Respiratory Research and Treatment

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Review

Combating Tuberculosis with Nature's Pharmacy: Role of Natural Products in Anti-TB Drug Development

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Abstract

Tuberculosis (TB) remains a major global health challenge, further complicated by multidrug-resistant (MDR), extensively drug-resistant (XDR), and latent *Mycobacterium tuberculosis* infections. Although current therapies are effective in drug-sensitive TB, prolonged treatment duration, toxicity, poor adherence, and emerging resistance highlight the need for safer and more effective alternatives. Natural products represent a valuable source of structurally diverse bioactive compounds with antimycobacterial, resistance-modifying, and host-directed therapeutic potential. This review summarizes recent advances in natural and plant-derived compounds with anti-TB activity. Major natural sources, including medicinal plants, microorganisms, and marine organisms, are discussed along with important bioactive classes such as alkaloids, flavonoids, terpenoids, coumarins, quinones, and peptides. Reported mechanisms include inhibition of cell wall biosynthesis, disruption of energy metabolism, efflux pump modulation, interference with nucleic acid synthesis, and host immunomodulation through autophagy and inflammatory signaling pathways. however, most evidence remains preclinical and heterogeneous in methodology bergenin, berberine, curcumin, resveratrol, quercetin, tetrandrine, calanolide A, ecumicin, and gladiolin. Several compounds have shown encouraging *in vitro* antimycobacterial activity, while selected candidates demonstrate efficacy in macrophage and animal models or synergistic effects with standard anti-TB drugs. However, robust clinical evidence remains limited. Major translational barriers include poor bioavailability, rapid metabolism, formulation challenges, toxicity concerns, lack of standardization, and insufficient pharmacokinetic/pharmacodynamic validation. Future progress will depend on integrated approaches involving artificial intelligence-guided screening, nanoformulations, synthetic biology, and well-designed preclinical and clinical studies. Natural products may therefore provide valuable leads and adjunct therapies for next-generation TB treatment.

Keywords

Tuberculosis, Natural products, Plant-derived compounds, Anti-*Mycobacterium tuberculosis* activity, Drug-resistant TB, Host-directed therapy

Article History

Received: 02 April 2026 Revised: 26 May 2026

Accepted: 27 May 2026 Available Online: 04 June 2026

1. Introduction

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (*M. tuberculosis*), remains one of the most consequential infectious diseases worldwide and continues to impose a substantial clinical, social, and economic burden [1]. Historical evidence suggests that TB has affected human populations for millennia, including documented lesions in ancient Egyptian mummies. Despite the availability of antimicrobial therapy since the twentieth century, TB remains a persistent global health challenge. According to the World Health Organization (WHO) global tuberculosis report 2024, an estimated 10.6 million people developed TB in 2023, with approximately 1.3 million deaths among HIV-negative individuals, reaffirming TB as one of the leading causes of death from a single infectious pathogen [2].

Although standard first-line treatment is generally effective in drug-susceptible disease, conventional therapy requires prolonged multidrug administration for at least six months, creating major challenges related to adherence, adverse drug reactions, pill burden, and treatment interruption. These limitations are particularly important in pulmonary TB, where delayed microbiological clearance, persistent lung inflammation, and structural lung damage may contribute to long-term respiratory morbidity even after microbiological cure [3,4].

The emergence of multidrug-resistant tuberculosis (MDR-TB), rifampicin-resistant tuberculosis (RR-TB), and extensively drug-resistant tuberculosis (XDR-TB) has further complicated disease control. Drug-resistant TB often requires longer, more expensive, and potentially more toxic regimens with variable outcomes [5]. Although newer agents such as bedaquiline, delamanid, pretomanid, and linezolid have improved treatment options, access remains uneven in many low- and middle-income countries, and safety monitoring is frequently required. In parallel, TB outcomes are strongly influenced by coexisting risk factors including HIV infection, diabetes mellitus, malnutrition, smoking, overcrowding, and poverty [6,7].

Recent clinical evidence also indicates that drug resistance is shaped not only by bacterial mutations but also by patient-level determinants. In a prospective observational study of pulmonary TB patients, tobacco use, low body weight, reduced body mass index (BMI), and lower socioeconomic status were significantly associated with drug-resistant TB, with tobacco users showing markedly higher odds of resistance development. These findings highlight that successful TB management requires both effective pharmacotherapy and mitigation of modifiable risk factors [6].

Natural products have historically played a central role in antimicrobial drug discovery. Streptomycin, the first effective anti-TB antibiotic, originated from *Streptomyces griseus*, while rifampicin (RIF) was developed from rifamycin-class metabolites produced by *Amycolatopsis rifamycinica* (formerly *Streptomyces mediterranei*). This legacy has renewed interest in terrestrial plants, microorganisms, marine organisms, and traditional medicinal systems as sources of structurally diverse anti-mycobacterial agents [8].

Several natural compounds, including curcumin, berberine, resveratrol, quercetin, bergenin, tetrandrine, and gladiolin, have demonstrated inhibitory activity against *M. tuberculosis* in *in vitro* assays, intracellular macrophage models, or selected animal studies. Some also exhibit immunomodulatory, antioxidant, or anti-inflammatory effects that may support host-directed therapeutic strategies [9]. However, most candidates remain in preclinical development, and relatively few have progressed to robust pharmacokinetic studies, lesion penetration assessments, standardized toxicity evaluation, or controlled human trials [10].

A major translational challenge in TB drug development is that promising *in vitro* activity alone is insufficient. Candidate compounds must ideally demonstrate potency against drug-sensitive and drug-resistant strains, intracellular efficacy in macrophages, activity against non-replicating bacilli, acceptable selectivity toward host cells, favorable pharmacokinetics, penetration into pulmonary lesions and granulomatous tissue, compatibility with multidrug regimens, and low propensity for rapid resistance emergence [11]. Many natural compounds fail during translation because of poor solubility, low oral bioavailability, metabolic instability, formulation difficulties, or inadequate *in vivo* efficacy. In this context, natural products remain attractive because they provide novel chemical scaffolds, potential multi-target mechanisms, and opportunities for adjunctive therapy alongside existing regimens. Their greatest near-term clinical value may lie not only as standalone antimicrobials, but also as resistance-modifying agents, efflux pump inhibitors, biofilm disruptors, or host-directed adjuncts that improve treatment outcomes [12].

From a clinical and translational respiratory medicine perspective, TB is primarily a pulmonary disease in which *M. tuberculosis* resides within alveolar macrophages and granulomatous lung lesions. Therefore, therapeutic success is not determined solely by *in vitro* antimycobacterial potency but critically depends on adequate drug penetration into lung tissue, intracellular macrophage targeting, and lesion-specific exposure. In addition, patient-centered outcomes such as treatment adherence, reduction in drug-induced toxicity, and shortening of therapy duration are essential for improving real-world TB control. Despite promising preclinical evidence for several natural compounds, their clinical translation remains limited due to insufficient pharmacokinetic validation, lack of pulmonary distribution data, and absence of well-designed Phase II/III trials [13]. Future development strategies should therefore prioritize inhalable or lung-targeted delivery systems, host-directed therapeutic approaches, and integration with existing WHO-recommended regimens to ensure meaningful clinical impact in pulmonary TB.

This review provides a comprehensive overview of natural products with anti-TB potential, focusing on their biological sources, chemical classes, mechanisms of action, evidence across *in vitro*, macrophage, animal, and clinical settings,

activity against drug-resistant TB, synergistic interactions with existing drugs, and future translational opportunities in pulmonary and global TB care.

A structured literature search was conducted using PubMed, Scopus, Web of Science, and Google Scholar. Search terms included "tuberculosis," "*Mycobacterium tuberculosis*," "natural products," "phytochemicals," "anti-tuberculosis activity," "drug-resistant tuberculosis," "host-directed therapy," and "synergistic therapy." Priority was given to peer-reviewed original articles, mechanistic studies, translational reports, and recent reviews relevant to anti-TB natural compounds.

2. Sources of Natural Anti-TB Compounds and Evidence Stratification

Natural products with potential anti-TB activity are obtained from diverse biological sources, including medicinal plants, microbial metabolites, and other natural reservoirs such as trees, shrubs, and higher plants. These sources provide structurally diverse bioactive molecules capable of exerting direct antimycobacterial effects, host-directed immunomodulation, or synergistic enhancement of conventional anti-TB drugs [14]. Traditional systems of medicine such as Ayurveda, Traditional Chinese Medicine (TCM), and African ethnomedicine have significantly contributed to the identification of such compounds. However, the level of scientific validation varies considerably, ranging from preliminary *in vitro* screening studies to macrophage infection models, *in vivo* animal studies, and limited clinical investigations [15]. Therefore, evidence-based stratification is essential when evaluating their therapeutic potential.

