

Targeting Oxidative Stress Pathways for Improved Tuberculosis Treatment Outcomes

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ABSTRACT

Tuberculosis (TB) treatment remains challenged by prolonged therapy, drug resistance, and host–pathogen interactions driven by oxidative stress. This review examines oxidative stress not as a uniformly pathogenic process but as a cause, consequence, and mediator of TB pathology, drug response, and therapeutic outcome in *Mycobacterium tuberculosis* infection. Reactive oxygen and nitrogen species (ROS/RNS) generated by host phagocytes contribute to antimicrobial activity and are integral to the activation of key anti-TB prodrugs such as isoniazid and pyrazinamide. However, excessive or sustained oxidative stress promotes bacterial adaptation through redox-sensitive regulators, including SigH and WhiB7, which enhance antioxidant defences, efflux pump activity, and phenotypic persistence, and may contribute to, but do not alone determine, disease reactivation. Host redox imbalance, exacerbated by comorbidities such as diabetes and HIV, further impairs drug efficacy and increases toxicity. Emerging host-directed therapies, including N-acetylcysteine, glutathione supplementation, and Nrf2 modulators, aim to restore redox homeostasis and improve treatment outcomes. Targeting the oxidative stress–resistance axis therefore represents a promising, though still evolving, strategy for combating multidrug-resistant tuberculosis and optimising therapeutic success.

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INTRODUCTION

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (Mtb), continues to be a major global public health issue. As reported by the World Health Organization (WHO, 2024), there were approximately 10.8 million new TB cases in 2023, the highest number since global tracking began in 1995, with most cases found in low- and middle-income nations. TB was linked to nearly 1.25 million deaths among HIV-negative individuals and an additional 167,000 deaths among those living with HIV, reestablishing it as the leading cause of death from a single infectious agent, overtaking COVID-19 (Goletti *et al.*, 2025; Zumla *et al.*, 2025).

The incidence of TB is highly uneven across the globe. Thirty high-burden countries account for 87% of all cases, with India (26%), Indonesia (10%), China (6.8%), the Philippines (6.8%), and Pakistan (6.3%) together responsible for over half of the global burden (WHO, 2024). Geographically, the WHO South-East Asia Region carries the highest burden (45%), followed by Africa (24%) and the Western Pacific (17%) (WHO, 2024). In terms of demographics, adult men are disproportionately affected, accounting for 55% (6.0 million) of cases, while adult women represent 33% (3.6 million) and children aged 0–14 years make up 12% (1.25 million) (WHO, 2024).

Mycobacterium tuberculosis is spread primarily through inhaled aerosol droplets that target alveolar macrophages in the lungs. The pulmonary environment mounts several layers of defence, among which oxidative stress responses are central to controlling early infection (Amaral *et al.*, 2019). During TB infection, phagocytic cells, particularly macrophages, produce reactive oxygen species (ROS) that create a complex relationship in which oxidative stress acts

simultaneously as a defence mechanism and as a challenge to host tissue integrity (Nangpal *et al.*, 2025).

The rationale for treating oxidative stress as a central regulator of TB pathogenesis, rather than as a uniformly pathogenic process, rests on three overlapping roles it plays across the course of infection. As a **cause**, host- and drug-derived ROS/RNS directly damage the bacillus and activate several first-line prodrugs, so that oxidative flux is itself an antimicrobial mechanism. As a consequence, chronic Mtb infection, granulomatous inflammation, and comorbid metabolic disease such as diabetes generate secondary oxidative injury to host tissue that follows from infection rather than triggering it. As a **mediator**, the same reactive intermediates function as signalling molecules that determine whether the host–pathogen interaction tips toward bacterial clearance, granuloma containment, or bacterial persistence and drug tolerance, depending on their magnitude, duration, and the cellular compartment in which they act. Distinguishing these three roles matters clinically: interventions that indiscriminately suppress or amplify oxidative stress risk undermining the very mechanism, drug-induced ROS generation, that clears the pathogen, whereas a stage- and compartment-specific approach can instead exploit oxidative signalling therapeutically. This distinction is developed further in Section 4, which examines how oxidative stress operates differently at the macrophage, granuloma, and tissue levels.

