

A REVIEW ON ANTITUBERCULAR DRUGS: MECHANISM OF ACTIONS RESISTANCE, SARS & SYNTHESIS**Ayush Jangde, Khushboo Gupta*, Pranjul Shrivastava, Sandip Tiwari****Faculty of Pharmacy, Kalinga University, Naya Raipur, Chhattisgarh India (492101)***Corresponding Author's E mail: khushboo.gupta@kalingauniversity.ac.in

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ABSTRACT

Mycobacterium tuberculosis is the second largest cause of death, following COVID-19. Drug resistance is contributing to rising death and morbidity rates. In underdeveloped nations, people often overlook tuberculosis symptoms, resulting in inadequate treatment and increased transmission. Researchers from several countries aim to identify and develop anti-tubercular medications. The primary goal is to eliminate tuberculosis globally through targeted therapy. Early diagnosis and treatment can help to prevent *Mycobacterium tuberculosis* transmission. This study provides a detailed review of *Mycobacterium tuberculosis* diagnosis and treatments, as well as the mechanisms of action and synthetic techniques of contemporary anti-tubercular medications. This review covers both established and fresh material to assist researchers in understanding tuberculosis and developing new anti-tubercular medications.

Keywords: *Mycobacterium tuberculosis*, anti-mycobacterial activity, mechanisms, resistance, synthetic methods, SARs.

INTRODUCTION

Tuberculosis, caused by *Mycobacterium tuberculosis*, is a leading cause of disease and mortality worldwide. Infection affects one-third of the global population, accounting for 85% of pulmonary tuberculosis infections and 15% of extra pulmonary tuberculosis cases¹.

The World Health Organization estimates that this infectious disease will affect around 10.6 million people by 2023, with poor nations contributing for more than 90% of mortality and morbidity rates. Tuberculosis is an airborne illness that spreads through coughing and sneezing. It is commonly observed in people with COPD, HIV, and diabetes. Potential contraindications include haemoptysis, pneumonia, bronchial stenosis, airway obstruction, and liver disease. Potential contraindications include haemoptysis, pneumonia, bronchial stenosis, airway obstruction, and liver disease. Unfortunately, no medication has yet been developed that can completely eliminate latent tuberculosis. Because of the

disease's intricacy, physicians usually struggle to diagnose and treat tuberculosis patients on time. To battle tuberculosis effectively, the World Health Organization's END-TB method must be strengthened and supplemented due to the growing prevalence of antimicrobial drug resistance in *Mycobacterium tuberculosis*. To eradicate tuberculosis, it is important to disrupt the disease's spread. Researchers aim to develop and recycle synthetic anti-tubercular medicines to eradicate tuberculosis permanently. This paper discusses synthetic and reused approaches for anti-tubercular medicines. Ongoing synthetic techniques for a few antitubercular medicines have also been described here².

2. Antitubercular Drugs and SARS (Severe Acute Respiratory Syndrome)

SARS and TB Co-Infection: While TB and SARS are caused by different pathogens, there have been concerns about co-infection, especially in immunocompromised individuals. Co-infection may complicate treatment and prognosis.

Impact on Drug Therapy: Some studies suggest that antitubercular drugs, particularly Rifampicin, might influence the metabolism of other drugs, including antivirals used for treating SARS. Rifampicin is known to induce cytochrome P450 enzymes, which could alter the pharmacokinetics of SARS-CoV-2 treatments in the future³.

Challenges in Treatment: TB and SARS both cause respiratory issues, and the treatment for one could potentially affect the management of the other. In regions with high TB prevalence, SARS-CoV-2 co-infection can complicate diagnosis and therapeutic strategies⁴.

3. Challenges and Future Directions⁵

Challenges in Drug Resistance: The growing emergence of drug-resistant strains of TB, including MDR-TB and XDR-TB, is a critical global health issue. New treatment regimens, novel drugs, and vaccines are needed to combat these resistant strains.

Nanotechnology in Drug Delivery: Nanoparticles are being investigated as potential drug delivery systems to improve the bioavailability and effectiveness of antitubercular drugs.

