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A Review on Pharmacological Strategies to Overcome Multidrug-Resistant Tuberculosis

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Abstract: Multidrug-resistant tuberculosis (MDR-TB), defined as resistance to Isoniazid and Rifampicin, Poses a major global health threat with treatment success rates around 60-75% using traditional regimens. Recent advances introduce shorter all-oral regimens like BPalm (Bedaquiline,Pretomanid,Linezolid 600mg, Moxifloxacin) for 6 months,achievieng up to 89-93% success in trials such as TB-PRACTECAL and Nix-TB, outperforming longer 18–20-month operations. These strategies leverage new drugs targeting ATP synthases,Mycolic acid, Alongside resistance mechanism s like Genetic mutation and efflux pumps,Emphasizing Nanotechnology and Host-Directed Approaches,while highlighting Future research priorities.

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I. INTRODUCTION

Tuberculosis (TB) remains a major infectious disease caused by Mycobacterium tuberculosis (M.tb). Despite advances in diagnosis and treatment, drug resistance has emerged as a significant barrier to TB elimination. MDR-TB affects hundreds of thousand of individuals annually and requires long, toxic, and costly treatments with variable outcomes. The complexity of therapy has driven the need for new pharmacological approaches, including novel drugs, optimized regimens, and targeted strategies to counter bacterial resistance. Traditionally lengthy, toxic second-line regimens led poor adherance and outcomes. Over the past decade, drug development and programmatic shifts towards all-oral, shorter regimens have substantially changed clinical practice. The World Health Organization (WHO) now recommends several shorter, bedaquiline-containing regimens (notably BPaLM/BPaL variants) for many patients with MDR/RR-TB, reflecting evidence that these regimens can improve treatment success while reducing durations and injectable exposure. This paper summarizes current knowledge and theraputic innovations aimed at overcoming MDR-TB.

➢ *Objectives:*

- Analyze current pharmacological strategies used in MDR-TB treatment
- Evaluate host-directed therapies (HDTs) as adjunctive strategies.
- Explore the potential of drug-delivery innovation precision medicine
- Outline WHO/NTEP guidelines for regimen selection, monitoring, and special populations to improve outcomes

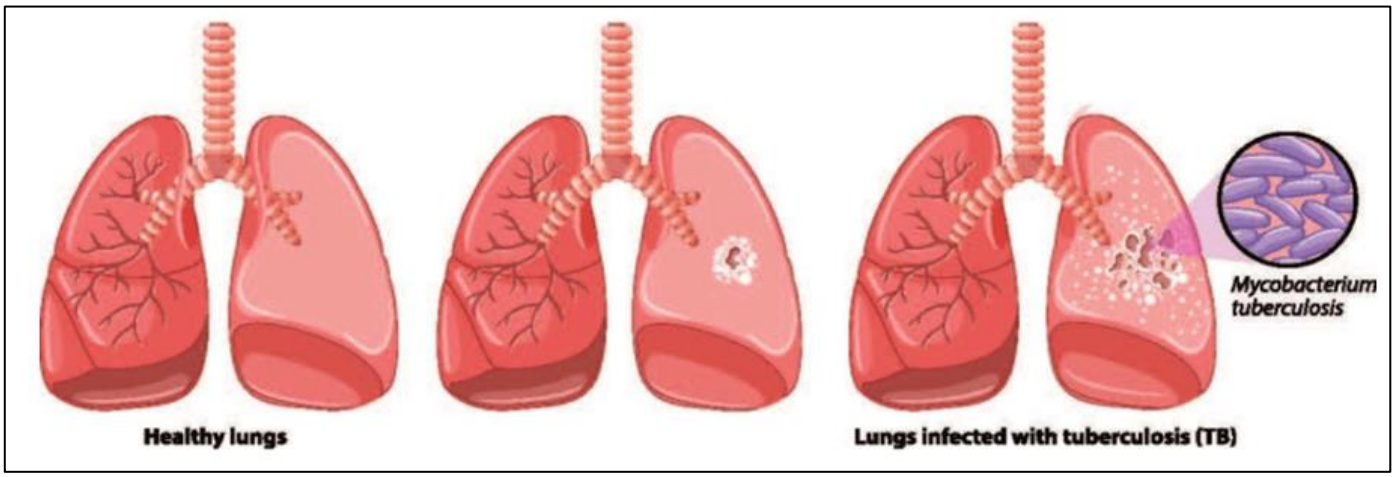

Fig 1 Development of Tuberculosis (TB)