Oxidative stress refers to the imbalance between the production of ROS, such as superoxide (O_2^-), hydrogen peroxide (H_2O_2), nitric oxide (NO), and hydroxyl radicals ($OH^\bullet$), and the cell's ability to neutralise these reactive substances and repair the resulting damage (Lushchak *et al.*,

2021; Remigante *et al.*, 2024). Endogenous ROS are produced during aerobic metabolism, including mitochondrial leakage, NADPH oxidase (NOX2) activity, and peroxisomal oxidation, while exogenous sources may include ultraviolet and ionising radiation, heavy metals, and xenobiotics. When ROS production overwhelms antioxidant defences, oxidative stress occurs, damaging lipids, proteins, nucleic acids, and signalling pathways, and contributing to a wide range of illnesses, including cardiovascular disease, neurodegeneration, metabolic syndrome, chronic inflammation, infection, and cancer. Oxidative stress also shapes immune responses, cell proliferation, apoptosis, and ageing through redox-dependent signalling and gene regulation (Selvaraj *et al.*, 2025).

Cells mitigate oxidative stress using enzymatic antioxidants such as superoxide dismutase, catalase, and glutathione peroxidase, alongside non-enzymatic agents such as glutathione, vitamins C and E, and uric acid. In TB, the ROS generated by macrophages form a key antimicrobial strategy, yet *Mtb* has evolved antioxidant and metabolic adaptations that disturb host redox balance and contribute to chronic inflammation and tissue damage (Rockwood *et al.*, 2024). Oxidative stress plays a dual role, contributing to both effective immune responses and to granuloma maintenance, a process that can later progress to lung cavitation in pulmonary TB (Nangpal *et al.*, 2025). Oxidative stress is also implicated in *Mtb* persistence through ferroptosis, an iron-dependent cell death pathway driven by lipid peroxidation (Amaral *et al.*, 2019); the bacterium appears to exploit host ROS to promote ferroptotic death of macrophages, facilitating its spread and evasion of phagolysosomal degradation. This interaction disturbs host iron balance and worsens oxidative damage, particularly in individuals with pre-existing antioxidant deficiencies, such as patients with diabetes, who face increased risk of severe complications including TB meningitis (Degner *et al.*, 2017).

From a treatment standpoint, oxidative stress complicates TB management by heightening drug-induced liver toxicity and immune dysfunction during extended chemotherapy (Trivedi *et al.*, 2012). First-line medications such as isoniazid and rifampicin can induce ROS-related mitochondrial damage, compromising treatment adherence and contributing to poor outcomes, particularly in multidrug-resistant TB (MDR-TB) (Kumar *et al.*, 2021). There is increasing evidence for the benefit of adjunctive antioxidant therapies in restoring redox balance: N-acetylcysteine (NAC) has been shown to lower oxidative biomarkers, reduce inflammation, and hasten sputum conversion, while liposomal glutathione helps maintain cytokine balance and offers hepatic protection in MDR-TB and TB meningitis (Degner *et al.*, 2017; Nasiri *et al.*, 2025). By reducing oxidative damage and supporting immune function, such agents represent promising host-targeted strategies for improving TB cure rates and reducing relapse (Rockwood *et al.*, 2024).

MATERIALS AND METHODS

Standard Anti-Tuberculosis Regimens and Mechanisms of Drug Action

Tuberculosis treatment relies on a multidrug regimen that simultaneously targets several metabolic and structural pathways in *Mtb*, ensuring bactericidal and bacteriostatic efficacy, preventing the emergence of resistance, and eradicating both actively replicating and dormant bacterial populations (Gouzy *et al.*, 2023; Vilch  ze and Jacobs, 2019). The standard regimen for drug-susceptible TB (DS-TB) is a six-month, two-phase combination therapy: an intensive phase (two months) comprising isoniazid (INH), rifampicin

(RIF), pyrazinamide (PZA), and ethambutol (EMB), followed by a four-month continuation phase of isoniazid and rifampicin (WHO, 2024). Drug-resistant TB (DR-TB) requires more complex second-line regimens. MDR-TB is defined by resistance to at least isoniazid and rifampicin, while extensively drug-resistant TB (XDR-TB) additionally involves resistance to fluoroquinolones and at least one second-line injectable agent, such as amikacin, kanamycin, or capreomycin (WHO, 2024). Across both regimen classes, drug action converges on cell wall biosynthesis, nucleic acid replication, protein translation, and energy metabolism, and the combined pharmacological pressure produces synergistic effects under the oxidative, hypoxic, and acidic conditions characteristic of granulomatous lesions (Gouzy *et al.*, 2023).