2.1 Medicinal Plants

Medicinal plants remain one of the most extensively investigated sources of anti-TB compounds. Many phytochemicals derived from these plants have shown encouraging antimycobacterial or immunomodulatory activity, although most evidence currently remains at the preclinical stage. Thymoquinone, the principal constituent of *Nigella sativa* (black seed), has demonstrated activity against multidrug-resistant (MDR) and extensively drug-resistant (XDR) *M. tuberculosis* strains in macrophage infection models [16]. In addition to direct antimycobacterial effects, thymoquinone modulates inflammatory cytokines and oxidative stress pathways, supporting its role as a host-directed therapeutic candidate.

Tetrandrine, isolated from *Stephania tetrandra*, has been evaluated primarily in *in vitro* studies, where it inhibits bacterial efflux pumps and enhances the activity of first-line drugs such as isoniazid (INH) and ethambutol (EMB) [17]. Its ability to restore intracellular antibiotic accumulation suggests promise as an adjunct agent against resistant TB. Piperine from *Piper nigrum* (black pepper) has shown modest direct activity in *in vitro* assays, while also improving drug bioavailability and intracellular penetration of co-administered antimicrobials. These properties make piperine particularly relevant as a pharmacokinetic enhancer [18]. Epigallocatechin gallate (EGCG), derived from *Camellia sinensis* (green tea), has demonstrated *in vitro* growth inhibition of *M. tuberculosis* and activity in selected cellular infection models. Its reported mechanisms include induction of autophagy and disruption of mycobacterial cell wall integrity [19].

Silymarin from *Silybum marianum* (milk thistle) has limited direct antimycobacterial evidence but has been investigated in animal and supportive clinical settings for reducing anti-TB drug-induced hepatotoxicity. Thus, its relevance is mainly adjunctive rather than bactericidal. Curcumin, the major polyphenol of *Curcuma longa* (turmeric), is among the most studied phytochemicals in TB research. It has shown moderate antimycobacterial activity in *in vitro* studies, enhanced intracellular killing in macrophage models, and immunomodulatory benefits in animal studies. These findings support its potential use in host-directed therapy (HDT), particularly in combination with standard anti-TB regimens [20,21].

Critical Perspective: Although medicinal plants provide a rich source of anti-TB candidates, most compounds lack robust pharmacokinetic characterization and controlled human clinical trials. Translation into approved therapeutics will require standardization, toxicity profiling, and well-designed clinical studies.

2.2 Microbial Metabolites

Microbial metabolites represent an important source of potent anti-TB compounds because of their structural complexity and target specificity. Compared with many plant-derived agents, microbial natural products often exhibit stronger direct bactericidal activity. A notable example is gladiolin, a macrolide metabolite produced by *Burkholderia gladioli*. Gladiolin has demonstrated potent activity in *in vitro* studies against drug-sensitive and drug-resistant *M. tuberculosis* strains through inhibition of bacterial RNA polymerase at a site distinct from RIF. This unique mechanism suggests reduced cross-resistance with RIF-resistant isolates [22]. Several microbial metabolites are also being explored in animal efficacy studies, although clinical evidence remains limited or absent. Their high potency and synthetic modifiability make them promising leads for future anti-TB drug development.

Critical Perspective: Microbial compounds may offer faster translational potential than many phytochemicals; however, toxicity, manufacturing scalability, and resistance emergence require careful evaluation.

2.3 Other Natural Sources

In addition to medicinal plants and microbes, several trees and higher plants have yielded compounds with reported anti-TB activity. Polyphenolic compounds from *Anogeissus leiocarpa* have shown inhibitory effects against active and dormant bacilli in *in vitro* studies, suggesting possible utility against latent TB. Similarly, CU1 isolated from *Cassia fistula* has been reported to exhibit *in vitro* antimycobacterial activity; however, mechanistic understanding remains limited and requires further validation [23,24].

Flavonoids such as quercetin and isorhamnetin, found in *Capparis spinosa*, *Allium cepa*, and berries, have shown moderate activity in *in vitro* and macrophage-based studies, largely through DNA gyrase inhibition, antioxidant activity, and reduction of intracellular survival. Totarol, isolated from *Podocarpus* species, has shown *in vitro* activity and synergistic interaction with INH by disrupting mycobacterial respiration. Calanolide A, obtained from *Calophyllum lanigerum*, has demonstrated activity against drug-sensitive and resistant strains in preclinical studies and is notable for progressing to early-phase clinical evaluation, making it one of the few natural compounds with translational advancement (Table 1) [25].

Table 1. Natural products exhibiting anti-TB potential with their bioactive compounds, biological origins, mechanisms of action, and reported activity against *M. tuberculosis*.

Natural Source	Bioactive Compound(s)	Mechanism of Action	Reported Anti-TB Activity	MIC / IC_{50}*	Synergy	Refs.
Nigella sativa	Thymoquinone	ROS generation, membrane damage	Inhibits *M. tuberculosis* growth (*in vitro*)	MIC: 25-50 µg/mL	Limited data	[26]
Stephania tetrandra	Tetrandrine	Efflux pump inhibition, autophagy	Enhances intracellular killing	MIC: NR	FIC: 0.31-0.45	[27]
Piper nigrum	Piperine	Efflux inhibition, bioavailability enhancer	Moderate activity + drug potentiation	MIC < 100 µg/mL	RIF synergy	[28]
Camellia sinensis	EGCG	Cell wall stress, oxidative damage	Inhibits *M. tuberculosis* H37Rv	MIC: 12.5 µg/mL	Additive effect	[29]
Curcuma longa	Curcumin	Immunomodulation, autophagy	Reduces intracellular survival	MIC: 4 to 28 mg/ml	INH/RIF potentiation	[30]
Burkholderia gladioli	Gladiolin	RNA polymerase inhibition	Potent antimycobacterial activity	MIC: 0.06 µg/mL	Active *vs.* resistant strains	[31]
Anogeissus leiocarpa	Polyphenolics	Membrane disruption	Activity *vs.* replicating bacilli	MIC: 16 µg/mL	NR	[32]
Cassia fistula	Anthraquinones	Cell wall perturbation	Moderate bactericidal activity	MIC: 12.5 µg/mL	NR	[33]
Podocarpus totara	Totarol	Respiratory inhibition	Active against clinical isolates	MIC: 8 µg/mL	~2× MIC reduction with INH	[34]

Critical Perspective: Compounds from alternative natural reservoirs remain underexplored. Many show promising laboratory activity, but validation in animal models and human studies is still insufficient.

3. Classes of Anti-TB Natural Products

The data summarized in Table 2 highlight the structural and mechanistic diversity of natural compounds exhibiting anti-TB activity. Each chemical class contributes uniquely to the inhibition of *M. tuberculosis* through distinct targets and pathways. Polyphenols such as resveratrol, curcumin, and bergenin have been widely recognized for their antioxidant, anti-inflammatory, and immunomodulatory properties, which can enhance host defense mechanisms and disrupt mycobacterial metabolic functions. Flavonoids like quercetin and isorhamnetin further contribute to antimycobacterial effects by inhibiting key enzymes involved in bacterial cell wall synthesis and energy metabolism [35].

Alkaloids, including berberine, piperine, and tetrandrine, demonstrate remarkable potential as both direct inhibitors and adjuvant–enhancing the efficacy of standard anti-TB drugs through mechanisms such as efflux pump inhibition and increased intracellular drug retention. Terpenoids like totarol, derived from gymnosperms, target bacterial membrane integrity and respiratory enzymes, thereby exerting bactericidal effects. Similarly, macrolides and polyketides such as gladiolin represent a promising new class of bacterial-derived compounds that inhibit RNA polymerase at non-RIF binding sites, showing activity even against drug-resistant strains [36].

Table 2. Representative classes of natural compounds with anti-TB potential, their key sources, and reported biological activity including MIC values and experimental models.

