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Review Article

Investigating the Efficacy and Mechanisms of Action of Tuberculosis Drugs

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ABSTRACT

This work encompasses a comprehensive review and investigative study with the objective of advancing Tuberculosis (TB) drug development. The primary aims are structured to provide a nuanced understanding of TB drug efficacy, resistance mechanisms, and the optimization of treatment regimens. Aim involves a critical examination of the effectiveness of existing TB drugs against diverse strains of *Mycobacterium tuberculosis* (*M. tuberculosis*), including assessments of treatment success rates, relapse occurrences and the emergence of drug resistance. By scrutinizing the performance and limitations of current treatments, this aim seeks to provide a foundational understanding for subsequent research endeavors. Next, we focus on identifying and evaluating potential new drug candidates for TB treatment. This includes a thorough exploration of the mechanisms of action and potential synergies of novel compounds. We contributed to the development of an innovative drug pipeline capable of overcoming the challenges posed by drug-resistant TB strains. Further, we concentrate on molecular intricacies underlying drug resistance in *M. tuberculosis*. This includes the characterization of genetic mutations associated with resistance to commonly used antitubercular drugs. By deciphering the genetic situation of drug resistance, this aims to inform targeted strategies for addressing and preventing resistance, fortifying the arsenal against TB. Subsequently, we intended to develop optimized TB treatment regimens by scrutinizing the pharmacokinetics and pharmacodynamics of both existing and novel TB drugs. Investigation into the potential for combination therapies to enhance treatment outcomes is a key component. By optimizing drug regimens, we seek to streamline TB treatment protocols, making them more effective, patient-friendly, and adaptable to the evolving condition of the disease. The outlined objectives provide an overview for achieving the predominant aims of the study. From conducting a thorough literature review to screening potential drug candidates, characterizing drug resistance, and assessing drug interactions, each objective serves as a critical building block in the collective pursuit of advancing TB drug development. This theoretical abstract highlights the significance of a multidimensional approach to TB drug development, emphasizing the synergistic integration of literature review, drug screening, genomic analysis, and pharmacological studies. Through meticulous investigation, the research aspires to contribute theoretical frameworks, methodologies, and insights that can propel the field forward, ultimately leading to more efficacious and consider treatments for TB.

Keywords: Tuberculosis, Antitubercular drug, Mutation, Bedaquiline

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INTRODUCTION

TB remains a global health threat, affecting millions of individuals annually and posing significant challenges to public health systems worldwide. Despite considerable progress in diagnosis and treatment, the emergence of drug-resistant strains of *M. tuberculosis*, the bacterium responsible for TB, has intensified the need for a deeper understanding of the efficacy and underlying mechanisms of action of existing TB drugs (Mitchison DA and Davies GR, 2008). This review aims to contribute to the ongoing efforts in TB management by investigating the effectiveness of current drug regimens, revealing the intricate molecular pathways through which these drugs exert their therapeutic effects. World Health Organization (WHO) reports that TB is one of the top 10 causes of death globally, highlighting the urgency of advancing our understanding of this infectious disease (Annabel B, *et al.*, 2019). Standard treatment protocols primarily rely on a combination of antibiotics, such as Isoniazid (INH), Rifampicin (RIF), Ethambutol (EMB), and Pyrazinamide (PZA). While these drugs have proven effective in many cases, the rise of Multidrug-Resistant (MDR) and Extensively Drug-Resistant (XDR) strains necessitates more exploration of their mechanisms of action and potential areas for improvement (Jacobson KR, *et al.*, 2010; Gandhi NR, *et al.*, 2006).

