fatty acid makes the bacteria less susceptible to antimicrobial agents and also helps the bacteria to vitiate the immune system and then hide from it. Although exact host-bacillus interactions and mechanisms are still not very well understood, still this Mtb and host interaction during these initial stages of successful infection determine the outcome of TB disease. Based on clinical

manifestation, TB can be categorised into two types: pulmonary TB (PTB) and extrapulmonary TB (EPTB) (Maurya *et al.*, 2015). TB that affects organs except the lungs, specifically the lymph nodes, stomach, genitourinary system, skin, skeleton and meninges, is referred to as EPTB(P. Singh et al., 2018). A patient with EPTB is classified under pulmonary TB (as military TB) if they additionally have a tubercular lesion in their lung parenchyma. EPTB is defined as the presence of intra-thoracic mediastinal and/or hilar lymph node TB, TB pleural effusion, or both without radiographic abnormalities in the lung (Natarajan *et al.*, 2020). It may progress to active TB (pulmonary or extra pulmonary) or latent TB or just simply driving clearance (Hunter, 2020; Orme, 2014). The spread of the most deadly infectious disease is made possible by the ongoing emergence of multidrug and extensively drug-resistant (MDR/XDR) strains (Magiorakos *et al.*, 2012).

Tuberculosis in India. Tuberculosis remains one of the major public health problems in India. It has been estimated that about 30% of the world's tuberculosis patients are residing in India (Imtiyaz & Jagdish 2013). The Indian government currently asserts that from 2.2 million to 2.6 million people worldwide are presently afflicted with TB, based on examinations of medicine sales. India's Ministry of Health and Family Welfare said on World TB Day, March 24, 2019, that 2.15 million new TB cases were diagnosed in 2018. India is one of the eight countries that accounted for 28% of cases worldwide and more than two-thirds (68.3%) of all TB cases. India accounted for 36% of all TB-related deaths in HIV-negative people globally (Bagcchi, 2022). Current TB treatment, Program support the particular effects of each bactericidal agent govern the rational usage of antituberculosis treatments. Isoniazid is particularly effective against big cavities, although it also has limited efficacy in caseous lesions and macrophages. Rifampin is effective against the intermittently increasing population in caseous lesions and is active in all populations. Streptomycin is only effective against the extracellular population, but Pyrazinamide (PZA) is only active in an acidic environment and has a particular effect on macrophages. PZA produces its maximal impact only within the first few months of medication, according to clinical trials (Addington, 1979; Laurenzi *et al*., 2008).

The Revised National TB Control Plan (RNTCP) in India is a TB management programme with official support that combats the disease in the neighbourhood. Although it is a government-sponsored programme offering free treatment and diagnostic services, many people still resort to private clinics when they experience a symptom (Narayan and Walt 1998). According to investigations, 50-80 percent of TB patients seek treatment from private practitioners. Ayurvedic medications are currently not included in the RNTCP. Private practitioners, including general practitioners and chest specialists, employ a variety of ayurvedic remedies to help in TB care (McDowell and Pai 2015).

Current therapeutic strategies and limitations. First-line anti-TB medications like isoniazid, rifampicin, ethambutol, and PZA had an 86% success rate in regular TB, compared to a 59% success rate in MDR or rifampicin resistant (RR-TB) (Mirzayev *et al.*, 2021). Among the 3 million cases of pulmonary TB that were bacteriologically diagnosed in 2020, 2.1 million patients, or almost 71% of the total number of cases, had RR-TB (Shah *et al.*, 2022). For MDR/ XDR-TB patients, a long and challenging anti-TB medication regimen is used which includes overpriced antimicrobial drugs that are toxic, poorly tolerated, and have undesirable consequences. The USFDA's approval of three second-line anti-TB medications, bedaquiline (Bdq), delamanid (Dlm), and pretomanid (Ptm), during the past ten years has marked a significant advancement in the therapy of drug-resistant TB (DR-TB).For the treatment of MDR/XDR-TB, these second-line anti-TB medications provide the potential of shorter and easier all-oral regimens. Bdq has been included in the treatment regimen of DR-TB in 109 countries by the end of 2020. All-oral extended and shorter regimens are used in several nations to treat MDR/RR-TB (Black and Buchwald 2021; Dookie *et al.*, 2022; Ignatius and Dooley 2019).