First-Line Drugs and the Standard Regimen

- i. **Isoniazid (INH):** INH is activated by the catalase–peroxidase enzyme KatG, generating an isonicotinoyl radical that forms a covalent adduct with NAD⁺. The resulting INH–NAD adduct inhibits InhA (enoyl-acyl carrier protein reductase) in the fatty acid synthase II (FAS-II) pathway, blocking mycolic acid synthesis and compromising cell wall integrity. INH additionally perturbs NAD⁺ metabolism and increases ROS accumulation, contributing directly to oxidative stress within the bacillus. It is highly bactericidal against replicating bacilli but considerably less effective against dormant forms. Resistance typically arises from *katG* mutations, most notably *katG* S315T (Vilch  ze *et al.*, 2024).
- ii. **Rifampicin (RIF):** RIF targets the β -subunit of DNA-dependent RNA polymerase (RpoB), inhibiting RNA chain elongation and blocking transcription in both actively replicating and non-replicating bacilli. It exhibits potent bactericidal and sterilising activity that significantly shortens treatment duration. Resistance results primarily from *rpoB* mutations (Vilch  ze *et al.*, 2024).
- iii. **Pyrazinamide (PZA):** PZA is a prodrug converted to pyrazinoic acid (POA) by the enzyme pyrazinamidase (PncA). POA disrupts membrane potential and ATP synthesis under the acidic conditions typical of the phagolysosome, inhibits trans-translation (via RpsA), and interferes with coenzyme A synthesis. Recent work indicates that POA also synergises with host-derived ROS, particularly through thiol oxidation, to enhance bactericidal killing within macrophages, which helps to explain why PZA is markedly more potent *in vivo* than in axenic culture (Dillon *et al.*, 2025). PZA is especially active against semi-dormant bacilli in inflammatory lesions, contributing to overall therapy shortening. Resistance commonly arises from *pncA* mutations.
- iv. **Ethambutol (EMB):** EMB inhibits arabinogalactan and lipoarabinomannan (LAM) synthesis by targeting arabinosyl transferase (EmbB), increasing cell wall permeability and enhancing INH efficacy. It is primarily bacteriostatic and helps prevent resistance development to the other first-line drugs. Mutations in the *embCAB* operon confer resistance (Gouzy *et al.*, 2023).

Second-Line and Novel Agents for Drug-Resistant TB

Modern regimens for DR-TB incorporate new and repurposed drugs that interfere with cell wall biosynthesis, energy metabolism, or protein synthesis, several of which also perturb bacterial redox status.

- i. **Bedaquiline (BDQ):** inhibits the ATP synthase subunit AtpE, causing ATP depletion and loss of proton motive force. It is active against both replicating and non-replicating Mtb and induces mild oxidative stress as a metabolic uncoupler. Mutations in *atpE* or in efflux regulators confer resistance (Hards *et al.*, 2024).
- ii. **Delamanid and Pretomanid:** Nitroimidazole prodrugs activated by Ddn (deazaflavin-dependent nitroreductase), releasing nitric oxide under low oxygen tension and causing DNA, protein, and lipid damage; they also inhibit mycolic acid synthesis and remain active under both aerobic and anaerobic conditions. Resistance arises chiefly from *ddn* and *fgd1* mutations (Bates *et al.*, 2025).
- iii. **Linezolid (LZD):** Binds the 50S ribosomal subunit at the peptidyl-transferase centre, inhibiting protein synthesis initiation, and is effective against intracellular Mtb. Resistance is associated with *rrl* (23S rRNA) and *rplC* mutations (Zong *et al.*, 2024).
- iv. **Moxifloxacin:** A fluoroquinolone that inhibits DNA gyrase (GyrA/B) and topoisomerase IV, preventing DNA supercoiling; it shows strong bactericidal activity and can substitute for EMB in short-course regimens.

Resistance develops through *gyrA* mutations (Dookie *et al.*, 2025).

- v. **Clofazimine (CFZ):** Generates intracellular ROS that contribute to bactericidal activity but also drive redox-stress adaptation in Mtb, illustrating the same drug-induced ROS/antioxidant-response paradox discussed throughout this review.

The shorter 6–9 months MDR-TB regimen endorsed by WHO (2024), combining bedaquiline, linezolid, levofloxacin, and clofazimine, has replaced older regimens that required up to 24 months. Despite this progress, drug toxicity, limited accessibility, and redox-driven tolerance mechanisms remain major barriers to universal treatment success.

Oxidative Stress and Drug Resistance in *Mycobacterium tuberculosis*

M. tuberculosis relies on intrinsic, acquired, and adaptive mechanisms to withstand drug-induced and host-derived oxidative stress. Oxidative stress contributes not only to the evolution of genetic resistance but also to phenotypic persistence under hostile redox environments (Kumar *et al.*, 2021) (see Figure 1).