Class	Compound	Source	Reported Activity / MIC*	Experimental Model	Refs.
Polyphenol	Resveratrol	Grapes (*Vitis vinifera*)	MIC: 64 µg/mL against *M. tuberculosis*	*In vitro*	[36]
Polyphenol	Curcumin	*Curcuma longa*	Inhibits intracellular survival of *M. tuberculosis*; adjunct immunomodulatory	Macrophage / animal	[37]
Flavonoid	Quercetin	Fruits, vegetables	Inhibits D-alanine-D-alanine ligase (cell wall synthesis target); antimycobacterial activity reported	Enzyme + *In vitro*	[38]
Alkaloid	Piperine	*Piper nigrum*	*Enhances RIF efficacy via efflux pump inhibition (no standalone MIC)*	*In vitro* (combination study)	[39]
Terpenoid derivative	Isoxazole curcuminoids	Synthetic (curcumin analogs)	MIC: 0.09-0.78 µg/mL (MDR-TB strains)	*In vitro*	[40]
Natural antibiotic	Ecumicin	Actinomycetes	MIC: ~0.26 µg/mL; targets ClpC1; active *in vivo*	*In vitro* + animal	[41]
Natural antibiotic	Gladiolin	*Burkholderia gladioli*	MIC: 0.06 µg/mL; RNA polymerase inhibitor	*In vitro*	[42]
Polyphenol	EGCG	Green tea (*Camellia sinensis*)	Enhances anti-TB drug activity; reduces bacterial survival	*In vitro* (combination)	[39]

4. Mechanisms of Action

4.1 Inhibition of *M. tuberculosis* Cell Wall, Protein Synthesis, and Nucleic Acid Metabolism

The survival of *M. tuberculosis* depends on several essential biological pathways, among which cell wall biosynthesis, protein translation, and nucleic acid metabolism are of primary importance. These pathways remain highly attractive therapeutic targets because they are indispensable for bacterial viability and sufficiently distinct from host cellular systems. *M. tuberculosis* possesses a specialized lipid-rich cell envelope composed of peptidoglycan, arabinogalactan, and mycolic acids, which contributes to intrinsic resistance against environmental stress and many antimicrobial agents. Consequently, disruption of cell wall assembly remains one of the most effective anti-TB strategies (Figure 1) [41].

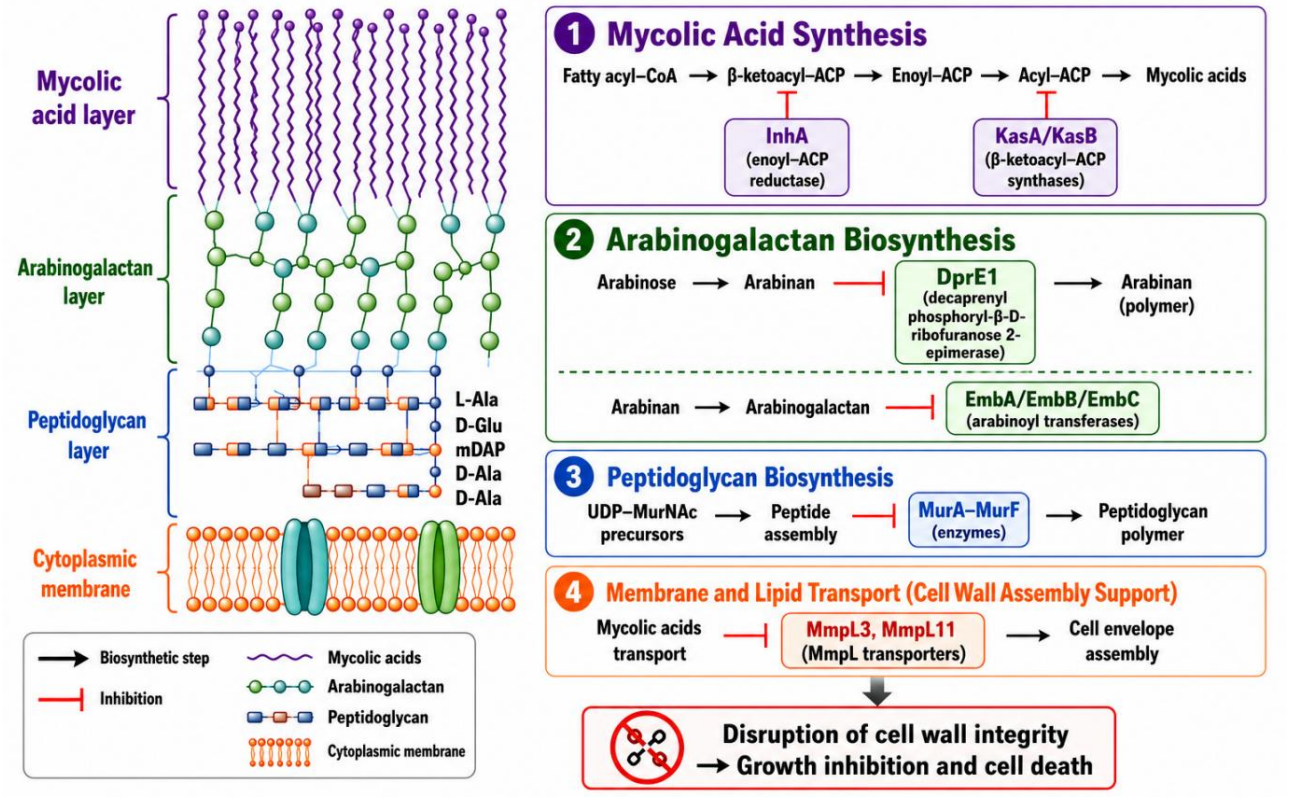

Figure 1. Inhibition of cell wall biosynthesis pathways in *M. tuberculosis* by natural products and anti-TB agents.

Figure 1 highlights the essential cell wall biosynthetic pathways of *M. tuberculosis*, including mycolic acid, arabinogalactan, and peptidoglycan assembly, which collectively maintain structural integrity and contribute to intrinsic drug resistance. Key enzymes such as InhA, DprE1, Emb proteins, and Mur enzymes represent validated molecular targets inhibited by both conventional anti-TB drugs and emerging natural compounds. Disruption of these interconnected pathways compromises cell envelope stability, leading to impaired growth and eventual bacterial death. The figure also emphasizes membrane-associated transport processes, such as MmpL-mediated lipid trafficking, as critical supporting mechanisms in cell wall assembly.

Several established anti-TB drugs target this pathway. INH and ethionamide inhibit InhA, an enoyl-acyl carrier protein reductase required for mycolic acid synthesis, whereas resistance frequently involves mutations in katG**,** inhA promoter regions**,** or compensatory pathways. EMB inhibits arabinosyl transferases encoded by the embCAB operon involved in arabinogalactan formation. DprE1 inhibitors such as benzothiazinones have shown strong preclinical and emerging clinical relevance through inhibition of arabinan biosynthesis. DprE1 is considered a genetically validated TB target, and benzothiazinone susceptibility has been linked to covalent interaction with the catalytic Cys38**7** residue. Multiple natural phytochemicals with lipophilic properties have demonstrated *in vitro* membrane-disruptive or permeability-enhancing effects that may sensitize *M. tuberculosis* to conventional drugs, although confirmatory macrophage, animal, and human data remain limited [42].

Protein synthesis is another validated target in *M. tuberculosis*. Streptomycin binds the 30S ribosomal subunit and induces translational errors, whereas linezolid inhibits formation of the initiation complex on the 50S ribosomal subunit. Several natural metabolites have shown *in vitro* ribosomal inhibitory effects or additive interactions with existing protein synthesis inhibitors, but most remain at an early discovery stage without *in vivo* confirmation. Nucleic acid metabolism is equally critical for replication and persistence [43]. RIF inhibits the β-subunit of RNA polymerase, while fluoroquinolones such as moxifloxacin inhibit DNA gyrase. Resistance to RIF commonly arises through mutations within the rpoB RIF resistance-determining region (RRDR), whereas fluoroquinolone resistance is associated with mutations in gyrA and gyrB**.** Natural products including gladiolin have demonstrated potent *in vitro* activity through inhibition of RNA polymerase at a binding region distinct from the RIF-associated pocket, potentially preserving activity against selected RIFn-resistant strains. However, translational validation beyond laboratory models remains limited [44].

Critical Perspective: Although cell wall and nucleic acid targets remain clinically validated, resistance mutations in katG, inhA, rpoB, gyrA**,** and gyrB **c**ontinue to compromise treatment outcomes. Most natural compounds targeting these pathways are supported mainly by *in vitro* evidence; therefore, progression into macrophage, animal, and clinical studies is essential.

