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Advances in Anti-Tubercular Agents: A Comprehensive Review

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Humans have been afflicted with Tuberculosis (TB) since the beginning of time. In 2023, the WHO reported that the South-East Asia Region had the highest number of new TB cases (45%), followed by the African Region (24%) and the Western Pacific Region (17%). India, Indonesia, China, the Philippines, Pakistan, Nigeria, Bangladesh, and the Democratic Republic of the Congo accounted for over two-thirds of global TB cases. In 2022, eight countries accounted for over two-thirds of global TB cases: India (27%), Indonesia (10%), China (7.1%), the Philippines (7.0%), Pakistan (5.7%), Nigeria (4.5%), Bangladesh (3.6%), and the Democratic Republic of the Congo (3.0%). Although, TB is a worldwide hazard, it excessively affects individuals in developing nations. According to estimations, almost one-third of the world's population coexists in dormant form with the pathogenic bacteria. Despite the fact that TB is curable, the probability of a effective treatment decreases as the illness develops multidrug resistance, and the situation degrades as the illness becomes widely drug resistant. With the development of new medications like recent years have seen some encouraging developments with the introduction of new types of anti-tubercular drugs, such as Bedaquiline and Delamanid after several decades without the development of a new TB medication. Hepatitis, hypersensitivity responses, nausea, vomiting, and other adverse effects are produced by allopathic anti-TB medications used to treat the symptoms of the condition. Toxicity and also adverse properties of allopathic medications have led to a rise in the usage of herbal remedies. TB has been effectively treated with medicinal plants from both foreign and Ayurvedic (Indian traditional medicine) sources. This review has described a few plants that may have anti-tubercular properties that have been found in the literature from a variety of sources. Several botanicals and synthetic medications are discussed in this review paper, along with the chemical components that give them their anti-tubercular properties. This study encourages more research on the possible applications of synthetic medications and medicinal plants with anti-TB activity.

Keywords: Chemical constituents; Medicinal plants; Pathogenic bacteria; Synthetic drugs; TB.

A Latin term for nodule or something protruding is the source of the name TB. *Mycobacterium tuberculosis* is the microorganism that causes TB. When an infected individual coughs, sneezes, or spits, the bacterial disease known as TB is spread through the air. Although the lungs are typically affected, the kidneys, spine, or brain may also be affected. Although it is assessed that over 25% of the world's people has contracted TB germs, only 5-10% of those individuals will go

on to exhibit symptoms and acquire TB disease. In 2020, around 1.5 million people worldwide lost their lives to TB, and over 10 million people contracted the disease. Once the top cause of death in the United States, TB cases rapidly decreased in the 1940s and 1950s as a result of medicines discovered by researchers. In 2021, 7,860 instances of TB were reported in the United States, according to statistics. The incidence rate nationwide is 2.4 cases per 100,000 individuals. Although some types of TB have developed drug resistance, TB can be treated with a typical six-month course duration of antibiotics. Since the introduction of rifampicin in the 70s', an effective short course regimen for drug-susceptible (DS) forms of TB has been saving millions of lives worldwide.[1] A standardized regimen characterized by a 2-month intensive (bactericidal) phase with four drugs [isoniazid (H), rifampicin (R), ethambutol (E), and pyrazinamide (Z); 2HRZE] and a 4-month continuation (sterilizing) phase is key to achieve microbiological and clinical cure, if taken correctly.[2] A four-drug combination of isoniazid, rifampicin, ethambutol, and pyrazinamide is now used to treat drug-susceptible TB. This treatment lasts for two months, then for four months, isoniazid and rifampicin.[3] Drug contraindication and harmfulness, that occasionally lead to therapy interruptions and regimen modifications, are additional issues related to current therapy. Additionally, there are drug-drug interactions, particularly with antiretroviral medications for TB and HIV patients, which leave these patients with intolerance, toxicities, and decreased efficacy[4]. Natural antioxidants, predominantly in vegetables and fruits extended growing attention among consumers[5]. The usage of herbal medicines is increasing day by day. Traditionally, the roots of *Mucuna pruriens* is used in the treatment of Asthma, cholera and it is used as blood purifier and diuretic[6]. It is important to finish the entire prescription as prescribed by your provider, and they may employ multiple medication for TB. Importance of the research done so far and a review on novel anti-tubercular medications is the goal of this study. Hence, the objective of the current review is to show the drugs, phytocompounds and novel drugs proved and progress the present-day researchers in the direction to undertake further investigations on antitubercular drugs.