Drug Repurposing: With the advent of SARS-CoV-2, there has been renewed interest in repurposing existing drugs for tuberculosis treatment, including antivirals and immunomodulatory agents.

Development of a Vaccine: The Bacillus Calmette–Guérin (BCG) vaccine is the only available TB vaccine, but its effectiveness is limited, prompting researchers to look for more effective alternatives.

4. Diagnosis of Tuberculosis

Tuberculosis can be difficult to diagnose due to symptoms similar to other respiratory illnesses. The United Nations aims to treat 40 million drug-sensitive tuberculosis patients and 1.5 million HIV patients by 2022, which requires effective intervention and accurate diagnosis. million drug-resistant tuberculosis patients. There are various diagnostic techniques for tuberculosis (TB), including traditional methods like acid-fast bacillus smear microscopy and microbiological culture, as well as modern ones like CRISPR Cas, Gene Xpert, and LAMP⁶.

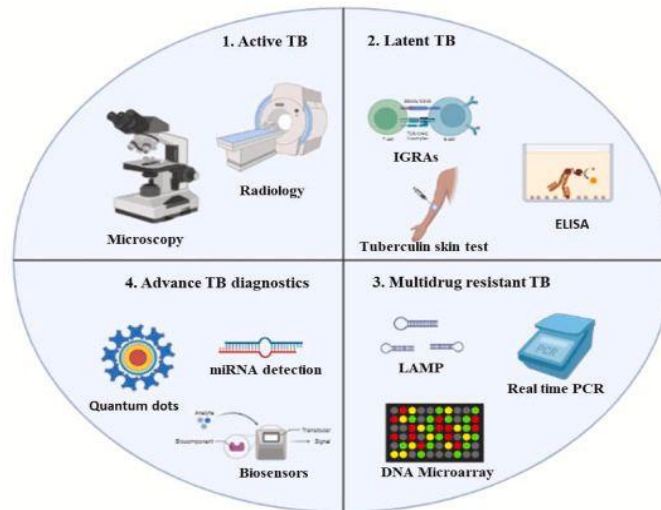


Figure 5 depicts diagnostic approaches for various tuberculosis illnesses.

5.1 Conventional Diagnostic Methods

Microscopy is commonly used to diagnose active tuberculosis by collecting samples from infected persons and detecting bacteria under a microscope. The typical recommendation is light-emitting diode fluorescence microscopy^{7,25}.

Radiological imaging, including CT scans, PET-CT scans, chest X-rays, and MRI scans, is necessary for identifying active pulmonary tuberculosis. Chest X-rays check the lungs and pleural membrane, CT scans separate TB from pneumonia and reveal disease progression, MRI scans offer comprehensive lung anomalies without radiation, and PET-CT scans detect TB granulomas and examine specific body areas. Radiological reports are delivered on the same day^{8,9}.

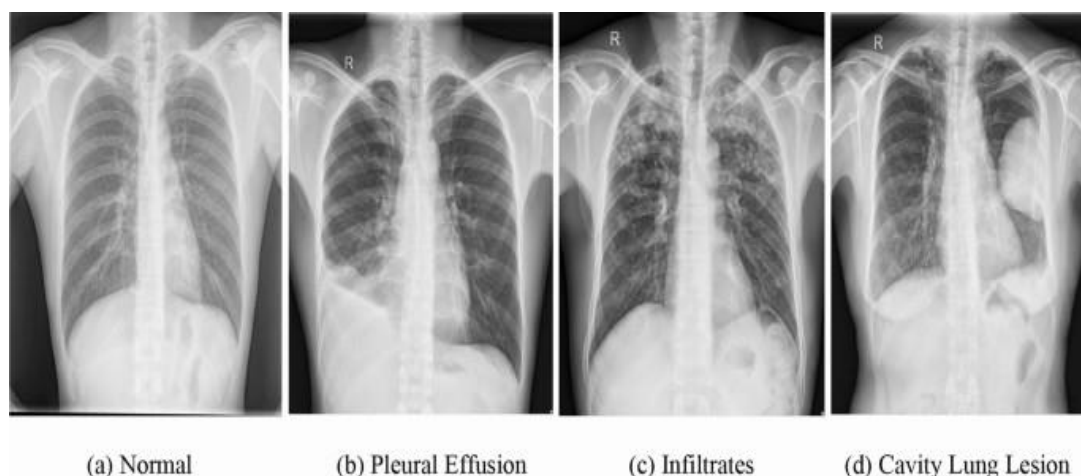


Figure 6: : Chest X-ray in (A) indicates normal X-ray, whereas (B), (C), & (D) X-rays expose pleural effusion, infiltrates, and cavity lung lesions