4.2 Energy Metabolism Disruption and Efflux Pump Inhibition

Energy metabolism has emerged as a highly promising target in *M. tuberculosis* because the pathogen can persist in metabolically altered states during latent infection. ATP generation, redox homeostasis, and membrane potential are essential for both actively replicating and dormant bacilli. Interference with these processes can therefore eliminate bacterial populations that are less susceptible to conventional antibiotics [14]. A clinically validated example is bedaquiline, which selectively inhibits the c-subunit (AtpE) of mycobacterial ATP synthase. By blocking ATP production, bedaquiline induces severe energy depletion and shows proven efficacy against MDR and extensively XDR-TB, including activity against non-replicating bacilli [45]. Resistance-associated mutations have been reported in *atpE* as well as regulatory changes involving *Rv0678*, which can alter susceptibility through efflux-related mechanisms. Recent advances in synthesis and manufacturing, including continuous-flow processes and scalable production strategies, are improving accessibility and cost-effectiveness [46].

In addition to ATP synthase inhibition, disruption of the proton motive force (PMF) represents another critical metabolic vulnerability in *M. tuberculosis*. PMF is essential for ATP synthesis, nutrient transport, and maintenance of membrane integrity. Additional validated respiratory targets include cytochrome bc1-aa3 oxidase (QcrB) and menaquinone-dependent electron transport pathways, which are particularly important for the survival of persistent bacilli [47]. Efflux-mediated tolerance in *M. tuberculosis* contributes significantly to intrinsic and acquired drug resistance [48]. Key mycobacterial efflux systems include MmpL5-MmpS5, Tap (Rv1258c), and other ATP-binding cassette (ABC) transporters that reduce intracellular drug accumulation [49]. Overexpression of these transporters has been associated with reduced susceptibility to first-line and second-line anti-TB drugs in resistant clinical isolates [48]. Natural alkaloids such as reserpine and berberine derivatives have demonstrated efflux inhibitory activity in experimental systems, including reduced intracellular drug efflux and modulation of MIC values [50]. Additionally, tetrandrine has been reported in preclinical studies to enhance intracellular retention of anti-TB agents through efflux modulation [50]. However, direct molecular validation of specific transporter binding sites in *M. tuberculosis* remains limited for many of these compounds.

The combination of metabolic inhibitors with efflux pump blockers represents a rational multitarget strategy. Simultaneous disruption of energy homeostasis and inhibition of drug extrusion can enhance intracellular drug accumulation and improve bactericidal efficacy against both replicating and persistent *M. tuberculosis* populations [48].

Critical Perspective: Although strong mechanistic evidence supports both energy metabolism and efflux inhibition as therapeutic strategies, most natural product-based efflux inhibitors remain at the preclinical stage. Future progress will depend on improving selectivity, pharmacokinetic stability, and toxicity profiles, along with validation in *in vivo* models and clinical studies specifically targeting *M. tuberculosi*s.

4.3 Host-Directed Immunomodulation

HDT focuses on strengthening host immune defenses and limiting excessive inflammatory damage rather than directly targeting *M. tuberculosis* [51,52]. Since TB pathology is strongly influenced by the host immune response, modulation of immune pathways may enhance bacterial clearance, reduce tissue destruction, and improve treatment outcomes when used as an adjunct to standard chemotherapy [53]. Curcumin, resveratrol, and EGCG have been reported in preclinical studies to modulate key immunometabolic signaling pathways, including AMP-activated protein kinase (AMPK) activation, mechanistic target of rapamycin (mTOR) suppression, and nuclear factor kappa B (NF-κB) inhibition, which are central regulators of macrophage autophagy and inflammatory signaling [54,55]. These effects collectively promote autophagic flux in infected macrophages, thereby enhancing phagolysosomal fusion and intracellular clearance of *M. tuberculosis*.

Macrophages serve as the primary cellular niche for *M. tuberculosis* survival; therefore, they represent a central target for host-directed strategies [53]. Natural compounds such as curcumin, bergenin, and resveratrol have demonstrated, in cell-based and macrophage infection models, enhanced antimicrobial activity through increased reactive oxygen species (ROS) production, nitric oxide (NO) generation, and cytokine regulation associated with protective M1 macrophage polarization [53]. In some preclinical animal studies, these compounds have also been linked to improved Th1-type immune responses, contributing to granuloma stabilization and enhanced intracellular killing [52]. Autophagy is a key intracellular defense mechanism against *M. tuberculosis*, which can actively block phagosome maturation to ensure its survival; compounds such as resveratrol, EGCG, piperine, and curcumin have been shown in preclinical studies to restore autophagic flux via AMPK activation or mTOR inhibition, thereby promoting lysosomal degradation of intracellular bacilli [55].

Excessive inflammatory responses during TB infection can contribute to pulmonary tissue damage. Polyphenolic compounds such as silymarin and luteolin exhibit antioxidant and anti-inflammatory effects through suppression of NF-κB signaling and reduction of oxidative stress in experimental systems, supporting their role as adjuncts to limit host-mediated pathology during prolonged therapy [56]. Furthermore, modulation of host immunometabolism is emerging as an important therapeutic strategy; compounds such as resveratrol may enhance mitochondrial function through SIRT1 activation, thereby improving cellular energy homeostasis and immune competence in infected host cells [52].

Critical Perspective: Although HDT offers a promising strategy by exerting minimal selective pressure on bacteria, the current evidence base is largely restricted to *in vitro* cell culture and animal studies. Importantly, while similar immunological pathways are studied in other infectious disease models, this section specifically focuses on host–*M. tuberculosis* interactions. Well-designed clinical trials are required to establish optimal dosing, safety, and compatibility with standard anti-TB regimens before clinical translation.

4.4 Activity Against Drug-Resistant and Latent TB

Drug-resistant and latent tuberculosis remain major barriers to global TB elimination (WHO) [57]. MDR-TB, XDR-TB, and RIF-resistant TB require prolonged treatment with costly, toxic, and complex multidrug regimens, while latent TB infection serves as a long-term reservoir for disease reactivation [56]. Therefore, there is an urgent need for novel agents capable of targeting resistant and persistent bacillary populations [56].

Gladiolin has emerged as a promising natural macrolide with potent *in vitro* activity against *M. tuberculosis*. It inhibits bacterial RNA polymerase at a binding site distinct from RIF, suggesting a reduced likelihood of cross-resistance associated with common rpoB mutations [58]. However, current evidence is restricted to *in vitro* systems, and there is a lack of *in vivo* efficacy and clinical pharmacokinetic data; further validation in animal infection models and pharmacological studies is required [58].

Thymoquinone, the principal bioactive constituent of *Nigella sativa*, exhibits antimycobacterial, antioxidant, and immunomodulatory properties. It has demonstrated activity in *in vitro* assays and intracellular macrophage infection models, including against selected resistant strains [59]. Proposed mechanisms include disruption of redox homeostasis and interference with bacterial respiratory processes; however, a definitive molecular target in *M. tuberculosis* has not yet been validated [59]. At present, no clinical anti-TB trials have been reported for thymoquinone.

Tetrandrine has primarily been investigated as a chemosensitizing adjunct rather than a direct antimycobacterial agent. In *in vitro* checkerboard assays and limited cellular infection models, it has been shown to enhance the activity of INH and EMB against resistant isolates, likely through inhibition of efflux-mediated tolerance and modulation of host autophagy pathways [48,50]. Nevertheless, key translational gaps remain, including transporter-specific target validation, pharmacokinetic profiling, and *in vivo* efficacy confirmation. Latent TB infection presents additional therapeutic challenges due to the metabolic dormancy of bacilli, which reduces susceptibility to most conventional antibiotics. Compounds targeting energy metabolism, respiratory pathways, membrane energetics, or host-mediated

intracellular killing may therefore provide potential advantages; however, for most natural products, the supporting evidence remains limited to preclinical *in vitro* or *ex vivo* systems.

The present study highlights the multifactorial nature of drug-resistant tuberculosis (DR-TB) development among pulmonary TB patients and emphasizes the importance of socioeconomic, nutritional, and behavioral determinants in MDR-TB progression. Among the evaluated variables, low body weight, low BMI, lower socioeconomic status, and tobacco use were identified as statistically significant risk factors associated with DR-TB [60]. These findings are consistent with previous epidemiological studies demonstrating that malnutrition and poor socioeconomic conditions impair host immunity, thereby increasing susceptibility to persistent infection, treatment failure, and emergence of resistant *M. tuberculosis* strains. Nutritional deficiency may compromise cell-mediated immune responses, which are essential for controlling intracellular mycobacterial infection, while poverty-related factors such as overcrowding, delayed diagnosis, and limited healthcare access may further contribute to disease transmission and inadequate treatment adherence.