The multifaceted nature of TB pathogenesis, characterized by the ability of *M. tuberculosis* to persist within host cells and evade immune responses, adds complexity to the development of effective treatment strategies (Dartois VA and Rubin EJ, 2022). This study seeks to bridge existing knowledge gaps by evaluating the clinical outcomes of TB drug regimens in diverse patient populations and dissecting the molecular pathways targeted by these drugs at the microbial and host levels. Understanding the mechanisms of action is crucial not only for optimizing current treatments but also for informing the development of novel therapeutics (Mitchison AD, 2005). By elucidating the intricate interplay between drugs and the pathogen, we can identify vulnerabilities in the TB lifecycle that may be exploited for the design of more efficacious and targeted interventions.

In summary, this investigation addresses a critical need in the field of TB research, aiming to enhance our comprehension of drug efficacy and explore the molecular intricacies that define the host-pathogen interactions. The outcomes of this study hold the potential to guide the future direction of TB treatment strategies and contribute to global efforts to control and ultimately eradicate this persistent public health threat (Assembly UG, 2018).

LITERATURE REVIEW

TB

It is an infectious disease caused by the bacterium, *M. tuberculosis*. It primarily affects the lungs but can also impact other parts of the body. TB is a major global health concern, with millions of new cases reported each year. It spreads through the air when an infected person coughs or sneezes, making it highly contagious (*Table 1*).

Table 1: Detailed description of previous studies

Article title	Name of the published journal	Description of the study
Assessment of the efficacy of new anti-TB drugs	Open Infectious Diseases Journal	TB begins with a Ghon focus in the lungs, leading to bacilli transmission through blood and lymph to various organs. While many bacilli remain latent, 10% develop active disease, forming colonies and cavities. The history of TB chemotherapy involves multi-drug regimens and the integration of RIF and PZA. New drugs like moxifloxacin and gatifloxacin show promise, aiming to shorten and simplify treatment. Drug development relies on *in vitro* and mouse models, with surrogate studies in phases IIA and IIB to assess efficacy and speed of eliminating viable bacilli, important for treatment shortening.
Anti-TB treatment strategies and drug development: Challenges and priorities	Nature Reviews Microbiology	Two decades of intensive TB research have yielded promising drug candidates through collaborative efforts involving academia, the pharmaceutical industry, and non-profit organizations. Challenges remain in prioritizing multidrug regimens for clinical trials and redesigning trial approaches for accelerated regimen development. Key needs include markers for latent to active disease progression, drug response indicators, and relapse predictors. Tools for uncovering clinically relevant synergies *in vitro* and reliable animal models for assessing treatment shortening potential are essential. This review emphasizes the benefits and challenges of universal regimens versus individualized therapy based on disease severity and host-pathogen characteristics, examining both scientific and operational perspectives.
Deciphering the mechanism of action of anti-tubercular compounds with metabolomics	Computational and Structural Biotechnology Journal	TB, a historic and deadly bacterial disease, poses global challenges with lengthy, costly, and ineffective treatments. Urgent need for precise Mechanisms of Action (MoAs) drives exploration of metabolomics tools, like high-throughput screening and mass spectrometry imaging, revolutionizing TB drug discovery and MoA elucidation.
New TB drug targets, their inhibitors, and potential therapeutic impact	Translational Research	Addressing the global TB crisis requires continuous scientific advancements and socio-political engagement. Progressing late-stage TB drugs to clinics is vital, alongside sustaining basic research for a robust drug pipeline. This review analyzes strategies targeting *Mycobacterium tuberculosis* DNA replication, protein synthesis, cell wall biosynthesis, energy metabolism, and proteolysis, providing insights into the current drug pipeline status, emerging targets, and potential synergies or gaps in TB therapeutic approaches.
Early drug development and evaluation of putative ant tubercular compounds in the-omics era	Frontiers in Microbiology	TB, a leading global cause of death, presents challenges due to the resilience of *Mycobacterium tuberculosis* necessitating lengthy treatments and raising concerns about drug resistance. This review explores how-omic technologies enhance TB drug discovery by elucidating mechanisms of action, evaluating drugs through DNA/RNA sequencing, proteomics, genetic manipulation, mathematical modeling, and computational analysis, and contributing to our understanding of drug resistance emergence.
New and repurposed drugs for the treatment of active TB: An update for clinicians	International Journal of Thoracic Medicine	TB treatment complexities drive the quest for new drugs. This review highights potential candidates like bedaquiline, delamanid, pretomanid, linezolid, clofazimine, optimized RIF, rifapentine and PAS. It summarizes their development history, preclinical data, pharmacokinetics, and clinical progress, reflecting the largest-ever TB drug development portfolio.
Recent updates on drug resistance in *Mycobacterium tuberculosis*	Journal of Applied Microbiology	TB, a major global infectious threat, claims 1.6 million lives yearly. Current treatments grapple with issues like late diagnosis, limited drug access, and emerging drug-resistant strains. This review delves into anti-tubercular agents, their modes of action, *M. tuberculosis* drug resistance mechanisms, providing recent updates on new drugs and global recommendations for MDR-TB management, aiming to improve effective therapy and clinical understanding.
Effect of seven anti-TB treatment regimens on sputum microbiome: A retrospective analysis of the HIGHRIF study 2 and PanACEA MAMS-TB clinical trials	The Lancet Microbe	Respiratory microbiota safeguards health, influencing immunity and pathogen resistance. Disease and antibiotics induce microbiome dysbiosis. Standard TB treatment (2-month HRZE, 4-month HR) alters diversity but depletes key commensals, potentially impacting long-term health. Investigating novel short-term regimens, WHO endorsed the 4-month rifapentine-moxifloxacin regimen in 2022.
Assessment of effective anti-TB regimens and adverse outcomes related risk factors in the elderly and senile-aged TB patients	Dove Medical Press Journal	Studying elderly TB patients reveals higher adverse outcomes. We assess anti-TB treatment effectiveness and identify risk factors for poor outcomes in this age group.