Drug repositioning or repurposing is another proactive strategy for the therapy of TB. It entails reassessing already-approved and established medications for alternative therapeutic applications. The need for repurposing in the treatment of DR-TB is urgent, and clofazimine (Cfz) is one of the most thoroughly studied compounds. It is a riminophenazine that has been shown to be active against Mtb both in vitro and in vivo (Cardoso *et al.*, 2022*;* Zhai *et al.*, 2019).The necessity for the development of novel drugs has grown significantly as a result of the rise of different resistant Mtb strains. An effective approach to combat DR-TB is to use medicinal plants, which are a significant source of physiologically active secondary metabolites and have a wide range of therapeutic possibilities. Among the medicinal plants with anti-Mtb actions, *Zanthoxylum leprieurii*, *Lantana camara*, and *Cryptolepis sanguinolenta* are most commonly used. A novel and promising idea for treating TB is host-directed therapy which can alter host reactions to more effectively and downregulate the disease's progression *(Tuyiringire et al*., 2020).

Despite the numerous treatment options available, TB still poses a serious threat to public health since the majority of antituberculosis medications on the market have side effects including haematological reactions, gastrointestinal intolerance, hepatitis, renal failure, and dermatological reactions. It is important to identify these detrimental effects as soon as possible in order to reduce infectious complications and mortality. The most serious adverse reactions of rifampin are hemolysis, thrombocytopenia, and renal failure. During complement fixing, platelet loss occurs because anti-rifampin antibodies infiltrate into platelets and cause thrombocytopenia. Because of its numerous gastrointestinal adverse effects, PAS is no longer recommended for use as a main medication in adults.

The liver damage caused by isoniazid and rifampin seems to be supplementary. Because they are not synergistic, neither one nor the other should be given to individuals even without liver disease who are alcoholics. Ethambutol's most severe side effect is retrobulbar neuritis. Considering that isoniazid is known to interfere with the metabolism of diphenylhydantoin, patients taking both dilantin and isoniazid must be advised of the risk of dilantinover dosage (Addington, 1979; Bahuguna and Rawat 2020; Laurenzi *et al.*, 2008).

Table 1: Common ADR of anti-tubercular medications.

Groups	Drugs	ADR
First-line oral	Isoniazid (INH)	GI upset, epigastric pain, hepatotoxic, psychosis, convulsive seizures, mental confusion, and coma etc.
	Rifampin	hepatotoxicity, immunological reactions, dizziness, headache, dyspnoea, and ataxia etc.
	PZA	Severe exanthema, pruritus, rhabdomyolysis with myoglobinuria, kidney failure, acute arthritis in gouty individuals and hepatotoxicity.
	Ethambutol	Retrobulbar neuritis, hepatotoxicity, haematological symptoms, haematological symptoms and hypersensitivity etc.
Second-line drugs/ Oral bacteriostatic	Aminoglycosides	Ototoxic, neurotoxic, nephrotoxic, neuromuscular blockage and hypersensitivity.
	Fluoroquinolones	Adversely impact gastrointestinal, central nervous system, cardiovascular system, urinary tract, endocrine system, also cause skin reactions and allergies.
	second-line anti-TB drugs	Neurological and psychic alterations

Importance of Herbal medicine. One of the largest plant-based medical traditions is found in India. There are over 25,000 effective herbal remedies used in religious medicine in India that are well-known to rural residents. Traditional medicine, which employs herbal remedies for therapeutic, preventive, and promotional objectives, is practised by almost 1.5 million people. With approximately 2000 tonnes of herbs used annually, India is estimated to have 7800 medicinal medication production facilities (Mangwani *et al*., 2020). The development of potent therapeutic drugs is primarily on medicinal plants. Between 1950 and 1970, the US drug industry the introduction of almost 100 innovative herbal drugs; deserpidine, reserpine, vinblastine, vincristine, and reseinnamine are only a few examples of chemicals derived from plant species (Verma and Singh 2008). New drugs such ectoposide, artemisinin, teniposide, eguggulsterone, plaunotol, lectinan, nabilone, and ginkgolides were developed worldwide between 1971 and 1990. Between 1991 and 1995, many new medications—including paciltaxel, toptecan, gomishin, and irinotecan—were approved, representing for 2% of all applications. Serpentine, for instance, was discovered in the plant Rauwolfiaserpentina's root in 1953 and was discovered to be a game-changer in the treatment of hypertension. As vincristine, the active ingredient in vinblastine, is a kind of vitamin C, it is used in cancers such as choriocarcinoma, paediatric leukaemia, and neck melanoma. Possible causes include cervical cancer, breast cancer, advanced Hodgkin's disease, lymphosarcoma, acute lymphocytic leukaemia in children, and lymphosarcoma. Phophyllotoxin, a constituents of the Phodophyllum, is being used to treat lymphomas, testicular cancer, and small lung tumours. Drugs made from plants are used to treat diabetes, hypertension, cancer, TB, jaundice, and skin conditions. The development of potent therapeutic drugs is primarily reliant on medicinal plants (Khusro *et al*., 2018*;* Jamshidi-Kia *et al.*, 2018)