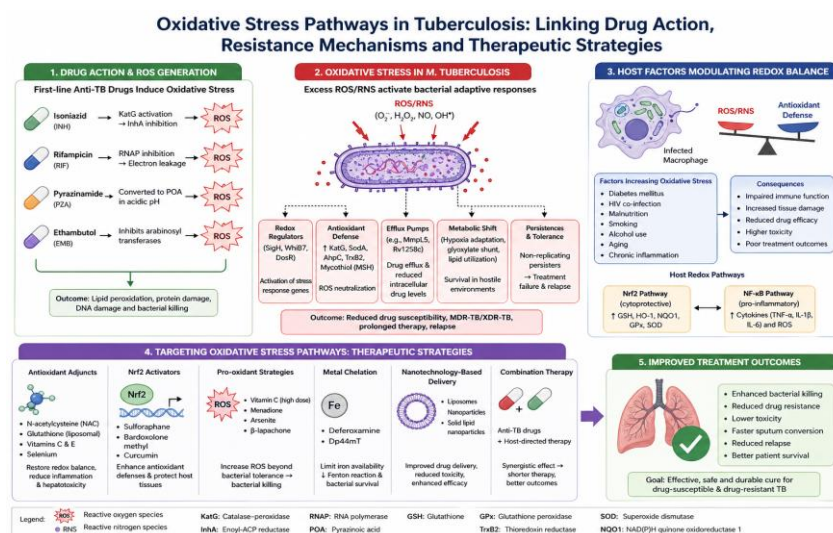


Figure 1: Schematic Illustration of the Oxidative Stress–drug Response–resistance Axis in *Mycobacterium tuberculosis*. Anti-tuberculosis Drugs induce Reactive Oxygen Species (ROS) that Enhance Bacterial Killing; however, Excessive Oxidative Stress can Activate Bacterial Redox Regulators (*SigH*, *WhiB7*), Antioxidant Systems, and Efflux Pumps, Contributing to Persistence and Reduced Drug Susceptibility. Host Redox Imbalance Further Modulates Drug Efficacy, Underscoring Oxidative Stress as a Candidate Therapeutic Target

Host ROS/RNS Generation and Bacterial Redox Defence: Directionality of the Interaction

A central theme of this review is the reciprocal, directional relationship between host oxidative defences and bacterial redox adaptation. The interaction proceeds broadly in three steps. First, host phagocytes generate ROS/RNS: activated macrophages use NADPH oxidase (NOX2) to produce superoxide and hydrogen peroxide, and inducible nitric oxide synthase (iNOS) to generate nitric oxide, as a direct antimicrobial response to Mtb infection. This host-derived oxidative burst also potentiates several anti-TB drugs, most notably the ROS-dependent bactericidal action of PZA described above. Second, the bacillus senses and responds to this oxidative challenge: redox-sensitive transcriptional regulators, principally *SigH*, *WhiB7*, and *WhiB3*, detect shifts

in intracellular thiol and Fe–S cluster status and, in response, upregulate a coordinated set of bacterial defences, including the enzymatic antioxidants KatG, SodA, and AhpC, and the low-molecular-weight thiol buffers mycothiol (MSH) and thioredoxin (Trx), which together neutralise host-derived ROS/RNS and repair the resulting macromolecular damage. Third, this bacterial response produces measurable biological outcomes: reduced net oxidative injury to the bacillus, increased survival within the hostile phagosomal environment, and, where the same regulators also control efflux gene expression, reduced intracellular accumulation of drugs such as INH, RIF, and fluoroquinolones. Explicitly separating what the host generates, how the bacillus responds, and what outcome results (rather than describing host and bacterial systems in isolation) clarifies why interventions

aimed at bacterial thiol systems (Section 8) are expected to restore, rather than replace, the host's own oxidative killing mechanism.

Intrinsic Resistance

The lipid-rich, mycolic acid-containing cell wall of *Mtb* forms an inherent permeability barrier against antibiotics. Efflux pumps such as Rv1258c (Tap-like), Rv1410 (P55), and Rv1218c expel INH, RIF, and fluoroquinolones from the bacterial cytoplasm. Several of these pump genes lie within regulons controlled by *WhiB7* and, to a lesser extent, *SigH*, and *in vitro* evidence indicates that oxidative or nitrosative stress can trigger conformational changes in the Fe-S cluster of *WhiB7*, favouring efflux gene expression. This association should be interpreted as a contributing regulatory link rather than proof that oxidative stress alone is sufficient to establish genetically stable, heritable resistance; intrinsic tolerance mediated through efflux is, in most cases, reversible and metabolically costly rather than a fixed genetic trait (Kumar *et al.*, 2021).