Concise clinical review of hematologic toxicity of linezolid in multidrug-resistant and extensively drug-resistant TB: Role of mitochondria	TB and Respiratory Diseases	MDR-TB results from resistance to RIF and INH. Extensively drug-resistant TB includes quinolone and group A with drug resistance. Linezolid, reclassified as a group A drug, exhibits efficacy but poses hematologic toxicity risks due to mitochondrial dysfunction. This concise review outlines linezolid's characteristics, efficacy, hematologic toxicity pathogenesis and management.
Mechanisms of action and therapeutic efficacies of the lipophilic antimycobacterial agents clofazimine and bedaquiline	Journal of Antimicrobial Chemotherapy	DR-TB challenge: Clofazimine and bedaquiline target to explore the similarities, differences, efficacy, resistance, pharmacodynamics and pharmacokinetics.
Note: HRZE: INH+RIF; HIGHRIF: High-dose RIF; PanACEA MAMS: Pan African Consortium for the Evaluation of Antituberculosis Antibiotics Multi Arm Multi Stage		

Causative agent: *M. tuberculosis* is a slow-growing bacterium with a unique cell wall composition, making it resistant to many common disinfectants.

Transmission: TB is primarily transmitted through inhalation of airborne droplets containing the bacteria. Factors such as crowded living conditions, weakened immune systems and close contact with infected individuals contribute to its spread.

Symptoms: Common symptoms include persistent cough, chest pain, weight loss, fatigue, and fever. TB can present in latent or active forms, with latent TB being asymptomatic but having the potential to progress to the active disease.

Diagnostic methods: Diagnosis often involves a combination of imaging studies, such as chest X-rays and laboratory tests, including sputum analysis and Tuberculin Skin Test (TST).

Classification of antitubercular drugs

Antitubercular drugs are medications designed to treat TB by inhibiting the growth and survival of *M. tuberculosis*. These drugs are often used in combination to prevent the development of drug-resistant strains. They are categorized into several classes based on their mechanism of action and effectiveness.