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II. DISEASE

Tuberculosis (TB) is a chronic infectious disease caused primarily by Mycobacterium tuberculosis, a slow-growing, acid- fast bacillus that predominantly affects the lungs but can involve virtually any organ system. It remains one of the leading causes of morbidity and mortality worldwide, particularly in low- and middle-income countries, where socioeconomic factors, overcrowding, and limited healthcare access contribute to its persistence. TB is transmitted through airbone droplets expelled when infected individuals cough, sneeze, or speak, allowing the pathogen to establish infection within the alveolar macrophages. Despite the availability of effective chemotherapy, global TB control continues to face major challenges including delayed diagnosis, treatment non-adherence, co-infection with HIV and the rising prevalence of multidrug-resistant TB (MDR-TB) strains.

The disease's complex host-pathogen interplay, asymptomatic latent phase, and evolving drug resistance underscore TB as not only a biomedical problem but also a significant public health concern and requiring sustained research and strategic interventions.

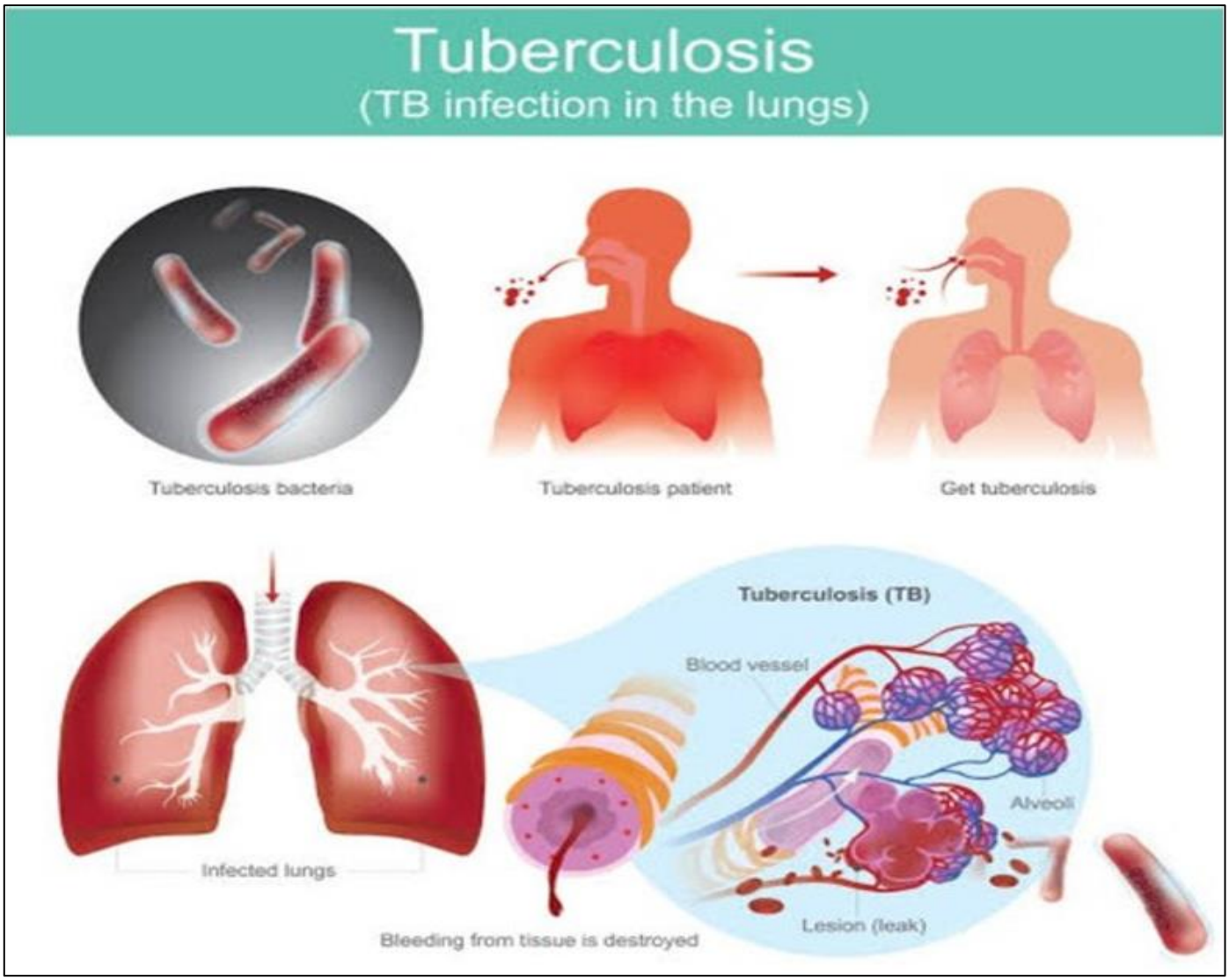

Fig 2 Transmission of T.B

➢ *Symptoms:*

- *MDR-TB Presents Similarly to Pulmonary TB, with:*

✓ Persistent cough (>2-3 weeks)
✓ Hemoptysis (blood-stained sputum) Fever
✓ Night sweats
✓ Weight loss and fatigue Chest pain
✓ Loss of appetite

- *Causes of MDR-TB:*

✓ Poor adherence
✓ Insufficient treatment duration Incorrect prescribing practices Poor drug quality
✓ Transmission of resistance M.tb strains
✓ genetic mutations in drug targets, such as KatG, inhA, and rpoB
✓ HIV co-infection

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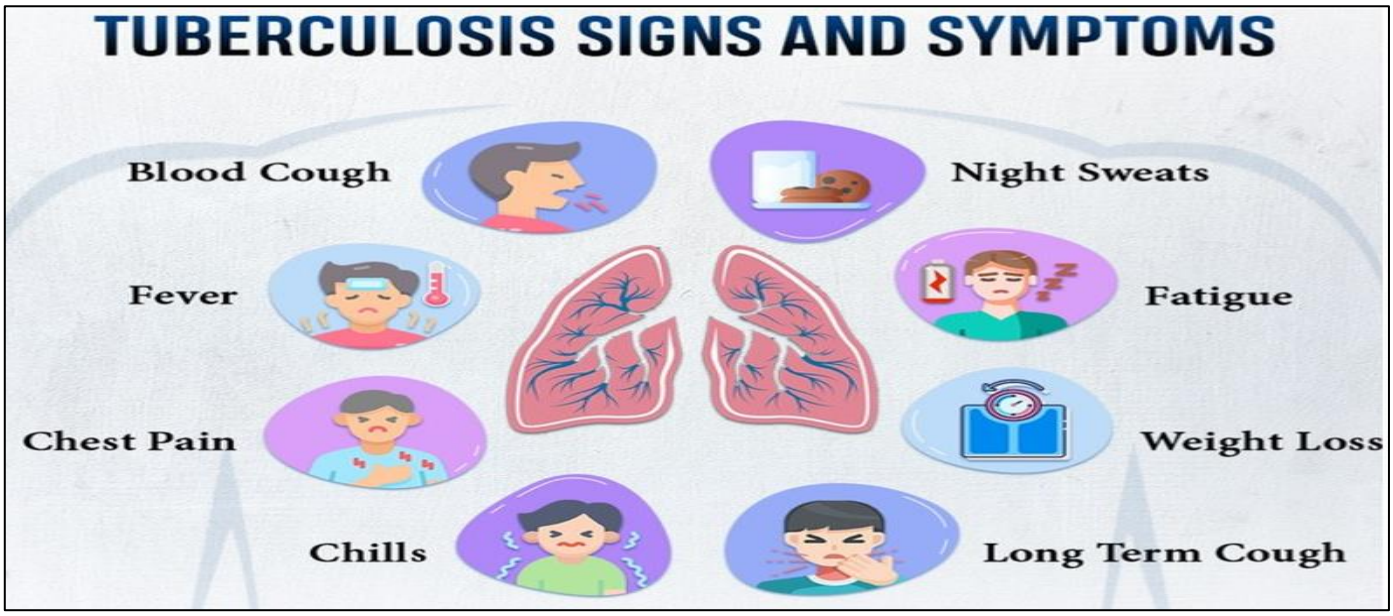