Acquired (Genetic) Resistance

Mtb also acquires resistance through spontaneous chromosomal mutations at drug-target loci, including *katG* (INH), *rpoB* (RIF), *embB* (EMB), and *pncA* (PZA) (Chai *et al.*, 2023). These canonical resistance mutations frequently co-occur with compensatory redox adaptations. For example, *katG* S315T mutants lose the capacity to activate INH but retain partial catalase activity for ROS detoxification, a deficit that is partly offset by *SigH*-mediated *AhpC* overexpression (Trivedi *et al.*, 2012). Similarly, *pncA* mutants rely on *SigH*-regulated mycothiol to neutralise hydroxyl radicals, while *rpoB* mutations have been associated with oxidative DNA damage acting through the error-prone DnaE2 polymerase pathway.

Adaptive Persistence (Phenotypic Tolerance)

Independent of genetic mutation, *Mtb* can enter a non-replicating persistent (NRP) state under hypoxia, nutrient depletion, or drug exposure, mediated by the DosRST two-component system. ROS accumulation and oxidative DNA damage (8-oxodG) are associated with the induction of dormancy and phenotypic drug tolerance (Tyagi *et al.*, 2021). *SigH* activation in this state enhances mycothiol and thioredoxin expression, buffering oxidative damage and supporting long-term bacterial survival within granulomas. Because this state is phenotypic rather than mutational, it is, in principle, reversible once the oxidative or hypoxic pressure is relieved, which is the rationale underlying several of the adjunctive strategies discussed in Section 8.

Host-Pathogen Redox Interactions

Mtb also actively manipulates host redox signalling. Through the ESX-1 secretion system, the bacillus promotes degradation of host *Nrf2*, reducing glutathione (GSH) and GPX4 availability and thereby impairing the oxidative activation of INH and PZA. Simultaneously, host haem oxygenase-1 (HO-1)-derived carbon monoxide can mimic a hypoxic signal that favours bacterial dormancy. In individuals with diabetes, suppressed *Nrf2* signalling and reduced GSH further weaken redox-dependent drug activation, providing one mechanistic explanation for the poorer TB treatment outcomes observed in this comorbid population (Rockwood *et al.*, 2024).

Redox Master Regulators and the Drug-Response Paradox

Oxidative stress plays a paradoxical role in TB chemotherapy. Certain anti-TB drugs, including isoniazid, clofazimine, and bedaquiline, act in part by inducing ROS to kill bacilli, yet excessive or prolonged oxidative pressure activates bacterial antioxidant defence systems that blunt drug activity and favour persistence. The *Mtb* redox master regulator *WhiB7* coordinates transcription of genes conferring multidrug tolerance, including efflux pumps, ribosomal protection proteins, and detoxification enzymes, while *SigH*, together with OxyR/SoxR-like regulatory circuits, governs the broader bacterial oxidative-stress response. On the host side, antioxidant capacity, reflected in glutathione, thioredoxin, and catalase levels, and controlled upstream by the *Nrf2*–Keap1–ARE pathway, shapes intracellular drug efficacy. In individuals with impaired redox homeostasis due to HIV, diabetes, or malnutrition, drug response tends to be weaker and relapse more frequent (Chai *et al.*, 2022). The dynamic interplay between bacterial and host redox balance therefore critically shapes therapeutic outcome, and strategies that deliberately modulate oxidative stress, in either direction depending on context, may help restore drug susceptibility and limit the amplification of resistance.

Oxidative Stress Across the Stages of TB Pathogenesis

Because oxidative stress does not act uniformly throughout infection, its contribution to pathogenesis is best understood as occurring in at least three distinguishable compartments, each with a different balance of protective and damaging effects.

Macrophage-Level Oxidative Stress

At the point of first contact, alveolar macrophages mount a NOX2- and iNOS-dependent oxidative burst that is predominantly protective, killing a substantial proportion of the infecting bacilli and initiating prodrug activation. In macrophages that fail to clear the bacillus, however, *Mtb* infection is associated with reduced glutathione and GPX4 levels alongside increased labile iron and lipid peroxidation, hallmarks of ferroptosis, a regulated form of necrotic cell death that appears to favour bacterial spread rather than containment (Amaral *et al.*, 2019). At this level, oxidative stress is therefore best described as having an early protective phase followed by a later, host-detrimental phase once antioxidant capacity within the infected cell is exhausted.