5.2 Advanced Diagnostic Method

Better tuberculosis diagnosis tests require technological advancements. Advanced tests like CRISPR, mass spectrometry, whole genome sequencing, nanodiagnostics, and digital PCR can accurately identify drug-sensitive and drug-resistant microbes for exact therapy^{10, 11}.

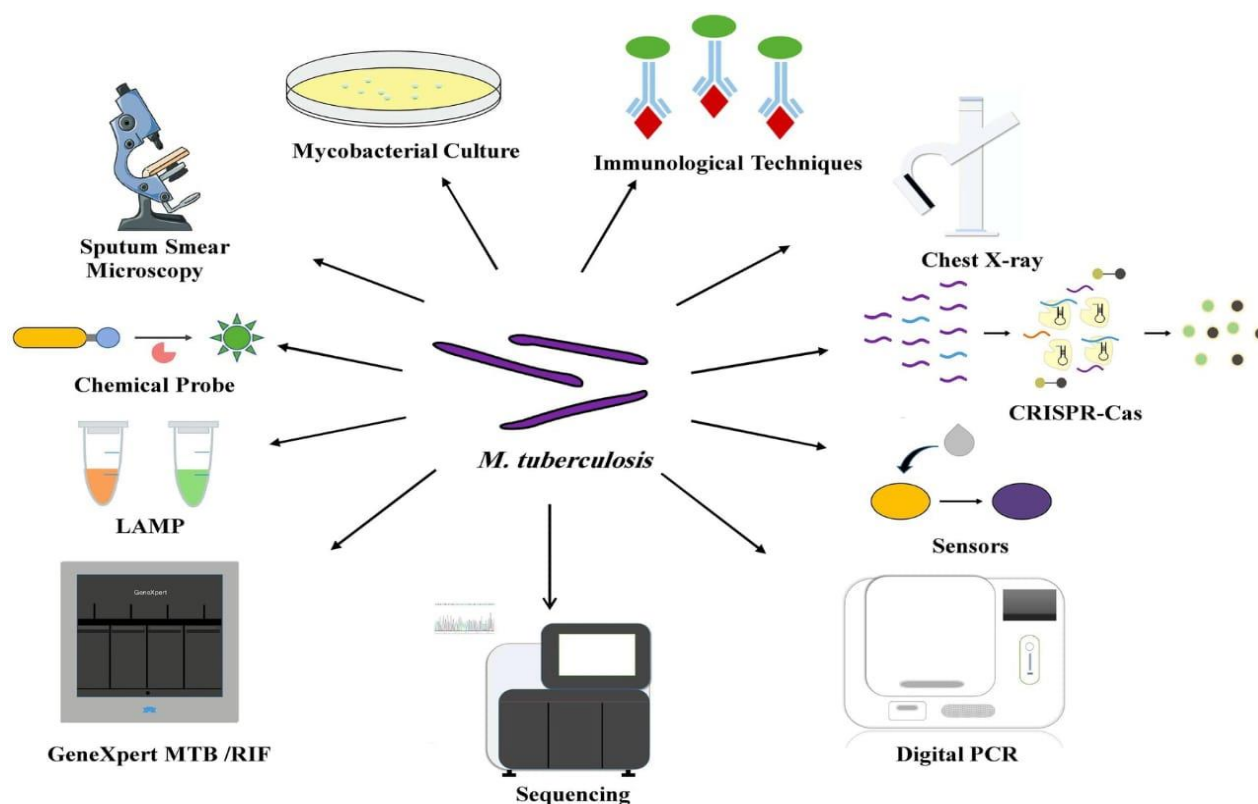


Figure 7: Different advanced techniques to detect TB infection

Digital PCR can improve the accuracy and consistency of diagnostic tests like the Xpert MTB/RIF test. It can identify tuberculosis outside the lungs, even if DNA levels are minimal¹².