Fig 3 Tuberculosis signs and Symptoms

➢ *Pathophysiology of Mycobacterium Tuberculosis (MTB):*

- MTB begins when inhaled droplet nuclei containing the bacilli reach the alveolar spaces and are internalized by resident macrophages.
- MTB successfully evades innate immune clearance by preventing phagosomes-lysosome fusion, resisting reactive oxygen and nitrogen intermediates, and altering macrophage signaling through virulence factors such as lipoarabinomannan, ESAT-6, and trehalose dimycolate.
- These mechanisms enable intracellular survival and replication, followed by lymphatic spread and early hematogenous dissemination.
- The adaptive immune response develops over several weeks, with Th1-mediated production of interferon-γ and TNF-α driving the formulation of granulomas- structured aggregates of macrophages, epithelioid cells, and Langhans giant cells that serve to contain the bacilli.
- Within granulomas, MTB may persist in a non-replicative dormant state, contributing to latent tuberculosis infection.
- Reactivation occurs when immune control is compromised, leading to granuloma breakdown, caseous necrosis, cavitary lesions, and renewed transmission.
- This intricate host–pathogen interaction explains the chronicity, latency, and tissue-destructive nature of tuberculosis disease

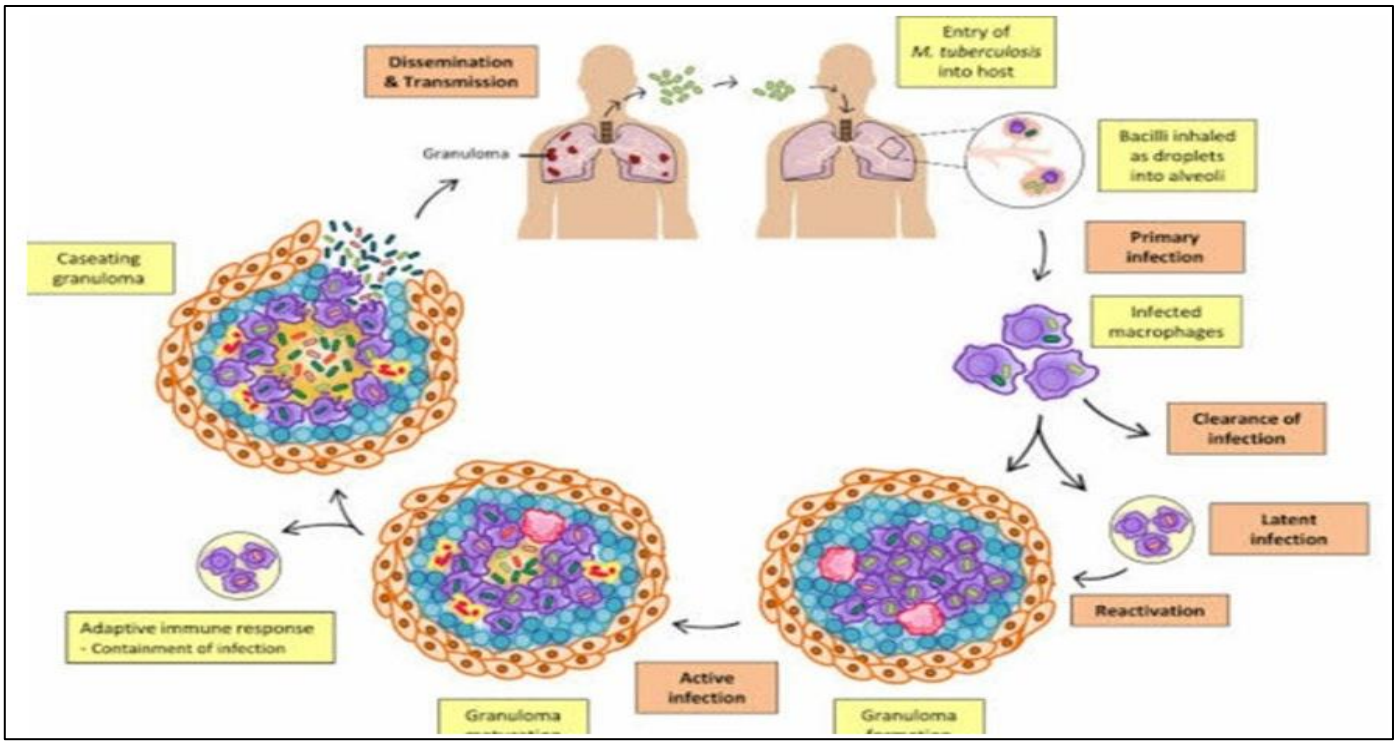

Fig 4 Pathophysiology of (MTB)