Granuloma-Level Oxidative Stress

Within the granuloma, oxidative and nitrosative stress contribute to structural containment of the bacillus by supporting macrophage activation, epithelioid transformation, and formation of a fibrotic capsule. The same reactive intermediates, sustained over the chronic timescale typical of granuloma maturation, also contribute to central caseous necrosis and, in advanced pulmonary disease, cavitation (Rockwood *et al.*, 2024). Oxidative stress at this level is thus dual-purpose: it is a structural requirement for granuloma maintenance and immune containment, while simultaneously predisposing the lesion to the tissue breakdown that facilitates transmission.

Tissue-Level Oxidative Stress

At the tissue level, sustained oxidative and inflammatory signalling drives lipid peroxidation, extracellular matrix remodelling, and, in the lung parenchyma, progressive fibrosis and cavitory damage that extend well beyond the immediate site of bacterial replication (Amaral *et al.*, 2016).

This systemic component of oxidative injury is compounded by comorbid oxidative burden, for example from hyperglycaemia in diabetes, and is the level at which oxidative stress most directly contributes to long-term lung function impairment and to the pathological features associated with disease transmission, independent of the bacterial killing that occurs earlier at the macrophage level.

Oxidative Activation of Anti-TB Prodrugs

Several anti-TB drugs are prodrugs that require oxidative or reductive activation within Mtb to exert bactericidal effects. Isoniazid is oxidatively activated by KatG, generating an isonicotinic acyl radical that forms adducts with NAD⁺/NADP⁺ and inhibits InhA, a key enzyme in mycolic acid synthesis (Timmins and Deretic, 2006). Pretomanid, a nitroimidazole, undergoes F₄₂₀-dependent nitroreduction via Ddn, yielding nitric oxide and other reactive nitrogen species that are lethal to non-replicating bacilli (Singh *et al.*, 2008). Ethionamide and prothionamide are activated by the monooxygenase EthA in an oxidative, NADPH-dependent process that generates metabolites capable of inhibiting InhA (DeBarber *et al.*, 2000; Banerjee *et al.*, 1994). Collectively, these examples show that oxidative and reductive enzymes that Mtb otherwise deploys for protection or metabolism are, in the context of chemotherapy, paradoxically exploited to trigger lethal radical cascades against the bacillus itself.

Reactivation of Latent TB Infection: A Cautious Interpretation of Oxidative Contributions

Oxidative and redox mechanisms are frequently proposed as contributors to reactivation of latent TB infection, but the manuscript here treats this association cautiously, consistent with the multifactorial nature of reactivation. Depleted host glutathione, expression of bacterial antioxidant systems (SigH-regulated mycothiol and AhpC), and ferroptosis-associated tissue injury may plausibly weaken local containment of dormant bacilli and create conditions favourable to bacterial reawakening from the DosRST-regulated non-replicating state (Tyagi *et al.*, 2021). However, reactivation in clinical populations is better explained as multifactorial, driven principally by waning cell-mediated immunity, TNF- α blockade or other immunosuppressive therapy, HIV coinfection, malnutrition, and advancing age, with oxidative imbalance acting as one contributing factor among several rather than as a sole or primary determinant (Chai *et al.*, 2022; Rockwood *et al.*, 2024). Framed this way, the proposed roles of depleted glutathione, bacterial antioxidant systems, and ferroptosis are best regarded as mechanistically plausible contributors to the permissive tissue environment for reactivation, not as an established causal pathway sufficient on its own to explain why latent infection becomes active disease.

Host Factors, Comorbidities, and Redox-Driven Drug Resistance

Host-mediated resistance arises from pharmacokinetic variability, immune dysfunction, and oxidative stress, and is exacerbated in comorbidities such as diabetes and HIV.

- i. **Drug Metabolism Impairment:** cytochrome P450 enzymes (CYP3A4, CYP2E1) responsible for INH and RIF metabolism can be inactivated by excess ROS and by suppression of *Nrf2* signalling, leading to hepatotoxicity and subtherapeutic drug levels (Degner *et al.*, 2017).
- ii. **Host Efflux Pumps:** ABC transporters (MDR1, MRP1, BCRP), upregulated by oxidative and inflammatory signals, expel drugs from macrophages and blood–

brain-barrier endothelial cells, reducing intracellular and CNS drug concentrations (Rockwood *et al.*, 2024).

- iii. **Immune Dysregulation:** chronic oxidative stress can suppress NOX2 and iNOS activity, impairing the macrophage ROS/RNS production required for drug activation, an effect that is particularly relevant in HIV-associated and diabetes-associated TB.
- iv. **Tissue-specific Barriers:** in TB meningitis, oxidative damage depletes GPX4, upregulates MDR1, and limits INH and RIF penetration into the central nervous system (Rockwood *et al.*, 2024).