Symptoms

Symptoms of active TB include

• Bad cough
• Discomfort in Chest
• Cough with sputum
• Fatigue
• Loss in weight
• Fever and Night sweats

Prevention

In certain nations, neonates and young children receive the Bacille Calmette-Guerin (BCG) vaccine to help prevent TB outside of the lungs.

• Regularly and thoroughly washing hands.
• When coughing, cover your mouth or cough into your elbow.
• Steering clear of intimate relationships.
• Ensure that all of your medications are taken as prescribed.[7]

Diagnosis

TB can also be diagnosed using a variety of tests, including:

• **Biopsy:** A biopsy of the lungs or other tissues can be performed to identify the bacteria under a microscope
• **Cough sample:** A cough sample can be tested in a lab to check for the presence of the bacteria
• **Blood test:** An interferon-gamma release assay (IGRA) blood test can measure the immune system's response to the bacteria

Stages

Latent TB infection • Active TB disease
• Primary infection
• Worldwide surveillance has revealed that drug-resistant TB is pervasive and poses a danger to TB control initiatives in numerous nations.[8]

Synthetic Drugs

First Line Drugs

First-line anti-tubercular drugs are the cornerstone for treatment and are typically used in combination to prevent resistance and ensure effective treatment.[9] Here are the main first-line anti-TB drugs, along with their classification and mechanisms of action. [10]

Isoniazid (INH)

Mechanism of Action

Mycolic acid production, a crucial A portion of the cell wall of mycobacteria, is inhibited. Drug targets a InhA enzyme specifically.[11]

Adverse effects

Unusual bleeding, dark yellow orange urine, hepatotoxicity, hypersensitivity, peripheral neuritis

Rifampicin (RIF)

A naturally occurring metabolite of *Nocardia mediterranei*, rifamycin B, is the source of rifampicin.[12] Rifampicin, sometimes referred to as rifampin.[13] It has been an essential part of the treatment of TB since its discovery in 1968 due to its sterilizing qualities and ability to shorten treatment at high dosages.[14,15]

A naturally occurring byproduct of *Nocardia mediterranei.*[16]

Mechanism of Action

Inhibits DNA-dependent RNA polymerase in mycobacteria, thereby blocking RNA synthesis and leading to cell death.

Adverse effects

Orange-red coloured urine, sputum, sweat, feces

Pyrazinamide (PZA)

Mechanism of Action

Drug interferes with the transport and metabolism of mycobacterium cell membranes. Pyrazinoic acid is produced from it, lowering the environment's pH and disrupts the membrane potential and energy production. [17]

Adverse effects

Yellow eyes or skin, hepatotoxicity, gout

Ethambutol

Mechanism of Action

Drug prevents the polymerization of arabinogalactan, an essential component of the mycobacterial cell wall, by blocking the Arabinosyl transferase enzyme.

This action inhibits cell wall synthesis.[18]

Adverse effects

Arthralgia, optic neuritis, red-green blindness, peripheral neuropathy, visual disturbances, GI disturbances

Table 1. First line drugs for the treatment of TB

S no.	Drug name	MOA	Uses	Limitation of use
1	Isoniazid (INH)	The production of mycolic acids, which are vital parts of the mycobacterial cell wall, is inhibited. It primarily targets the InhA enzyme.	To cure TB or stop it from recurring (reactivation).	Liver disease or heavy alcohol use, the risk of developing drug resistance due to improper usage. [11]
2	Rifampicin (RIF)	Inhibits mycobacteria's DNA-dependent RNA polymerase, which stops RNA production and causes cell death.	To control and treat a variety of gram-positive and mycobacterial infections.	Blood disorders, lung damage, and liver damage. [12]
3	Pyrazinamide (PZA)	Interferes with the transport and metabolism of mycobacterial cell membranes. It is transformed into pyrazinoic acid, which impairs energy generation and membrane potential while lowering the pH of the surrounding environment.	Treats only bacterial infections	Hepatotoxicity, Nausea, vomiting, loss of appetite. [17]
4	Ethambutol (EMB)	Inhibits arabinosyl transferase, an enzyme that is vital to the polymerization of arabinogalactan, a constituent of the mycobacterial cell wall. As a result, cell walls cannot develop.	Removes germs that cause TB.	Optic neuropathy/ optic neuritis. [18]