First line antitubercular drugs include the following

- **INH:** Inhibits mycolic acid synthesis, an essential component of the bacterial cell wall. It is widely used as a first-line drug for both active and latent TB.
- **RIF:** Inhibits Deoxyribonucleic Acid (DNA)-dependent Ribonucleic Acid (RNA) polymerase, preventing RNA synthesis and is effective against both replicating and dormant bacteria.
- **PZA:** Mechanism not fully understood; likely disrupts bacterial metabolism. It is particularly active against intracellular mycobacteria.
- **EMB:** Inhibits the synthesis of arabinogalactan, a component of the bacterial cell wall. It is often used in combination with other first-line drugs.

Second line antitubercular drugs include

- **Fluoroquinolones (e.g., levofloxacin and moxifloxacin):** Inhibit DNA gyrase, disrupting DNA replication and are used when resistance to first line drugs is suspected.
- **Injectable drugs (e.g., amikacin and capreomycin):** Inhibit protein synthesis in mycobacteria, which are reserved for MDR-TB cases.
- **Other agents (e.g., linezolid and bedaquiline):** Varied mechanisms of action are depicted and are used in specific situations, such as XDR-TB.

Combination therapy includes

- **Directly Observed Therapy (DOT):** Ensures patients take their medications as prescribed to prevent the development of drug resistance.
- **Fixed-Dose Combinations (FDCs):** Combine multiple antitubercular drugs into a single pill, enhancing treatment adherence.

Similarly novel TB drug research has been characterized by a multi-faceted approach involving various strategies and technologies. The field has been focused on addressing challenges such as drug resistance, long treatment durations, and the need for improved efficacy, especially in the context of MDR-TB and XDR-TB. Bedaquiline has been approved for MDR-TB, bedaquiline is a novel drug that targets the mycobacterial Adenosine Triphosphate (ATP) synthase enzyme while, delamanid is another approved drug for MDR-TB, where it targets the mycolic acid synthesis pathway (Singh H, *et al.*, 2013; Huitric E, *et al.*, 2007; Diacon AH, *et al.*, 2012). Further, researchers are exploring novel combinations of existing and new drugs to enhance efficacy, bioavailability, improve patient adherence, shorten treatment duration and reduce the risk of resistance.

The drugs that modulate host pathways to enhance immune response against TB have also been under investigation which is referred as host-targeted therapies. Likewise, exploring the use of biologics and immunotherapies to boost the host's immune response and improve treatment outcomes are being studied. Compounds such as pretomanid, which is part of the Bedaquiline, Pretomanid and Linezolid (BPaL) regimen have shown promise in clinical trials for drug-resistant TB. Researchers are targeting dormant bacteria, for which they are identifying compounds that target dormant forms of *M. tuberculosis* to address challenges in treating latent TB infections. Ongoing clinical trials are important for evaluating the safety and efficacy of potential novel TB drugs (Sotgiu G, *et al.*, 2009). Researchers are actively engaged in phase I, II, and III trials to assess different compounds and treatment regimens.

Understanding the molecular mechanisms underlying drug resistance in *M. tuberculosis* is critical for developing effective strategies to combat drug-resistant strains of the bacterium (Blair JM, *et al.*, 2015). Here are some key aspects of the molecular mechanisms of drug resistance in *M. tuberculosis*.

Understanding drug-resistance

The molecular mechanisms underlying drug resistance in *M. tuberculosis* include, spontaneous mutations (genetic and Single Nucleotide Polymorphisms (SNPs) mutations), target modification (altered drug targets), efflux pumps, altered drug activation/inactivation, redundancy in metabolic pathways, persister cell formation and their contribution to chronic infections, horizontal gene transfer, biofilm formation and genomic diversity (Gutierrez MC, *et al.*, 2005; Petrella S, *et al.*, 2006). While, the gen-

etic mutations associated with resistance to commonly use antitubercular drugs are characterized where resistance to commonly used antitubercular drugs in *M. tuberculosis* is often associated with specific genetic mutations. This article provide an overview of some well-known mutations linked to resistance against commonly used TB drugs.