These host-side barriers are a key reason adjunctive, host-directed strategies are increasingly considered alongside conventional chemotherapy, and are discussed in the following section.

Host-Directed Therapies and Redox-Modulating Adjunctive Strategies

Host-directed therapies (HDTs) target host pathways rather than bacterial structures, reducing the likelihood of selecting for resistant strains while addressing the redox barriers described above (Mayer-Barber *et al.*, 2014).

Antioxidant and Thiol Modulation

Agents such as N-acetylcysteine and glutathione precursors restore redox balance and can augment the bactericidal activity of standard drugs, in part by supporting the host oxidative burst that activates INH and PZA rather than by suppressing it indiscriminately (Nasiri *et al.*, 2025).

Nrf2–Keap1–ARE Pathway Activation

Nrf2 activators such as dimethyl fumarate and sulforaphane restore host antioxidant enzyme expression, improve drug penetration, and may reduce hepatotoxicity associated with first-line therapy (Rockwood *et al.*, 2024).

Autophagy Induction

Repurposed agents such as metformin and statins promote phagolysosomal fusion and enhance intracellular bacterial killing, offering a metabolically distinct route to bacterial clearance that is less dependent on oxidative burst alone.

Anti-Inflammatory and Immunomodulatory Regulation

Vitamin D, corticosteroids, and TNF modulators can help optimise immune responses and limit excessive tissue destruction associated with prolonged inflammation, although immunosuppressive agents in this category require caution given their independent association with TB reactivation (Section 6).

Pro-Oxidant, Efflux-Targeting, and Cell-Death-Pathway Adjuncts

A distinct and, in some respects, opposite strategy uses controlled pro-oxidant challenge rather than antioxidant support. Efflux pump inhibitors such as verapamil can enhance intracellular drug retention, and the thiol-oxidising agent diamide depletes mycothiol, restoring PZA susceptibility in experimental systems. High-dose vitamin C synergises with isoniazid and rifampicin through Fenton-type hydroxyl radical generation, accelerating bacterial killing in preclinical models (Vilch  ze *et al.*, 2017; Dey *et al.*, 2022), and cysteine/glutathione modulation can disrupt intracellular thiol homeostasis to enhance drug penetration and reduce tolerance (Schoen *et al.*, 2019). Targeting the iron- and copper-dependent death pathways ferroptosis and cuproptosis is also an area of active investigation: inducers such as erastin, iron chelators such as deferoxamine, and copper ionophores

such as elesclomol have been shown to impair Mtb metabolism and potentiate antimycobacterial drugs in preclinical models (Wang *et al.*, 2023; Chen *et al.*, 2024). Because these pro-oxidant approaches act in the opposite direction to the antioxidant strategies above, their clinical translation will likely require patient- and stage-specific selection rather than uniform application, reinforcing the compartment-specific framework introduced in Section 4.

Redox Imbalance as a Determinant of Drug Failure and Therapeutic Outcome

The host and Mtb antioxidant systems engage in what can be described as a redox tug-of-war that underlies disease progression, drug efficacy, and resistance evolution. The host mounts ROS/RNS responses to eliminate the pathogen, while Mtb counters through *SigH*, *WhiB3*, and mycothiol-mediated detoxification systems that neutralise these reactive intermediates. When oxidative stress exceeds host compensatory capacity, owing to impaired *Nrf2* signalling, depleted glutathione, or suppressed GPX4, tissue injury, immune dysregulation, and therapeutic failure can follow (Rockwood *et al.*, 2024). Conversely, excessive activation of bacterial antioxidant defences dampens the bactericidal effects of drugs such as INH and PZA, both of which depend on oxidative and hydroxyl radical mechanisms for efficacy; elevated *SigH* and *AhpC* expression buffers drug-induced ROS and favours the emergence of multidrug-resistant and persister phenotypes, whereas successful therapy is associated with restoration of redox homeostasis, including *Nrf2* reactivation, normalisation of the GSH/GSSG ratio, and suppression of bacterial oxidative-defence genes. Persistent elevation of oxidative damage biomarkers, such as malondialdehyde (MDA) and 8-oxodG, alongside low antioxidant indices (GSH/GSSG ratio, *Nrf2* activity), may indicate sustained redox imbalance and could plausibly help flag patients at risk of poor treatment outcome or MDR-TB evolution, although these biomarkers remain to be validated prospectively for this purpose (see Section 10). Redox-guided interventions, including *Nrf2* activators, glutathione restoration, and strategies that target *SigH*-dependent bacterial defences, therefore represent candidate dual-target approaches for disrupting the oxidative equilibrium that supports drug tolerance and persistence in Mtb.