Table 2. Second line drugs for the treatment of TB

S no	Name of drug	MOA	Uses	Limitations of Use
1	Levofloxacin	Inhibit the transcription, DNA replication, and DNA repair enzymes topoisomerase IV and DNA gyrase. As a result, the production of DNA by bacteria is inhibited.	Used to prevent and treat plague.	Should not normally be given to children younger than 18 years of age. [22]
2.	Moxifloxacin	Constrains DNA gyrase and stops bacterial cell DNA and RNA synthesis	Used for pneumonia, plague, and prevention	Should be used with caution or avoided with other drugs or drug classes known to cause QTc interval prolongation.
3.	Amikacin	bind to the 30S ribosomal subunit, which results in mRNA misreading and protein synthesis suppression, ultimately killing the bacterium.	Treat meningitis, blood infections, and severe bacterial infections.	It was associated with a high incidence of hearing loss
4	Capreomycin	Comparable to aminoglycosides, binds to the ribosome to inhibit protein synthesis and causes bacterial cell death.	Treat TB as a supplemental. [23]	Its significant potential for causing ototoxicity (hearing loss) and nephrotoxicity (kidney damage)
5	Ethionamide	Disrupts the mycobacterial cell wall by inhibiting mycolic acid.	To treat TB	Contraindicated in patients with severe hepatic impairment. [24]
7	Cycloserine	Interferes with the peptidoglycan production-related enzymes, inhibiting the development of cell walls.	Therapy for certain urinary tract infections and TB	Neurological toxicity
8	Para amino salicylic acid	Uses para-aminobenzoic acid (PABA) as a competitive inhibitor to prevent the synthesis of folate, which is necessary for DNA synthesis and cell division.	Combination therapy for TB and other active ingredients. In patients with multi-drug-resistant TB, it is most frequently utilized.	Persistent nausea, vomiting and diarrhoea.
9	Bedaquiline	Inhibits the enzyme mycobacterial ATP synthase, which is necessary for the bacterial energy metabolism by producing ATP.	For the treatment of lung multidrug-resistant TB (MDR-TB)	Contraindicated in patients with cardiac problems.
10	Delamanid	Prevents the bacterial cell wall from producing mycolic acid, which kills the cell off.	Has a sterilizing and antibacterial effect on M. TB.	Contraindicated in patients with albumin<2.8 g/dL. [25]

11	Linezolid	Ceases after binding to the 50S ribosomal subunit the translation initiation complex from forming, inhibiting the production of proteins.	Management of vancomycin-resistant enterococcal infections, bacterial pneumonia, and skin and skin structure infections	Contraindicated in patients with hypertension. [25]
12	Clofazimine	Interferes with bacterial growth and replication by binding to the DNA of mycobacteria.	Treatment for Hansen's disease, which includes dapsone-resistant lepromatous leprosy.	Allergy to Clofa zimine

Table 3. Phytocompounds used to treat TB

S no	IUPAC name	Part used	Phytoconstituents
1	(1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione	Rhizome of *Curcuma longa* (Turmeric)	Curcumin [26]
2	3-(4-Hydroxyphenyl)-1-(2,4,6-trihydroxyphenyl) propan-1-one	Peels and leaves of *Malus domestica* (Apple)	Phloretin [27]
3	2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one	Juice and also peel of *Punica granatum* (Pomegranate)	Quercetin [28]
4	5,7-Dihydroxy-3-(4-hydroxyphenyl)-4H-1-benzopyran-4-one	Soybeans - Glycine max	Genistein [29]
5	1,2,3,4,6-penta-O-{3,4-dihydroxy-5-[(3,4,5-trihydroxybenzoyl) oxy] benzoyl}-D-glucopyranose	Perennial flowering plant of *Globularia alypum*	Perennial flowering plant [30]
6	(2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl) chroman-3-yl	Leaves of *Camellia sinensis* (L) Kuntze - Green and black tea	Epigallocatechin gallate
7	(3,5,4'-trihydroxystilbene)	Root and also rhizome of *Rheum rhaponticum* (Rhubarb)	Resveratrol extracts
8	(2R)-2-Acetamido-3-({(2R,3S,4R)-3-hydroxy-2-[(1S)-1-hydroxy-2-methylpropyl]-4-methyl-5-oxopyrrolidine-2-carbonyl}sulfanyl) propanoic	Microorganism - Streptomyces lactacystinaeus	Lactacystin
9	(2S)-2-[[(2S)-4-amino-2-[[(3R)-3-hydroxydodecanoyl] amino]-4-oxo-butanoyl]amino] -N-[(1S)-1-formyl-3-methyl-butyl]pentanediamide	Marine fungus - *Penicillium fellutanum*	Lipopeptide aldehyde - Fellutamide B

Streptomycin
An Aminoglycoside antibiotic
Mechanism of Action

Causes misinterpretation of mRNA and suppression of the production of proteins by binding to 30S ribosomal subunit, ultimately resulting in the death of bacterial cells.