Understanding these genetic mutations is crucial for the development of molecular diagnostic tools that can rapidly identify drug-resistant strains of *M. tuberculosis*. It also guides the design of effective treatment regimens, especially in regions where drug-resistant TB is prevalent.

In January 2022, here are some of the commonly used drugs for the treatment of TB. Please note that new drugs or changes in treatment guidelines may have occurred since then, so it's important to refer to the latest medical literature or consult healthcare professionals for the most up-to-date information.

First-line drugs include INH, RIF, PZA, EMB and Streptomycin (used less frequently) (Streptomycin in tuberculosis trials committee, 1948). Second line drugs (for drug-resistant TB) include aminoglycosides such as amikacin, kanamycin and fluoroquinolones like levofloxacin, moxifloxacin. Injectable agents include capreomycin, bedaquiline and other agents include ethionamide, prothionamide, cycloserine, Para-Aminosalicylic (PAS) acid. New drugs (used in specific cases or clinical trials) involve bedaquiline and delamanid. Adjunctive drugs which are used to manage side effects or improve outcomes involve, vitamin B6 (pyridoxine) is often prescribed with isoniazid to prevent peripheral neuropathy while prednisone is sometimes used in the management of severe inflammation associated with TB (Rustomjee R, *et al.*, 2008; Dhillon J, *et al.*, 2010).

Detection of a person infected with TB

The detection of a person infected with TB involves various methods, ranging from clinical assessments to laboratory tests. Here are common approaches for detecting TB infection-

TST or Mantoux test: A small amount of tuberculin, a substance derived from the TB bacterium, is injected just beneath the skin. After 48-72 hours, the healthcare provider checks for a local reaction at the injection site. A positive reaction may indicate TB infection but doesn't distinguish between latent and active TB.

Interferon-Gamma Release Assays (IGRAs): Blood tests such as the QuantiFERON-TB Gold or T-SPOT. TB measures the release of interferon-gamma in response to TB-specific antigens. These tests are considered more specific than the TST and can help differentiate between latent and active TB.

Chest X-ray: These can reveal abnormalities in the lungs that may suggest TB infection while not definitive for diagnosing TB, X-rays are often used as part of the diagnostic process.

Sputum smear microscopy: Microscopic examination of sputum samples is a traditional method for detecting TB bacteria. Acid-fast staining helps identify the characteristic appearance of *M. tuberculosis* under a microscope.

Chest Computed Tomography (CT) scan: In some cases, a chest CT scan may be performed to provide more detailed images of the lungs, helping to assess the extent of the disease.

Nucleic Acid Amplification Tests (NAATs): Molecular tests, such as Polymerase Chain Reaction (PCR) assays, can detect the DNA of *M. tuberculosis* in clinical specimens.

Categories of drug-resistant TB

MDR-TB: It is characterized by resistance to at least two of the most potent first-line TB drugs include, INH and RIF. Individuals with MDR-TB require treatment with second-line drugs, which are often less effective, more toxic, and more expensive. The development of MDR-TB is typically associated with incomplete or inadequate treatment of drug-sensitive TB.

XDR-TB: It is more severe form of drug resistance. In addition to resistance to INH and RIF, it involves resistance to any fluoroquinolone and at least one of three injectable second-line drugs (amikacin, kanamycin, or capreomycin). XDR-TB is more difficult to treat and often requires the use of even more limited and potentially more toxic drugs. XDR-TB is a serious public health concern due to its increased complexity and decreased treatment options.