Medicinal plants for DR-TB treatment. The term "phytonutrients" refers to the chemical compounds derived from plants that are formed during their metabolism to help in their defence against various infections. Although these chemical substances have a long history of application in therapeutic procedures, few studies have been performed to investigate these phytonutrients in the treatment of TB. The management of Mtb infection requires more research work into the phytoconstituents investigations (Memariani *et al.*, 2020). The natural supplements component garlic (*Allium sativum*) has potent antibacterial properties. The major component of garlic is allicin, chemically it is thio-2-propene-1-sulfinic acid Sallyl ester that prevents sulfhydryl metabolic enzymes to exert its antibiotic action. Extract of allicin has shown promising results against both drug-sensitive and -resistant strains of Mtb. Another component of garlic known as ajoene has been used to treat TB because it increases the production of ROS and autophagy. The efficiency of the garlic extracts against clinical strains of MDR-TB has scientific significance, and they provide opportunity for the development of substitute medications (Dwivedi *et al*., 2019; Silwal *et al*., 2021).

A yellow-colored curcuminoid called curcumin is obtained from turmeric. In the monocytic human cell line (THP-1), it has been seen to reduce the amount of Mtb bacilli. However at greater doses, it causes the death of infected THP-1 cells (Bai *et al.,* 2016). The major limitation of curcumin is its low bioavailability which could be effectively enhance by developing curcumin nanoparticles (Mohanty *et al.,* 2012). When combined with INH, these formulations not only improve effectiveness but also reduce the risk of hepatotoxicity (Tousif *et al.,* 2017). Recently, several more plants that may be useful in the treatment of DR-TB, including *Zanthoxylum leprieurii*, *Lantana camara*, *Cryptolepis sanguinolenta*, *Levisticum officinale*, *Punica granatum*, *Andrographis paniculate*, *Diospyros montana*, *Ventilago madraspatana*, *Plumeria bicolor*, *Urtica dioica*, *Vetiveria zizanioides*, *Piper nigrum*, *Croton tonkinensis*, *Ranunculi ternate* Radix, *Andrographis paniculata*, *Annona muricata*, *Centella asiatica*, *Pluchea indica* and *Rhoeo spathacea*.

Table 2: Herbs used in management of tuberculosis.

Botanical Name Common Name	Possible Mechanism	Therapeutic Applications	Reference
Justicia vasica Adulsa	• Inhibitory activity against initial step of fatty acid biosynthesis.	• Coughs • Chronic Bronchitis • Asthma • Colds • Antispasmodic	(Jha *et al*., 2012; Kumar *et al.*, 2016)
Withania somnifera Ashwagandha	• Immunomodulation by acting on the nervous and respiratory systems • Anti-inflammatory and rejuvenating • Down regulate TB symptoms such as cough, cold, and bronchitis	• Arthritic • Asthma • Cancer • Diabetes • Hypertension • Stress	(Dar *et al*., 2015; Singh *et al*., 2022)
Bacopa monnieri Brahmi	• Significantly reduces hepatotoxicity of INH and Rifampicin when administered in combination	• Alzheimer's disease • Dementia • Anxiety	(Prince *et al.*, 2016; Rai *et al*., 2017)
Ocimum tenuiflorum Tulsi	• Activates hypoxia-inducible factor which enhanced the autophagy in TB infected cells and production of IL-6 and TNF-α that control the Mtb infection. • Up-regulates the T cell receptor which results to enhances the immunity	• Bronchitis • Asthma • Malaria • Dysentery • Skin Diseases • Arthritis	(Mahajan *et al.*, 2013; Tabassum *et al.*, 2022)
Aloe barbadensis Alovera	• It can inhibit the production of TNF-alpha and the proportion of Th17 cells. • Strong antioxidant and antibacterial properties.	• Anti-tubercular • Skin Diseases	(Arjomandzadegan *et al*., 2016; Mawarti *et al.*, 2017)
Allium sativum Garlic	• Prevents sulfhydryl metabolic enzymes to exert its antibiotic action. • Modulate the production of ROS and autophagy in Mtb. • Strong Antioxidant properties • Immunomodulatory	• Immuno-modulatory • Hypolipidemic • Stomach disorders	(Bhatwalkar *et al.*, 2021; Muniyan and Jayaraman, 2016)
Cryptolepis sanguinolenta Karondorondo	• Antimicrobial • Fungicidal • Antibacterial • Strong antioxidant properties.	• Anticancer • Antidiarrheal • Antifertility	(Tuyiringire *et al*., 2020, 2022)
Zanthoxylum leprieurii	• Antimicrobial • fungicidal • Insecticidal • Strong Antioxidant properties.	• HIV/Aids • Malaria • Urinary infections • Rheumatic Pain	(Tuyiringire *et al.*, 2020, 2022)
Lantana camara	• Antimicrobial • Fungicidal • Antibacterial • Strong antioxidant properties	• Cancer • Skin Itches • Leprosy • Chicken Pox • Asthma • Ulcers	(Tuyiringire *et al.*, 2020, 2022)