Notably, tobacco use emerged as one of the strongest independent predictors of DR-TB, with logistic regression analysis indicating that tobacco users were approximately 7.77 times more likely to develop drug-resistant disease compared with drug-sensitive TB patients. Tobacco smoke has been reported to impair pulmonary immune defense mechanisms, alter macrophage function, and reduce mucociliary clearance, thereby facilitating mycobacterial persistence and poor therapeutic response. In addition, smoking is frequently associated with reduced treatment compliance and coexisting socioeconomic vulnerabilities, which may collectively enhance the risk of resistance development.

The study also reinforces the growing recognition that DR-TB is not solely a microbiological or pharmacological problem but is strongly influenced by host-related and environmental determinants. Identification of vulnerable populations through risk-factor assessment may therefore support targeted screening strategies, early diagnosis, nutritional intervention programs, smoking cessation initiatives, and improved treatment monitoring. Such integrated public health approaches are particularly important in high-burden settings where MDR-TB continues to compromise TB control programs. Although the study provides valuable regional epidemiological data, limitations including relatively small sample size and restricted geographic representation should be considered while interpreting the findings. Further large-scale multicenter studies are warranted to validate these associations and better define the interaction between socioeconomic, behavioral, and biological determinants contributing to drug-resistant TB [61-63].

Critical Perspective: A substantial translational gap exists between promising laboratory findings and clinically meaningful outcomes. *In vitro* MIC values alone are insufficient predictors of therapeutic success, as pharmacokinetics, lesion penetration, metabolic stability, and toxicity significantly influence *in vivo* efficacy. Importantly, none of the natural compounds discussed in this review have progressed to Phase II or Phase III clinical trials for TB treatment. Rigorous *in vivo* validation, pharmacokinetic optimization, and well-designed clinical studies are essential before clinical integration.

4.5 Clinical Translation Gap and Evidence Stratification

Despite extensive preclinical investigations, the translation of natural products into clinically approved anti-TB therapies remains limited. A key challenge is the poor correlation between *in vitro* antimycobacterial activity and *in vivo* or clinical efficacy. Most compounds demonstrate MIC-based inhibition of *M. tuberculosis* under controlled laboratory conditions; however, these results often fail to translate into therapeutic success due to differences in pharmacokinetics, lesion penetration, and host–pathogen complexity [64,65]. Animal models provide intermediate evidence for several candidate compounds, but variability in infection protocols, dosing strategies, and endpoints limits comparability across studies [49]. Similarly, macrophage infection models offer insight into intracellular activity but do not fully replicate the hypoxic, necrotic, and caseous microenvironments of human pulmonary lesions [65].

Among reviewed compounds, calanolide A represents one of the few natural molecules to reach Phase I clinical evaluation, demonstrating preliminary human safety and tolerability [66]. However, these early studies were not designed to assess anti-TB efficacy endpoints such as sputum conversion or sterilizing activity. Importantly, no compound discussed in this review has progressed to Phase II or Phase III clinical trials for TB, highlighting a major translational gap. This gap is further compounded by limited pharmacokinetic optimization, insufficient pulmonary distribution data, lack of standardized formulations, and weak industrial translation pathways for natural products. Consequently, most candidates remain confined to early discovery or preclinical validation stages.

4.6 Pulmonary Delivery and Lung-Targeted Therapeutic Strategies

TB is fundamentally a pulmonary disease, with *M. tuberculosis* residing within alveolar macrophages and granulomatous lung lesions [67]. Therefore, therapeutic efficacy depends not only on systemic exposure but also on efficient drug delivery to the lung microenvironment. Pulmonary drug delivery systems, including inhalable dry powders, liposomal aerosols, solid lipid nanoparticles, and polymeric nanocarriers, offer a promising strategy to enhance local drug concentration while reducing systemic toxicity [68]. These systems improve macrophage targeting, increase lung retention time, and bypass first-pass hepatic metabolism [69].

Several natural compounds, including curcumin, resveratrol, and EGCG, have shown improved stability, bioavailability, and intracellular uptake when formulated into nanocarriers [70]. Such formulations may enhance their potential as adjunctive anti-TB agents by improving delivery to infected alveolar macrophages. Lung-targeted approaches also address one of the major limitations of natural products—poor oral bioavailability and rapid systemic clearance—by ensuring higher local drug exposure at the primary site of infection [68]. Additionally, dose reduction through targeted delivery may minimize toxicity and improve patient adherence in long-term TB therapy. However, most pulmonary delivery systems for natural compounds remain at preclinical or proof-of-concept stages. Challenges include large-scale manufacturing, regulatory standardization, aerosol stability, and clinical validation of lung deposition efficiency [70].

Critical Perspective: Pulmonary delivery systems represent a highly relevant translational opportunity, but require rigorous clinical validation and regulatory alignment before integration into TB treatment protocols.

4.7 HDT and Immunomodulatory Integration

HDT aims to enhance host immune responses or limit pathological inflammation rather than directly targeting *M. tuberculosis* [52]. This approach is particularly relevant in TB, where disease progression is strongly influenced by host immune dysregulation [53]. Natural compounds such as curcumin, resveratrol, bergenin, luteolin, and EGCG have demonstrated immunomodulatory effects in preclinical studies. These include activation of macrophage bactericidal functions, enhancement of Th1-type immune responses, modulation of NF-κB and MAPK signaling pathways, and regulation of autophagy via AMPK-mTOR axis modulation [54].

Autophagy induction is particularly important, as *M. tuberculosis* can inhibit phagosome maturation to survive intracellularly. Restoration of autophagic flux enhances lysosomal degradation of intracellular bacilli, thereby contributing to host-mediated bacterial clearance [55]. In addition, several polyphenols exhibit antioxidant and anti-inflammatory effects that may reduce tissue damage caused by excessive immune activation during chronic infection. This balance between antimicrobial immunity and inflammation control is critical in pulmonary TB pathology. However, most HDT evidence remains limited to *in vitro* and animal models, with a lack of standardized clinical endpoints and limited translation into controlled human studies [52]. Optimal dosing strategies, long-term safety, and interaction with standard anti-TB regimens remain poorly defined.

Critical Perspective: HDT represents a promising adjunct strategy in TB management, but translation into clinical practice requires robust human studies and validated immunological biomarkers.

4.8 Future Perspectives and Translational Roadmap

The future development of natural products as anti-TB agents requires integration of multidisciplinary approaches, including pharmacology, nanotechnology, systems biology, and artificial intelligence. Advanced drug delivery systems such as nanoparticles, liposomes, and polymeric carriers can address limitations of poor solubility, instability, and low bioavailability. These systems may enable targeted delivery to lung tissue and intracellular compartments, significantly enhancing therapeutic efficacy. Systems biology and network pharmacology approaches can help elucidate multi-target interactions of phytochemicals, allowing identification of synergistic pathways and predictive modeling of therapeutic effects. Similarly, AI-based screening platforms can accelerate identification of promising natural scaffolds from large chemical libraries.

Synthetic biology and metabolic engineering offer additional opportunities for scalable production of bioactive natural compounds, reducing dependency on plant extraction and improving consistency. Importantly, future clinical translation must focus on well-designed Phase II/III trials, standardized formulations, pharmacokinetic validation, and lesion-level drug distribution studies. Integration with existing WHO-recommended TB regimens will also be essential to ensure clinical relevance (Table 3).

Critical Perspective: Natural products are unlikely to replace conventional TB therapy but may play a crucial role as adjuncts, resistance modulators, and host-directed agents in future combination regimens.

Table 3. Comparative overview of selected natural compounds with anti-TB potential, their natural sources, and mechanisms of action.