Challenges and Future Perspectives

Despite its therapeutic potential, integrating oxidative stress modulation into TB treatment is hindered by interrelated biological, pharmacological, and operational barriers. Mtb shows remarkable adaptability, surviving oxidative and nitrosative stress from host immunity and from drugs such as rifampicin and isoniazid by shifting into a non-replicating persister state involving upregulated efflux pumps, antioxidant enzymes (KatG, SodA, *AhpC*), and redox regulators (*WhiB3*, *DosR*). This adaptive tolerance can, over time, be reinforced by the emergence of genetic mutations in drug-target genes such as *rpoB*, *katG*, and *inhA*, contributing to MDR-TB (Siddiqi *et al.*, 2020). Comorbidities such as diabetes mellitus and HIV/AIDS aggravate redox imbalance by weakening immune responses, elevating basal ROS levels, and altering drug pharmacokinetics and pharmacodynamics. Hyperglycaemia promotes mitochondrial dysfunction and oxidative damage that favour Mtb persistence, while HIV infection impairs macrophage and CD4⁺ T-cell function, diminishing ROS-mediated bacterial killing (Huang *et al.*, 2021; Ronacher *et al.*, 2022). Several anti-TB drugs themselves intensify oxidative injury: isoniazid bioactivation via KatG generates

reactive intermediates linked to hepatotoxicity, while ethambutol and linezolid have been associated with optic neuropathy and mitochondrial stress, contributing to poor adherence, relapse, and secondary resistance, particularly in resource-limited settings (Tostmann *et al.*, 2008).

Achieving therapeutic redox balance remains a central dilemma. Moderate ROS supports immune clearance through phagolysosomal maturation and autophagy, whereas excessive ROS can cause oxidative tissue injury, ferroptosis- or cuproptosis-related macrophage necrosis, and granuloma breakdown, worsening disease pathology (Wang *et al.*, 2023). Environmental factors such as malnutrition, air pollution, and chronic toxin exposure further add to oxidative burden. Preclinical efficacy of oxidative-stress-modulating interventions has also not yet translated reliably into human therapy, reflecting species differences, a lack of validated biomarkers, and an incomplete understanding of redox dynamics within biofilms and hypoxic lesions (Datta *et al.*, 2023).

Nonetheless, several directions appear promising. Nanotechnology may enable targeted delivery of redox-active molecules to granulomatous sites while limiting systemic toxicity, and could facilitate co-delivery of oxidative modulators alongside immune-directed agents such as interferon-gamma or interleukin-10 inhibitors to restore macrophage bactericidal capacity (Mayer-Barber *et al.*, 2014). A priority for future research is the prospective validation of oxidative biomarkers, including MDA, 8-hydroxy-2'-deoxyguanosine (8-OHdG), and CellROX fluorescence, to enable redox-based patient stratification and more personalised therapy. Equally important is a deeper mechanistic understanding of host-pathogen redox interplay, since this will be central to designing interventions that exploit, rather than indiscriminately blunt, the oxidative mechanisms that Mtb chemotherapy already depends upon. Integrating microbiology, immunology, pharmacology, and nanomedicine may ultimately help transform oxidative stress from a therapeutic challenge into a more precisely targetable ally against TB.

CONCLUSION

Oxidative stress sits at the core of tuberculosis treatment dynamics, acting simultaneously as a facilitator of antimicrobial activity and, when dysregulated, as a contributor to drug resistance and therapeutic failure. Reactive oxygen and nitrogen species enhance the bactericidal effects of key anti-TB drugs through prodrug activation and immune-mediated killing, yet excessive or sustained oxidative stress promotes adaptive responses in Mtb, including activation of the redox-sensitive regulators *SigH* and *WhiB7*, efflux pump expression, and persistence in non-replicating states. These bacterial adaptations should be understood as contributing mechanisms operating alongside, rather than substituting for, the well-established immunological and pharmacokinetic drivers of resistance and reactivation. Concurrently, host factors such as impaired antioxidant defences, metabolic disorders, and co-infections further disrupt redox balance, reducing drug efficacy and increasing toxicity. Host-directed therapies aimed at restoring redox homeostasis, including N-acetylcysteine, glutathione, and *Nrf2* activators, together with more targeted pro-oxidant and efflux-modulating adjuncts, offer a promising avenue for improving treatment outcomes, provided their application is guided by the stage- and compartment-specific understanding of oxidative stress developed throughout this review. Ultimately, targeting the oxidative stress-drug resistance interface provides a strategic framework for improving TB

management and addressing the global burden of drug-resistant disease.

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