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III. TREATMENTS

➢ *New and Novel Agents (BDQ):*

- *Bedaq Uiline (BDQ):*

An ATP synthase inhibitor that significantly improved outcomes in MDR-TB when used in combination regimens; its incorporation into all-oral regimens is a cornerstone of recent guideline updates. BDQ's efficacy transformed programmatic approaches, though concerns about cardiotoxicity (QT prolongation) and emerging resistance require surveillance.

- *Delamanid (DLM) and Pretomanid (Pa):*

Nitroimidazole derivatives active against M. tuberculosis, used in combinations with BDQ and linezolid or moxifloxacin in short-course regimens. Clinical studies have demonstrated improved cure rates with these agents when used in carefully designed combinations.

➢ *Shortened all-Oral Regimens (BPaL/BPaLM and Variants):*

Randomized trials and programmatic data support short (6- month) all-oral regimens combining BDQ, Pa, Lzd, and a fluoroquinolone (or moxifloxacin) for many patients with MDR/RR-TB, producing high cure rates with shorter duration and improved tolerability compared with older regimens. WHO recommends use of BPaLM in eligible patients and supports 9- month bedaquiline-containing regimens where appropriate. These regimen changes are among the most impactful recent advances in MDR-TB management.

➢ *Repurposed Drugs and Optimized Use of Existing Agents :*

Linezolid, clofazimine, moxifloxacin/levofloxacin, and carbapenems (with clavulanate) have been repurposed or optimized for MDR-TB. Linezolid is highly active but dose-related myelosuppression and neuropathy mandate careful monitoring and possible dose adjustments or drug-holiday strategies. Clofazimine adds bactericidal activity and may improve outcomes, though its mechanism and resistance determinants are incompletely characterized and QT effects must be monitored.

➢ *Combination Therapy Principles:*

Combining drugs with different targets and non-overlapping resistance mechanisms reduces the likelihood of selecting resistant mutants. Regimen design must be guided by reliable DST (including molecular rapid tests for rifampicin, isoniazid, and fluoroquinolones and phenotypic DST where needed) and local resistance patterns. Rapid molecular DST accelerates initiation of effective regimens and limits the period of inadequate therapy.

➢ *Therapeutic Drug Monitoring (TDM) and PK/PD Optimization*

Interpatient variability in drug exposure (due to absorption, drug interactions, malnutrition, comorbidities like HIV, and genetic factors) can produce subtherapeutic levels and treatment failure. TDM—particularly for drugs with narrow therapeutic indices (linezolid, bedaquiline, fluoroquinolones)— can tailor dosing to maximize efficacy while limiting toxicity. PK/PD modeling and dose optimization are increasingly important components of personalized MDR-TB care.

➢ *Host-Directed Therapies (HDTs):*

HDTs aim to modulate the host immune response to improve bacterial clearance and limit tissue damage. Candidate strategies include repurposed immunomodulators (e.g., metformin, statins), cytokine modulation, and adjunctive therapies that reduce inflammation and enhance sterilizing immunity. These remain largely investigational but represent a promising adjunct to pharmacological regimens.

➢ *Drug Delivery Innovations and Formulations:*

Efforts to improve delivery -such as long -acting formulations, nanocarriers,inhaled delivery, and depost systems- seek to improve lesion penetration, reduce dosing frequency, and enhance. While many approaches are preclinical, they could address key barriers to completion and maintain therapeutic drug levels at difficult-to-reach sites.

➢ *Diagnostics, and Programmatic Integration:*

Pharmacological advances must be paired with rapid diagnostics (molecular DST), pharmacovigilance, access to medicines, and patient support systems. Surveillance for resistance to new drugs (e.g., BDQ, Pa) and pharmacovigilance for toxicity are critical to preserving drug effectiveness.