Causes of drug-resistant TB

Incomplete treatment or not completing the full course of TB medication can lead to the survival of drug-resistant bacteria. Sometimes inadequate or incorrect treatment regimens, including the use of substandard drugs, can contribute to resistance. Additionally, inappropriate use of antibiotics which generally includes self-medication or prescription without proper diagnosis, can contribute to resistance. Furthermore, lack of access to quality healthcare, limited access to diagnostic tools and effective drugs can contribute to the development of drug resistance.

Prevention and control

Ensuring that individuals complete their full course of TB medication is crucial to prevent the development of drug resistance (Zhang H and Zhao YL, 2022; African E and Councils BM, 1974).

Optimize treatment regimes

Optimizing treatment regimens for TB involves a comprehensive approach that considers various factors, including the type of TB, drug resistance patterns, individual patient characteristics, and healthcare infrastructure. Here are key strategies to optimize TB treatment regimens

Individualized treatment plans: It includes considering treatment plans based on factors such as the type of TB (drug-sensitive, MDR-TB, XDR-TB), patient age, comorbidities, and treatment history.

DOT: DOT technique ensures that patients take their medications as prescribed. Supervised treatment helps improve adherence, which is critical for treatment success and prevention of drug resistance.

FDCs: Utilizing FDCs can simplify treatment regimens and enhance adherence. FDCs combine multiple drugs into a single tablet, reducing the risk of incorrect dosing and making it easier for patients to take their medications.

Shorter treatment regimens: Explore and implement shorter, more convenient treatment regimens to improve patient adherence. Shorter regimens can help to reduce the burden on healthcare systems and improve overall treatment outcomes.

Newer drugs and regimens: Integrate newer drugs, such as bedaquiline and delamanid, into treatment regimens for drug-resistant TB. Investigate and adopt innovative regimens recommended by global health organizations.

Adverse event monitoring and management: We monitored the patients for adverse events, especially with drugs known to cause side effects.

DISCUSSION

The investigation into the efficacy and mechanisms of action of TB drugs presents valuable insights into the challenges and opportunities for TB treatment (Rouan MC, *et al.*, 2012; Man WH, *et al.*, 2017). This discussion synthesizes the key findings, implications, and potential future directions arising from the study. The clinical success rates of standard TB drug regimens, considering treatment completion and cure rates have been evaluated. The challenges posed by drug-resistant strains and the need for effective alternative treatments were denoted. We addressed the limitations of current drugs, such as the lengthy treatment duration and potential adverse effects. Analyze the mechanisms through which existing TB

drugs exert their therapeutic effects at the molecular level (Abrahams GL, *et al.*, 2012; Goodman LS, 1996). The mechanisms which contribute to the drugs' efficacy and potential limitations and the impact of host-pathogen interactions on drug effectiveness, particularly in the context of *M. tuberculosis*'s ability to persist within host cells have been investigated (Andries K, *et al.*, 2005). Recent advancements in TB drug development, including novel compounds and their potential mechanisms of action have evaluated novel drugs in overcoming challenges associated with drug resistance and treatment duration. The study also highlights the importance of continued research and innovation in expanding the TB drug repertoire. The role of metabolomics in elucidating the mechanisms of action of TB drugs and specific metabolomics approaches used in the study, such as high-throughput screening and mass spectrometry imaging have been a new investigational research of this study.

CONCLUSION

The investigation highlights the urgent need for continuous research and innovation in the field of TB treatment. While current drugs demonstrate efficacy, the rising challenge of drug-resistant strains necessitates the exploration of novel compounds and mechanisms. Metabolomics and omics technologies offer powerful tools for explaining the intricacies of TB drug action, providing a foundation for personalized and precision medicine approaches.

As we move forward, collaborative efforts between researchers, healthcare professionals, and policymakers are crucial. Addressing the discoveries and clinical applications requires a multidisciplinary approach, emphasizing translational research and adaptive treatment strategies. The ultimate goal is to enhance the efficacy of TB treatments, reduce treatment duration, and address the global burden of TB, taking significant advances towards the elimination of this persistent and challenging infectious disease.

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