Parameter	Gladiolin	Thymoquinone	Tetrandrine
Natural Source	*Burkholderia gladioli*	*Nigella sativa* (black seed)	*Stephania tetrandra*
Main Mechanism	Inhibits bacterial RNA polymerase (distinct from RIF binding site)	Induces oxidative stress, modulates host immune response	Efflux pump inhibition; enhances intracellular drug accumulation
Primary Evidence	*In vitro* antimycobacterial studies	*In vitro* + macrophage models (immunomodulatory effects)	*In vitro* + macrophage + combination studies
Reported Activity	Potent activity vs *M. tuberculosis* H37Rv and MDR strains	Reduces intracellular survival of *M. tuberculosis* (host-directed effect)	Enhances susceptibility of drug-resistant *M. tuberculosis*
Representative MIC / Activity	MIC: ~0.06-0.12 μg/mL	MIC: ~25-50 μg/mL (variable)	No strong standalone MIC; synergy-driven effect
Synergy With Standard Drugs	Limited data (novel mechanism focus)	Reported adjunct potential with first-line drugs	Strong synergy with INH / EMB (FIC <0.5)
Drug Resistance Relevance	Active against RIF-resistant strains (novel RNAP site)	Tested in intracellular/resistant models	Reverses efflux-mediated drug resistance
Host Immunomodulation	Limited evidence	Enhances macrophage response, NO production	Autophagy modulation reported
Translational Limitation	Early-stage discovery (no clinical data)	Bioavailability limitations	Toxicity & dose optimization needed
Clinical Status	No clinical trials	No clinical TB trials	No clinical TB trials

Note: Information for Gladiolin from [71]; Thymoquinone from [72,73]; Tetrandrine from [74].

5. Synergistic Combinations with Standard TB Drugs

Combination therapy remains the cornerstone of TB treatment because *M. tuberculosis* rapidly develops resistance when exposed to single-agent therapy. Standard regimens based on INH, RIF, pyrazinamide (PZA), and EMB have substantially improved outcomes; however, prolonged treatment duration, hepatotoxicity, poor adherence, and the emergence of MDR and XDR, TB continue to limit global control efforts [75]. In this context, natural products and resistance-modifying compounds are increasingly being investigated as adjuncts that may enhance antibiotic efficacy, reduce required doses, improve intracellular killing, and delay resistance development.

One of the most studied examples is tetrandrine, a bisbenzylisoquinoline alkaloid isolated from *Stephania tetrandra*. Tetrandrine has demonstrated synergistic activity with INH and EMB in preclinical models, particularly against resistant *M. tuberculosis* isolates. Its proposed mechanism involves inhibition of bacterial efflux systems that normally reduce intracellular antibiotic concentrations. By increasing intracellular retention of companion drugs, tetrandrine may lower effective MIC values and partially restore susceptibility in resistant phenotypes. In addition, tetrandrine has been associated with modulation of host autophagy and phagosome–lysosome fusion in macrophage systems, suggesting dual antibacterial and host-directed benefits. These properties make tetrandrine a promising chemosensitizing adjunct rather than a stand-alone anti-TB drug [76].

Totarol, a diterpenoid phenol obtained from *Podocarpus* species, has also shown potential synergy with first-line agents. Totarol is believed to disrupt membrane energetics and respiratory function, thereby impairing ATP generation and membrane homeostasis in mycobacteria. Such membrane-targeting effects may increase permeability to co-administered drugs and sensitize bacilli to INH or RIF. Because membrane bioenergetics are particularly important in persistent bacilli, totarol-like molecules may also hold value against metabolically adapted subpopulations that are less responsive to conventional chemotherapy [77].

Reserpine, an indole alkaloid from *Rauwolfia serpentina*, is widely recognized as a classical efflux pump inhibitor in antimicrobial research [48]. Although reserpine has limited direct antimycobacterial potency, it has been used experimentally to demonstrate the role of efflux-mediated drug tolerance. By inhibiting transporter-mediated drug extrusion, reserpine can increase intracellular exposure to INH, PZA, and other agents in laboratory models [48]. This supports the broader concept that efflux inhibition may enhance standard regimens and suppress early adaptive resistance mechanisms in *M. tuberculosis*.

Other natural compounds such as piperine, berberine, curcumin, and flavonoid-rich extracts have also shown additive or synergistic interactions with anti-TB drugs in checkerboard assays, macrophage infection models, or small animal studies [49]. Proposed mechanisms include membrane permeabilization, oxidative stress enhancement, inhibition of stress-adaptation responses, and improved drug absorption. For example, piperine has been explored as a bioenhancer capable of altering drug metabolism and improving systemic exposure of co-administered agents [78].

From a translational perspective, synergistic combinations may offer several advantages: (i) reduction in antibiotic dose requirements and associated toxicity, (ii) improved efficacy against intracellular or persistent bacilli, (iii) restoration of activity against partially resistant strains, and (iv) reduced probability of resistance emergence through multi-target pressure. These benefits are especially relevant in MDR-TB, where current regimens remain lengthy, expensive, and frequently associated with adverse effects. However, most evidence for natural product synergy remains limited to *in vitro* checkerboard studies, time-kill assays, macrophage infection systems, or preliminary animal experiments. Quantitative metrics such as fractional inhibitory concentration (FIC) indices, reproducibility across clinical isolates, pharmacokinetic compatibility, and toxicity during prolonged combination use are often insufficiently characterized. In addition, herb–drug interactions affecting cytochrome metabolism or QT prolongation must be carefully evaluated before clinical implementation [79].

Critical Perspective: Synergistic combinations with standard TB drugs represent one of the most realistic near-term applications of natural products in TB therapy. Rather than replacing established regimens, natural compounds may be more valuable as adjunct chemosensitizers, bioenhancers, or host-directed partners. Robust pharmacological validation and controlled clinical studies are still required before these combinations can be recommended for routine practice.

6. Pharmacokinetics and Safety Profiles

The successful development of natural anti-TB agents depends not only on antimycobacterial potency but also on favorable pharmacokinetics, adequate lung and macrophage exposure, metabolic stability, safety, and compatibility with multidrug TB regimens. Although many natural compounds demonstrate promising *in vitro* activity, a large proportion fail during translational development due to poor oral bioavailability, rapid systemic clearance, limited lesion penetration, formulation instability, and clinically relevant drug-drug interactions. In this context, bergenin, luteolin, and calanolide A represent important examples highlighting both the potential and limitations of natural-product-based TB drug discovery [80].

6.1 Bergenin

Bergenin, a C-glycoside derivative of 4-O-methyl gallic acid isolated from *Bergenia* species and related medicinal plants, has primarily been investigated as a host-directed adjunct rather than a direct bactericidal anti-TB agent. Preclinical pharmacokinetic studies indicate rapid oral absorption but short systemic persistence, with a relatively short elimination half-life suggesting rapid metabolic clearance [81]. From a translational perspective, such rapid clearance may reduce systemic toxicity but also limits sustained exposure required for direct antimycobacterial activity. Therefore, bergenin may be more suitable as an adjunct immunomodulator or as a candidate for formulation improvement strategies such as nano-delivery systems, sustained-release formulations, or prodrug approaches [82]. Mechanistically, bergenin has been reported in preclinical models to enhance Th1/Th17 immune responses, activate macrophages, and stimulate autophagy pathways that may contribute to improved intracellular clearance of *M. tuberculosis*. However, human pharmacokinetic data, pulmonary distribution studies, and TB-specific clinical trials remain unavailable [83].

Critical Perspective: Bergenin shows promise as a host-directed adjunct, but its short half-life, limited human PK data, and lack of defined exposure–response relationships remain key barriers to clinical translation.

6.2 Luteolin

Luteolin is a naturally occurring flavone widely present in fruits, vegetables, and medicinal plants. It is recognized for antioxidant, anti-inflammatory, and cytoprotective properties that may be beneficial during prolonged TB therapy [84]. Compared with rapidly eliminated phytochemicals, luteolin exhibits moderate systemic persistence in preclinical pharmacokinetic studies, suggesting a comparatively favorable exposure profile. Its principal translational relevance lies in host protection rather than direct antimycobacterial activity. Luteolin has been shown to reduce oxidative stress, modulate NF-κB/MAPK signaling pathways, and attenuate hepatocellular injury in experimental systems. These effects are particularly relevant because hepatotoxicity remains a major limitation of first-line TB regimens, including INH-, RIF-, and PZA-based therapies. Although luteolin demonstrates acceptable safety in preclinical studies, TB-specific human data are lacking. Given its potential to modulate cytochrome P450 enzymes and drug transporters, systematic evaluation of drug–drug interactions with anti-TB drugs is essential before clinical co-administration [5].

Critical Perspective: Luteolin should be considered a supportive adjunct agent for inflammation control and toxicity mitigation rather than a primary anti-TB compound. Clinical pharmacokinetic validation and interaction studies remain necessary.