Usually, these medications are taken together to guarantee successful treatment to prevent drug-resistant TB strains from emerging.

The synthetic drugs/medicines that are effective in the treatment of TB and other bacterial infections are shown in Table.1

Second Line Drugs

Compared to first-line anti-TB drugs, second-line drugs have considerably more serious adverse effects. Table 2 contains a summary of anti-TB drug adverse effects.[19] When first-line anti-TB medications cannot be administered because of resistance or intolerance, second-line medications are used primarily to treat multi-drug-resistant TB.[20] The following list of primary second-line anti-TB medications includes information on their classification and modes of action.[21]

Fluoroquinolones (e.g., Levofloxacin, Moxifloxacin)

Mechanism of Action: Treat pneumonia, TB, sinusitis and endocarditis. Inhibit the transcription, DNA replication, and DNA repair enzymes topoisomerase IV and DNA gyrase. This results in the inhibition of bacterial DNA synthesis.[22]

Adverse effects: Tendonitis, QT prolongation

Aminoglycosides (e.g., Amikacin, Kanamycin)

Mechanism of Action: The bacterial cell dies as a result of binding to the 30S ribosomal subunit, which misreads mRNA and prevents protein production.

Table 4. Medicinal herbs/plants used to treat TB

S. No.	Herbal drug	Botanical name	Chemical constituent	Uses
1	Garlic	*Allium sativum*	Allicin	Possess antibacterial qualities that protect against *Mycobacterium TB* and other infections. [32]
2	Turmeric	*Curcuma longa*	Curcumin	It has antibacterial, anti-inflammatory, and antioxidant properties, including the ability to combat *Mycobacterium TB*.
3	Neem	*Azadirachta indica*	Azadirachtin Nimbin and Nimbidin	Exhibits antimicrobial characteristics Substances that exhibit antibacterial properties against a range of diseases. [32]
4	Green tea	*Camellia sinensis*	Epigallocatechin Gallate (EGCG)	Strong antioxidant and antibacterial qualities, including the ability to combat *Mycobacterium* TB, are possessed by this potent catechin.
5	Holy basil	*Ocimum sanctum*	Eugenol	Has anti-inflammatory, antiviral & antibacterial properties.
			Ursolic Acid	Renowned for having antibacterial and anti-inflammatory properties. [31]
6	Andrographis	*Andrographis paniculata*	Andrographolide	It has an antibacterial, immunomodulatory qualities that could aid in preventing TB. [32]
7	Licorice	*Glycyrrhiza glabra*	Glycyrrhizin	Has antibacterial and anti-inflammatory qualities, as well as anti-TB bacterial action. [33]
8	Black pepper	*Piper nigrum*	Piperine	Increases bioavailability of other substances and demonstrates antibacterial qualities. [33]

Adverse effects: Ototoxicity, nephrotoxicity

Capreomycin

A Polypeptide antibiotic

Mechanism of Action: It binds to the ribosome and prevents the synthesis of proteins, similar to aminoglycosides, leading to bacterial cell death. [23]

Adverse effects: Ototoxicity, nephrotoxicity

Ethionamide

Mechanism of Action: It Inhibits mycolic acid synthesis, similar to isoniazid, disrupting the mycobacterial cell wall. [24]

Adverse effects: GI disturbances, hepatotoxicity, hypothyroidism

Cycloserine

Mechanism of Action: Interferes with the peptidoglycan production-related enzymes, inhibiting the development of cell walls.

Adverse effects: Neurotoxicity, psychosis, seizures

Fig. 1. Medicinal herbs/plants proven to treat TB

Para-amino salicylic acid (PAS)

Mechanism of Action: Inhibits folate synthesis, which is essential for DNA synthesis and cell replication, by acting as a competitive inhibitor of para-aminobenzoic acid (PABA).

Bedaquiline

An Diarylquinoline antibiotic

Mechanism of Action: Drug impedes mycobacterial ATP synthase, an enzyme essential for synthesis of ATP, which is critical for the energy metabolism of the bacteria.