New anti-TB drugs in clinical development. In the early stages of clinical trials, several new drugs are looking promising therapy in TB. The heterodimer enzyme decaprenylphosphoryl-D-ribose-2′-epimerase (DprE) is made up of the proteins DprE1 and DprE2. DprE1, a crucial enzyme in the arabinan biosynthesis pathway and thus in the cell wall synthesis of Mtb. TBA-7371, BTZ-043, Macozinone (PBTZ-169), and OPC-167832 are four new compounds that have been discovered using high-content screening technologies and are extremely effective DprE1 inhibitors. Both Macozinone (PBTZ-169) and BTZ-043 are members of the benzothiazinone class and extremely effective bactericidal medications against replicating Mtb bacillus and MDR strains. A 3, 4-dihydrocarostyril derivative known as OPC-167832 has bactericidal efficacy against bacilli that are continuously reproducing as well as intracellular bacilli. The azaindole TBA-7371 has the ability to shorten the normal duration of treatment. All of them are in the phase 2 trial except Macozinone (PBTZ-169) which is in the phase 1 trial (Black and Buchwald 2021; Mi *et al*., 2022; Yuan and Sampson 2018).

SQ109, a 1, 2-ethylene diamine similar to ethambutol but with significantly higher action in preclinical trials, is another new cell wall production inhibitor. Its potency and antibacterial activity, mode of action are different from those of ethambutol. It works by preventing the transmembrane transport protein MmpL3, which is necessary for the production of the cell wall. It has demonstrated excellent bactericidal activity against Mtb in the phase 2 trial and functions against both extracellular and intracellular bacteria. It improved the effectiveness of both MDR-TB regimens and first-line anti-TB medications. Moreover, it has demonstrated strong interactions with Bdq (Mi *et al.*, 2022; Tetali *et al.*, 2020)

SPR720 inhibits DNA synthesis by interfering with GyrB. Against FQ-resistant strains, it has displayed activity. A Cholesterol Catabolism Inhibitor called GSK2556286 (GSK-286) can enter TB lesions and lower recurrence rates. By functioning as an EthR

transcriptional repressor, BVL-GSK098 inhibits transcriptional regulators. It is a brand-new transcriptional regulator for bacteria which improves the effectiveness of ethionamide and slows the growth of Mtb resistance to it. These three new chemicals are currently under phase 1 research. The four new molecules TBAJ-876, TBAJ-587, TBI-166, and Telacebec (Q203) work on the electron transport chain. Two potential new second-generation diarylquinoline compounds are TBAJ-876 and TBAJ-587. Its safety profile has improved, and they have demonstrated effectiveness against Bdq-resistant strains. They are under phase 1 investigation and block ETC through inhibiting ATP synthase. The riminophenazine TBI-166 affects the generation of reactive oxygen and electron transport. It is the phase 1 trial and has better activity and safety profile in comparison to Cfz. Telacebec (Q203), an imidazopyridine amide, is another ETC inhibitor that affects the cytochrome bc1 complex. It shows high bactericidal action and is currently going through phase 2 of the trial. GSK 3,036,656 (GSK-656) is an oxoborole that has a unique mechanism of action where it down regulated Leucyl-tRNA synthetase leads to failure in production of new proteins. It may replace oxazolidinone as it doesn't impair mitochondrial protein synthesis, even though the phase 1 study is still underway (Mi *et al.,* 2022; Tetali *et al.,* 2020).