6.3 Calanolide A

Calanolide A, a coumarin-derived natural product isolated from *Calophyllum* species, is among the more clinically advanced natural compounds discussed in this review. Initially developed for antiviral applications, it has also demonstrated *in vitro* activity against both drug-susceptible and drug-resistant *M. tuberculosis* strains [85]. Importantly, calanolide A has undergone Phase I clinical evaluation in humans, where it demonstrated acceptable short-term tolerability, with predominantly mild adverse effects such as nausea and headache. However, these studies were

designed to assess safety rather than anti-TB efficacy, and therefore do not provide evidence of therapeutic effectiveness against TB. Accordingly, Phase I completion should be interpreted strictly as preliminary human safety confirmation [85].

The precise molecular target of calanolide A in *M. tuberculosis* remains incompletely defined, with proposed mechanisms involving interference with nucleic acid processes or other essential bacterial pathways. Further studies are required to establish pharmacodynamic targets, intracellular activity, lesion penetration, and compatibility with standard TB regimens such as RIF-, linezolid-, or bedaquiline-based combinations. Importantly, no Phase II or Phase III clinical trials evaluating calanolide A specifically for TB have been reported, and its clinical utility in TB remains exploratory.

Critical Perspective: Calanolide A represents one of the more translationally advanced natural compounds due to existing human safety data; however, its anti-TB efficacy, target validation, and regimen-level clinical evidence remain insufficient.

6.4 Ecumicin

Ecumicin is a novel cyclic peptide antibiotic obtained from microbial natural sources that has emerged as a promising candidate for TB therapy, particularly against MDR *M. tuberculosis*. Studies have demonstrated that ecumicin exerts potent antimycobacterial activity through inhibition of the ClpC1 ATPase complex, a critical regulator of bacterial protein homeostasis and stress response. This unique mechanism of action distinguishes ecumicin from conventional anti-TB drugs and highlights its potential role in overcoming existing drug resistance. In addition to strong *in vitro* activity, ecumicin has shown encouraging efficacy in macrophage and animal infection models, suggesting possible utility in future therapeutic strategies. Moreover, its potential synergistic interaction with standard anti-TB agents may contribute to improved treatment outcomes and reduced resistance development. Despite these promising findings, further investigations are required to address limitations related to pharmacokinetics, safety, formulation, and clinical validation before ecumicin can progress toward therapeutic application.

Recent advances in the synthesis and process development of Bedaquiline and its next-generation analogues have been briefly incorporated to better contextualize the discussion on anti-TB drug development. Although bedaquiline remains one of the most effective agents for the treatment of MDR-TB, its high production cost, synthetic complexity, and scalability limitations continue to restrict broader clinical accessibility. Therefore, recent innovations in asymmetric synthesis and manufacturing technologies are highly relevant to the current review, particularly in the context of developing safer, scalable, and economically feasible anti-TB therapeutics.

Recent studies have reported substantial progress in asymmetric catalytic strategies for bedaquiline and related diarylquinoline derivatives. A cooperative bimetallic activation and non-covalent interaction-promoted strategy enabled the first highly enantioselective asymmetric synthesis of bedaquiline, achieving excellent stereoselectivity (> 99% ee; 16:1 dr) together with successful gram-scale synthesis, thereby demonstrating significant industrial potential [86]. Subsequently, synergistic Li/Li bimetallic catalytic systems were successfully applied for the asymmetric synthesis of advanced analogues including TBAJ-587 and TBAJ-876 [87]. These methodologies provided high yields, improved stereocontrol, and scalable preparation of structurally optimized diarylquinoline derivatives [88,89]. Importantly, TBAJ-587 demonstrated promising pharmacological advantages, including potent antimycobacterial activity, lower toxicity, and improved pharmacokinetic properties compared with the parent compound bedaquiline.

Further advances were achieved through process intensification and continuous-flow manufacturing technologies. In continuous-flow synthesis of TBAJ-876 significantly improved reaction robustness, operational safety, scalability, and production efficiency, while enabling successful 100 g-scale preparation compared with conventional batch methodologies [90], Such approaches are particularly important for safer handling of reactive organolithium intermediates and may facilitate future industrial-scale manufacturing. In addition, the recent review [91] comprehensively summarized recent developments in asymmetric catalysis, continuous-flow synthesis, green chemistry principles, and sustainable manufacturing approaches for bedaquiline and its analogues.

6.5 Translational Evidence Gap and Clinical Relevance

A critical limitation across the natural compounds discussed in this review is the strong dependence on *in vitro* and early preclinical evidence, with relatively limited validation in robust *in vivo* infection models and very scarce clinical data in humans [56,90]. While several phytochemicals and natural products demonstrate promising minimum inhibitory concentrations (MICs), macrophage intracellular activity, and efficacy in selected animal models, these outcomes do not consistently translate into clinical effectiveness due to complex pharmacokinetic constraints, inadequate lesion penetration, metabolic instability, and the multifactorial nature of host–pathogen interactions in TB [14,90]. In particular, the distinction between preclinical activity and clinical efficacy must be clearly emphasized. Many reported effects are derived from cell-based assays or murine models, which do not fully replicate human pulmonary TB pathology, including caseous granulomas, hypoxic microenvironments, and intracellular persistence of *M. tuberculosis* [67]. Consequently, apparent *in vitro* potency may overestimate therapeutic potential in real-world clinical settings.

With respect to clinical translation, calanolide A represents one of the few compounds that has progressed to Phase I human evaluation; however, these studies primarily assessed safety and tolerability rather than anti-TB efficacy

endpoints [66]. Therefore, its clinical relevance in TB treatment remains unconfirmed. Importantly, none of the natural compounds discussed in this review have yet advanced to Phase II or Phase III clinical trials specifically for TB [56], highlighting a major translational gap.

7. Synergistic Combinations with Standard Anti-TB Drugs and Evidence Stratification

The increasing burden of MDR and XDR, *M. tuberculosis* has intensified interest in combination strategies that enhance the efficacy of existing anti-TB drugs [56]. Natural compounds are particularly attractive as adjuncts because they may restore drug susceptibility, inhibit resistance mechanisms, enhance intracellular drug accumulation, and potentially reduce required dosages and associated toxicity [48]. However, most reported synergistic effects are currently based on *in vitro* checkerboard assays, MIC reduction studies, or macrophage infection models, while robust *in vivo* and clinical validation remains limited [65].

7.1 Tetrandrine as an Efflux Pump Inhibitor

Tetrandrine, a bisbenzylisoquinoline alkaloid derived from *Stephania tetrandra*, is one of the most extensively studied natural adjuncts in TB research. *In vitro* studies have demonstrated that tetrandrine can reduce the MICs of INH and EMB when used in combination. Its primary mechanism is attributed to inhibition of mycobacterial efflux systems, thereby increasing intracellular retention of anti-TB drugs and partially restoring susceptibility in resistant strains [48]. In macrophage infection models, tetrandrine has also been associated with enhanced intracellular killing, potentially through modulation of autophagy and improved phagosome–lysosome fusion [55].

Critical Perspective: Although tetrandrine shows mechanistic promise as an adjunct therapy, its clinical translation is limited by insufficient *in vivo* efficacy data, safety profiling at therapeutic doses, and lack of controlled clinical TB studies.

7.2 Totarol as a Membrane and Bioenergetic Potentiator

Totarol, a diterpenoid phenol isolated from *Podocarpus* species, has demonstrated synergistic activity with INH in *in vitro* models. Its proposed mechanism involves disruption of bacterial membrane integrity and interference with respiratory energy metabolism [90]. By compromising membrane homeostasis, totarol may enhance intracellular penetration of co-administered drugs while simultaneously impairing bacterial energy production [64]. Current evidence is largely restricted to *in vitro* systems, and comprehensive *in vivo* pharmacokinetic, toxicity, and efficacy data are lacking [65].

7.3 Reserpine and Related Alkaloids

Reserpine, obtained from *Rauwolfia serpentina*, has been investigated primarily as an efflux pump inhibitor in *M. tuberculosis*. It enhances intracellular retention of drugs such as INH and PZA by inhibiting transporter-mediated efflux mechanisms [48]. Although reserpine exhibits weak direct antimycobacterial activity, its primary role is as a resistance-modifying adjuvant. Other plant-derived alkaloids, including berberine-related compounds, have shown similar efflux inhibitory potential, although most remain at a preliminary stage of evaluation [50]. Despite mechanistic relevance, systemic pharmacological effects of reserpine may limit clinical applicability, necessitating development of safer derivatives or analogues [48].