Delamanid

A Nitro-dihydro-imidazo oxazole derivative

Mechanism of Action: Drug inhibits mycolic acid synthesis, which is essential for the bacterial cell wall and causes cell death. [25]

Linezolid

An Oxazolidinone antibiotic

Mechanism of Action: binds to the 50S ribosomal subunit and prevents the formation of the translation initiation complex, inhibiting the production of proteins. [25]

Clofazimine

Mechanism of Action: Binds to mycobacterial DNA, interfering with bacterial growth and replication.

These drugs are used in various mixtures for the treatment of Drug-resistant TB that is extensively used (XDR-TB) and MDR-TB, ensuring that the bacteria are effectively targeted while minimizing the risk of further resistance development. These potent drugs, that are used in treatment of various diseases are displayed in Table.2

These Phytocompounds and extracts obtained from different plant sources are used as medicines for different TB disease and other disorders are exhibited in the Table.3

Medicinal Herbs Proved to Cure TB

Herbal drugs contain various bioactive constituents that have been studied for their potential anti-tubercular properties.[31] Garlic Possess antibacterial qualities that protect against *Mycobacterium TB* and other infections.[32] Catechin possess the ability to combat *Mycobacterium tuberculosis*.[33] Here are some key constituents from specific herbs known for their anti-tubercular effects. Various medicinal herbs/plants used to treat TB were indicated in Table.4

Novel Anti-tubercular Agents

In order to fulfill the global TB targets, new discoveries in TB research and development are need to achieve the Sustainable Development Goals and the End TB Strategy. A pair After nearly four decades of rigorous research and development, about 13 novel compounds (Table 1) have been discovered recently without any newly approved TB medications. Bedaquiline and Delamanid are two of these medications that have received accelerated or conditional regulatory approval as a result of the results of their phase IIb clinical trials.[34] Other medications in development include GSK-3036656, OPC167832, Delpazolid, Contezolid, and Pretomanid (Table 2). Sutezolid, SQ109, TBI-166, Q203, Macozinone, and TBA-7371.

Essential oils from plants as anti-tuberculosis agents

Pulicaria gnaphalodes and *Perovskia abrotanoides* essential oil extracts have strong inhibitory effects on (*Mycobacterium tuberculosis*) MTB. This activity for *Pulicaria gnaphalodes*

Table 5. Essential oils from plants as anti-tuberculosis agents

S. No	Plant name	Activity/Microbe inhibited	
1	*Pulicaria gnaphalodes* and *Perovskia abrotanoides* (Essential oils)	*Mycobacterium tuberculosis*	35
2.	Essential oils from different plants	*Mycobacterium tuberculosis*	36
3.	Essential oil *from Murraya koenigii* (L.)	*Corynebacterium tuberculosis, Pseudomonas aeruginosa, Streptococcus pyogenes, Klebsiella pneumonia* and *Enterobacter aerogenes*	37

was observed from very low (4%) to good (70.9%) effect; meanwhile, this activity for *Perovskia abrotanoides* was observed from very low (4%) to strong (86%) effect.[35] Essential oils extracted from plants have been shown to have anti-Mycobacterium tuberculosis effect in in-vitro experiments. Essential oil contains many chemicals and any one or more than one chemical may have the anti-Mycobacterium tuberculosis effect. Eugenol is one such chemical in the essential oil and the anti-Mycobacterium tuberculosis effect of eugenol is investigated.[36] The essential oil obtained from *Murraya koenigii* (L.) has a maximum zone of inhibition ability against *Corynebacterium tuberculosis, Pseudomonas aeruginosa, Streptococcus pyogenes, Klebsiella pneumonia* and *Enterobacter aerogenes*. The antioxidant profile of the sample was determined by different test systems. In all the systems, essential oil showed a strongest activity profile within the concentration range. [37]