With only a few copies, the process may amplify and produce precise results. Results take five hours to arrive, compared to four days for traditional DST testing. Improved identification of complex infections has led to decreased transmission of tuberculosis (TB)^{13, 23}.

5.3 Advanced TB Vaccination Approaches

The only licensed TB vaccine is BCG, which is safe for most people except those with HIV or other immune diseases. BCG offers 10 years of protection against meningeal and disseminated TB. Currently, 21 vaccines for tuberculosis are being clinically evaluated, including live whole-cell, inactivated whole-cell, mRNA, subunit, and viral vector vaccines^{14, 22}.

Vaccination trials struggle to establish quantitative diagnostic criteria for *M. tuberculosis* due to the difficulty in identifying asymptomatic individuals. Current microbiology procedures can be misleading and erroneous. TSTs are affordable, but cannot distinguish between BCG vaccination and *Mycobacterium tuberculosis* infection. The Interferon-Gamma Release Assay (IGRA) is the gold standard for tuberculosis diagnosis, detecting *Mycobacterium tuberculosis* infection even in persons immunized with BCG^{15,16}.

6. Standard Treatment for Tuberculosis

The treatment for tuberculosis patients includes a combination of drugs. The recommended therapy period (4-6 or 9 months) depends on the patient's condition. The most effective first-line treatment medications are isoniazid, pyrazinamide, rifampin, ethambutol, and streptomycin. The second-line treatment medicines include Ethionamide and Kanamycin^{17,18}.

7. Impact of the Review Article

Tuberculosis is tough to control because of its complex medication resistance. Current medications are being repurposed to find the most effective treatment regimen to eradicate tuberculosis globally. This review article contains detailed information on anti-tubercular medicines and their synthesis processes. This article explores numerous strategic approaches to existing medications and drug targets identified by researchers, which can aid in the development of new synthetic techniques and analogues^{19, 21}.

This review could help researchers explore new molecular pathways and treatment approaches to enhance clinical outcomes. The article also digs into each drug's methods of action, which will help future researchers understand drug-drug interactions, routes, and effectiveness. The article also addresses pharmacological trials for Gatifloxacin, Doxycycline, and Nitazoxanide to determine their efficacy in

treating tuberculosis infection. Gatifloxacin works by targeting DNA gyrase, whereas Nitazoxanide disrupts membrane potential to kill bacteria. More research is needed to establish if these novel medications can be integrated into the treatment strategy. Drug regimens might vary and cause adverse effects, making therapy problematic for a variety of reasons. Therefore, it is critical to produce medications with low to no negative effects^{20, 24}.

8. Conclusion

Research is focused on developing and improving anti-tubercular medications to combat *Mycobacterium* TB infection. This study provides detailed information on the diagnosis, treatment, difficulties, pharmacology, and synthetic techniques for current antitubercular medications. This resource provides comprehensive information about *Mycobacterium tuberculosis* including both traditional and advanced topics. While a few powerful molecules have been found potential anti-TB drugs, only a few have entered clinical trials. It is critical to identify effective, safe, and creative treatments for each strain of tuberculosis.

Cost-effective therapy and screening procedures are crucial for developing nations with low economic status, such as Bangladesh, India, and Pakistan, where many patients cannot afford treatment. Therefore, an economical treatment method is required. To create cost-effective treatment programs, stakeholders including researchers, medical professionals, and industry experts need adequate funding and research opportunities, which should be coordinated with the government. To accelerate progress towards health benefits, it is recommended to integrate new vaccine research approaches, strengthen laboratory models, speed up clinical trials, and remove barriers to successful program expansion. This review provides useful information for researchers and the public on tuberculosis, resistance mechanisms, and new antitubercular medications. Researchers want to use this knowledge to develop new or modify existing anti-tubercular medications.

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