7.4 Host-Directed Synergistic Combinations

Certain natural compounds enhance standard anti-TB therapy indirectly by modulating host immune responses or reducing drug-associated toxicity. Examples include curcumin, silymarin, EGCG, and resveratrol, which regulate inflammatory signaling and autophagy pathways [53]. Host-directed synergistic strategies may be particularly valuable for long-term TB therapy; however, standardized human clinical evidence remains insufficient.

7.5 Quantitative Synergy Assessment

Reliable evaluation of drug synergy requires standardized quantitative metrics, including FIC index, fold reduction in MIC, time-kill kinetics, and intracellular bacterial burden reduction assays [91,92]. A significant limitation in current literature is the frequent qualitative reporting of “synergy” without standardized numerical validation, limiting reproducibility and cross-study comparison. Future studies should consistently incorporate quantitative synergy metrics along with pharmacodynamic validation to strengthen translational relevance [92,93].

7.6 Summary of Translational Evidence

Overall, synergistic combinations involving natural compounds are predominantly supported by *in vitro* checkerboard assays and macrophage infection models, with limited progression into animal studies and very few controlled clinical investigations [77]. While combination therapy represents one of the most promising translational applications of

natural products in TB management, robust preclinical validation and clinical trials are essential before therapeutic adoption.

8. Future Perspectives

The future of natural product–based anti-TB drug discovery depends on overcoming key translational barriers through integrated approaches combining pharmacology, formulation science, systems biology, medicinal chemistry, and regulatory innovation. Although many phytochemicals demonstrate promising antimycobacterial activity *in vitro*, their progression to clinical use is frequently limited by poor aqueous solubility, rapid metabolism, low oral bioavailability, and inconsistent exposure at pulmonary infection sites. Advanced drug-delivery systems may help address these issues. Nanotechnology-based platforms such as solid lipid nanoparticles, polymeric micelles, liposomes, inhalable dry-powder carriers, and phytosomes are being investigated to improve stability, controlled release, macrophage targeting, and lung deposition. For compounds such as curcumin and EGCG, nanoformulations have shown improved pharmacokinetic behavior and sustained therapeutic exposure in preclinical studies. Future work should emphasize scalable manufacturing, cost-effectiveness, long-term stability, and compatibility with TB treatment programs in resource-limited settings. Integration of omics technologies and systems biology is also expected to accelerate discovery and validation. Metabolomics, transcriptomics, proteomics, and chemoinformatics can help identify active constituents from complex botanical extracts and clarify their molecular targets in *M. tuberculosis* or host cells. These approaches are particularly valuable for multi-component herbal preparations in which synergistic activity may arise from several metabolites rather than a single dominant compound. Network pharmacology and computational modeling can further map compound-target-pathway interactions, predict multitarget efficacy, identify liabilities, and prioritize leads before expensive animal studies.

Synthetic biology provides another promising route for sustainable production. Microbial engineering platforms using *Escherichia coli*, *Saccharomyces cerevisiae*, and other hosts are being developed to biosynthetically produce plant-derived metabolites and their precursors under controlled fermentation conditions. This may reduce dependence on seasonal harvesting, batch variability, and ecological pressure on medicinal plants. Future optimization should focus on pathway yield, downstream purification efficiency, and regulatory acceptance of bioengineered natural products. Clinical translation remains the major bottleneck. Many candidates fail because *in vitro* potency does not translate into adequate *in vivo* exposure, intracellular penetration, lesion distribution, or acceptable safety margins. Therefore, future development should incorporate clear pharmacological benchmarks such as low micromolar or sub-micromolar MIC values, selectivity over mammalian cells, activity in macrophage infection models, efficacy in animal TB models, favorable oral or inhaled pharmacokinetics, and compatibility with multidrug regimens. Adaptive trial designs, biomarker-guided studies, and real-world evidence models may help accelerate early clinical evaluation. Digital adherence tools, wearable monitoring systems, and mobile health platforms could also support longitudinal assessment of outcomes, toxicity, and compliance during adjunctive therapy studies.

Standardization remains essential for botanical therapeutics. Pharmacopeia-grade reference extracts, validated manufacturing processes, and chemometric fingerprinting using HPLC, LC-MS, NMR, and related methods can improve batch-to-batch consistency. Integration of machine learning with analytical profiling may further strengthen quality control and traceability. Regulatory frameworks may also need to evolve to better evaluate multi-component botanical drugs while maintaining modern standards of safety, efficacy, and reproducibility. Safety evaluation must progress beyond traditional empirical use claims. High-throughput toxicology screening, organ-on-chip systems, predictive AI toxicology, and pharmacogenomic tools may help identify hepatotoxicity, cardiotoxicity, nephrotoxicity, and clinically relevant herb–drug interactions earlier in development. This is particularly important in TB patients receiving prolonged multidrug therapy, where CYP-mediated interactions or QT-prolonging combinations may become clinically significant.

9. Conclusion

Natural products remain a valuable and scientifically relevant source for the discovery of new anti-TB therapeutics. Compounds derived from plants, microbes, and marine organisms have demonstrated activity against *M. tuberculosis*, including drug-sensitive, MDR, and persistent phenotypes that are often difficult to eradicate with conventional therapy. Candidates such as bergenin, berberine, curcumin, resveratrol, gladiolin, tetrandrine, and calanolide A have shown direct antimycobacterial, resistance-modifying, or host-directed immunomodulatory effects in preclinical systems.

However, enthusiasm must be balanced with translational reality. Most natural compounds remain confined to *in vitro*, macrophage, or early animal studies, and only a very limited number have entered formal human evaluation. Importantly, no natural anti-TB compound discussed in this review has yet progressed to Phase II or Phase III clinical trials specifically for TB treatment. Favorable MIC values alone do not ensure clinical success, as many candidates fail because of modest potency *in vivo*, poor solubility, rapid metabolism, inadequate lesion or lung penetration, toxicity concerns, lack of standardization, and manufacturing complexity. In many cases, promising laboratory findings have not yet demonstrated clear superiority or additive benefit over established WHO-recommended regimens.

Future progress will require rigorous prioritization of candidates using defined translational criteria, including reproducible activity against clinical isolates, efficacy in intracellular and dormant bacilli models, synergy with current regimens, acceptable pharmacokinetics, safety during prolonged dosing, and validated efficacy in relevant animal and human studies. Structure-activity relationship optimization, semisynthetic derivatization, inhaled or nanoformulation approaches, and AI-assisted target discovery may substantially improve success rates.

From a translational and clinical respiratory medicine perspective, the ultimate success of natural product–based anti-TB strategies will depend on their ability to demonstrate meaningful benefits in pulmonary disease outcomes, including improved drug penetration into lung lesions, enhanced intracellular clearance of *M. tuberculosis*, reduced treatment duration, and improved patient adherence. Given that TB is fundamentally a lung-centered disease, future therapeutic development must prioritize pulmonary pharmacokinetics, lesion-specific drug exposure, and host-pathogen interactions within the respiratory microenvironment. Importantly, despite encouraging preclinical findings, none of the natural compounds discussed in this review have yet advanced to Phase II or Phase III clinical trials for TB, highlighting a critical translational gap. Bridging this gap will require rigorous clinical validation, integration with existing WHO-recommended regimens, and development of lung-targeted delivery systems to achieve clinically meaningful impact.

Importantly, the greatest near-term value of natural products may lie in three areas: (i) serving as novel chemical scaffolds for next-generation anti-TB drug development, (ii) functioning as adjuncts that enhance existing therapy or reduce resistance emergence, and (iii) supporting host-directed strategies that limit pulmonary inflammation and improve bacterial clearance. With scientifically rigorous development and clinical validation, natural products may contribute meaningfully to future TB control strategies.

Acknowledgements

The authors sincerely acknowledge Government Danteshwari Post Graduate College, Dantewada, Chhattisgarh, India, for providing academic support and access to literature resources that facilitated the preparation of this review article.

Funding

No funding's received.

Ethics Statement

This study did not involve human participants or animals and therefore did not require ethical approval.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

Dharna Thakur: Conceptualization, literature review, writing–original draft. Mithlesh Mahilang: Supervision, review and editing, correspondence. Mamta Tripathi: Literature review, data curation, review and editing.

Conflict of Interest

The authors declare that they have no conflict of interest.

Generative AI Statement

The authors declare that no Gen AI was used in the creation of this manuscript.

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