New drug delivery system. The drugs prescribed for treating TB have a range of significant side effects, including hepatotoxicity, which could cause patients to quit taking prescribed medications, which results in anti-TB drug resistance (Yee *et al.*, 2003). Sub-therapeutic medication concentrations are also Contributing factor that lead to the development of resistance. All of this may be prevented with only administering the medication to the macrophages where Mtb proliferate. The development of resistance would be prevented by the appropriate concentration and non-systemic treatment. The medicine is delivered specifically to the macrophages of infected organs such the lungs, liver, and spleen via a nano-delivery technology. Also, it will protect the drug from metabolism before to distribution into the Mtb-infected tissues. The detection and management of TB have demonstrated encouraging outcomes using nanoparticles, a modern technology that has been thoroughly investigated in the field of healthcare (Rossi *et al.*, 2021; Xu *et al*., 2018).

The recent studies have demonstrated that carbon nanotubes (CNTs) in the form of nanoparticle suspension or nanofluids can be potential strategies for both diagnosis and treatment of TB (Sheikhpour *et al.*, 2022). By using targeted medication delivery, it can obstruct MDR and destroy cell walls of mycobacterium. It has been discovered that fluoxetine and isoniazid administered together in CNT suppress the development of Mtb. Fluoxetine causes the Mtb-infected macrophages to secrete more TNF- and to undergo autophagy. Silver nanoparticles trapped in biopolymers have a synergistic action that causes cytotoxicity and can serve as a nanocarrier for anti-Mtb medication delivery. The utilisation of Curdlan nanoparticles coupled with cyclodextrin is another evidence of these functionalized biodegradable polymers. Curdlan is recognised by the macrophage dectin-1 receptor. As a result, it has anti-infective and immunomodulatory effects and releases drugs into macrophages. Similar to this, isoniazid-loaded nanostructured lipid carriers can specifically target infected macrophages and boost the intracellular effectiveness of anti-TB medicines. Another recent study reported on a promising nano-delivery technology. It is a magnesium-layered hydroxide-based inorganic nanolayer (MgLH). Inorganic nanolayers are biocompatible as they are biodegradable and can carry a drug and release it in a sustained manner at the targeted site. The second-line anti-TB medication MgLH with intercalated PAS has demonstrated remarkably positive outcomes in the study. These findings demonstrate the extraordinary potential of nanostructures with prolonged shelf lives, improved drug absorption, improved safety profiles, and improved therapeutic results (Ibarra-Sánchez *et al.,* 2022; Saifullah *et al.,* 2021).

CONCLUSIONS

WHO has introduced all-oral regimens for better efficacy and safety but still there are concerns which are needed to be entertained efficiently and require the development of novel drugs and tremendous work in this field. Nature provides a plentiful supply of plants that can be utilized to treat human illnesses. Herbs have had a wide range of effects on human health as a foundational and important structure of traditional medicinal systems. Progress in the quest for exemplary treatments may be shown in the potency of chemically different compounds and herbs as prospective hepatoprotective and antimycobacterial agents. Combining the receptor specific characteristics of anti-TB medications with the many health advantages of medicinal plants might thus be a beneficial method to control TB and its adverse effects (Swain and Hussain 2022). Many medicinal plants have shown potential for the development of drug-hit candidates and many other drugs are currently in different phases of clinical trials (Tuyiringire *et al*., 2020). New drug delivery systems are currently being studied for the effective delivery of drugs to increase efficacy and reduce the chances of toxicity with the delivery of the drugs to the targeted site (Dua *et al*., 2018). Many people in poor nations use both prescription medications and herbal supplements at the same time. As a result, suitable research is needed to counteract this prevalent frequency. The mechanism behind the engagement of anti-TB drugs with herbal constituents has received little attention. There is a significant knowledge gap between attending physicians and the medicinal usage of herbal adjuvants. Plants having anti-tubercular and anti-oxidant capabilities might be investigated for their effective molecules and utilized in the development of new formulations that are acceptable to a larger range of doctors. In the present review, an enormous number of different compounds showed anti-TB activity as well. These provide fresh opportunities for the advancement of original anti-TB drugs. Some of the substances may

be used in clinical sector to treat deadly diseases. Thus, before large-scale human usage, detailed studies of herb–drug interactions in many conventional experimental setups are required to assure the safety and effectiveness of such combos.

FUTURE SCOPE

The traditional pharmacological intervention does not provide enough relief from the problems of TB as well as having many unexpected adverse effects. Therefore, using alternative medications like newer agents and plant based medications may be potential therapeutic intervention for the management of TB. The further investigation is required in order to develop more focused approach for treatment of TB patients

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