Fig.1. Anti-tubercular activity of Medicinal Plants

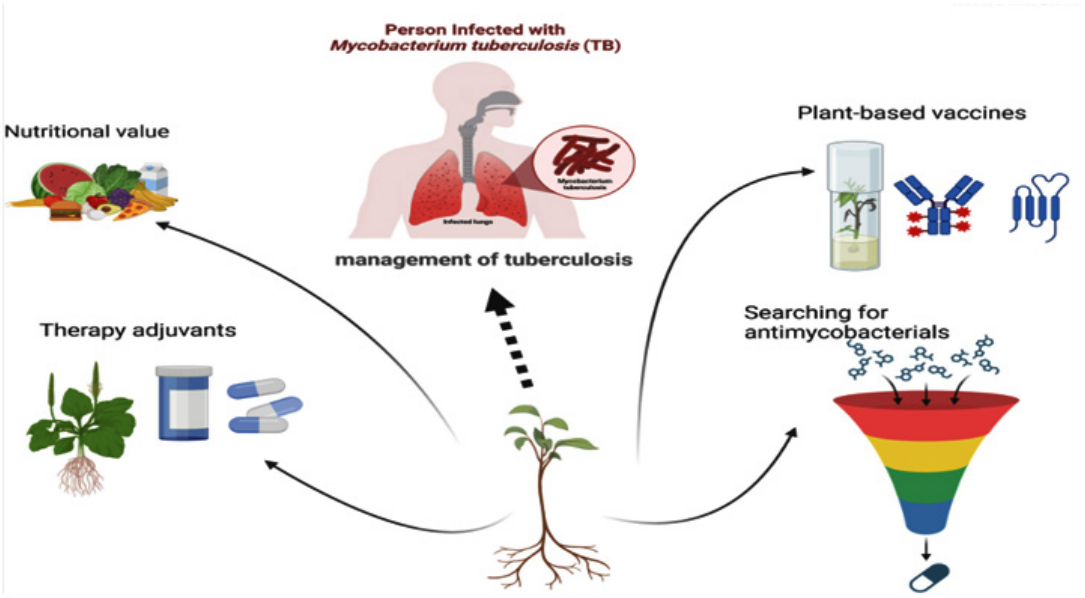

Fig. 2. Anti-tubercular activity of Medicinal Plants

DISCUSSION

The ambitious WHO goal of TB elimination can be achieved if a comprehensive strategy is implemented. The WHO TB Strategy, approved by the World Health Assembly in 2014, is built on three pillars. [38] One of them, which can be found in the previous WHO strategy, is based on the improvement of the clinical management of individuals infected by Mycobacterium TB strains. While these constituents show potential, it's crucial to note that further clinical research is needed to validate their efficacy and safety in treating TB. These compounds may conventional anti-TB treatments rather than replace them. The low toxicity, accessible availability and affordability of phytoconstituents make them a valuable tool in the study and development of novel medications.[39] Among these plant bioactive components, alkaloids, tannins, flavonoids and phenolic compounds are the most significant.[40] The mismanagement of patients with TB disease can be associated to a poor prognosis, increased risk of transmission of Mtb to susceptible individuals, and emergence (and spread) of drug-resistant strains.[41] Furthermore, the evolving drug market has a marginal impact in low-income countries where TB incidence is high. The combination of those epidemiological conditions does not help identifying the full pharmacological profile of the anti-TB drugs. More information can be retrieved from the HIV/AIDS-related evidence: major efforts have been performed since the 90s' to better describe the characteristics of the anti-HIV drugs. [42] More research is needed in this delicate field. The process of research and development does not finish after the market approval by the regulatory agencies. Post-marketing surveillance studies, supported by basic and translational research, could change the scenario, adding key insights to the expected improved management of TB patients.

CONCLUSION

Current efforts at developing new drugs or repurposing existing ones to combat the challenges of drug resistance, particularly MDR and XDR in the treatment of TB are highly commendable. Bedaquiline and Delamanid are two examples of drugs with novel modes of action that offer hope in this regard by potentially avoiding cross resistance that is frequently seen with current TB chemotherapies. More efforts should continue at developing new anti-TB drugs, and repurposing drugs used for the treatment of other diseases, particularly those that are used against other resistant bacteria. For anti-TB medications, alternative options that could be explored include the identification of new therapeutic targets and innovative targeted drug delivery techniques, which could increase treatment efficacy, decrease dosage, and lessen adverse effects. In this review, the use of synthetic drugs and medicinal plants to cure TB is intended to be described scientifically. Hence, the objective of this review is to progress the present-day researchers in the direction to undertake further studies on antitubercular drugs.

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Informed Consent Statement

This study did not involve human participants, and therefore, informed consent was not required.

Clinical Trial Registration

This research does not involve any clinical trials

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Authors' Contribution

Dr. Rakam Gopi Krishna: Conceptua-

lization, Methodology, Writing – Original Draft; Satya Lahari Boddu: Data Collection, Analysis, Writing – Review & Editing; Samhitha Damera: Visualization, Supervision, Project Administration; Akash Kumar Kadapa: Resources, Supervision; Krishna Mohan Reddy Dharmareddy: Supervision; Charithaa Katha: Supervision

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