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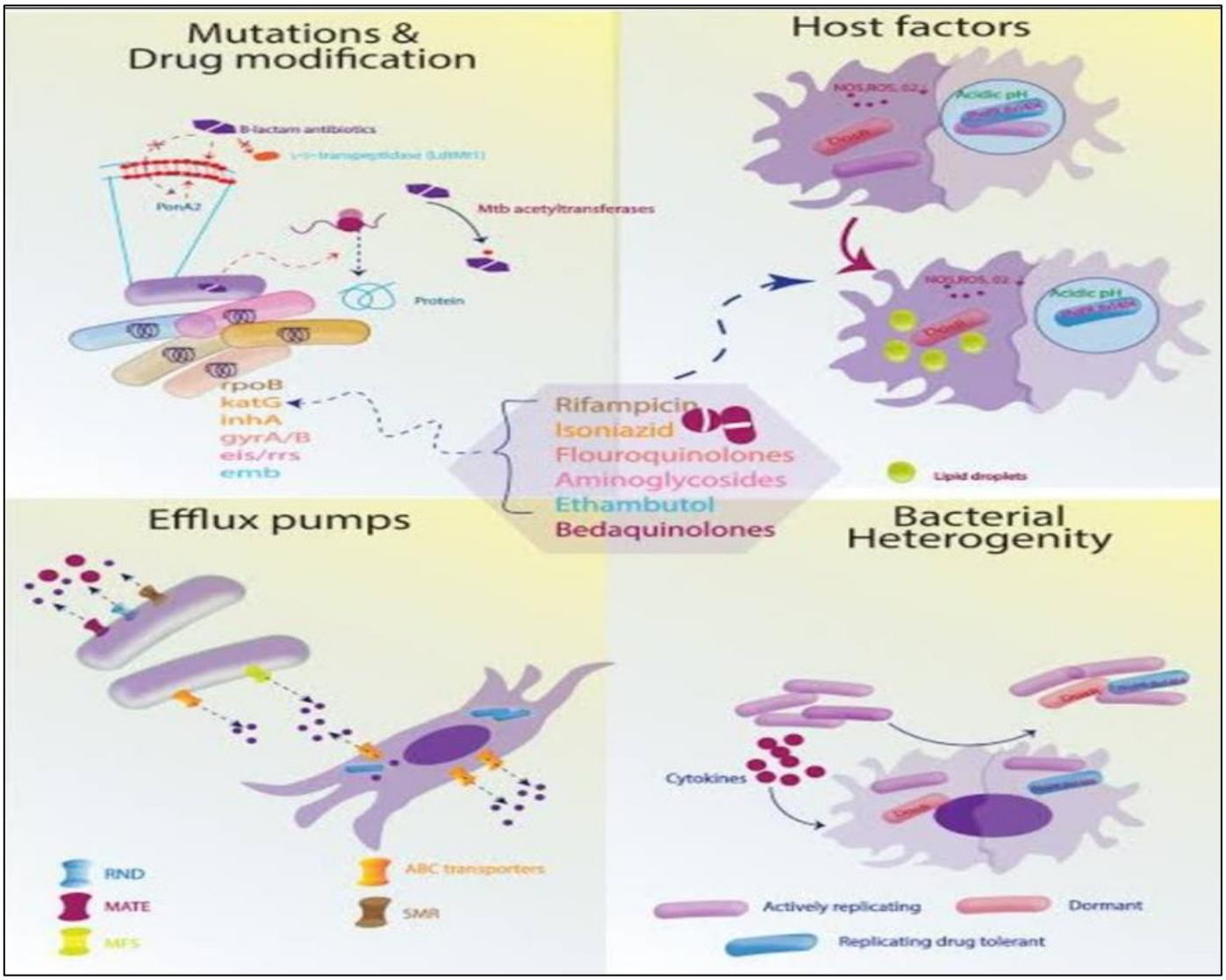

Fig 5 Actionable Mechanisms of Drug Tolerance and Resistance in Mycobacterium Tuberculosis

IV. CONCLUSION

This review is aimed at giving a Pharmacological strategies to overcome MDR-TB have evolved rapidly: novel drugs and shortened all-oral regimens (notably BDQ- and Pa-containing combinations) offer higher cure rates, shorter treatment durations, and improved tolerability compared with historical regimens.

Optimal deployment requires accurate and rapid DST, careful monitoring for toxicity and emerging resistance, PK/PD-guided dosing where feasible, and programmatic systems to guarantee access and adherence. Integrating these pharmacological advances with diagnostics, stewardship, and operational support is essential to control MDR-TB and prevent further spread.

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