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REVIEW

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Host-directed therapy for tuberculosis

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Abstract

Current TB treatment regimens are hindered by drug resistance, numerous adverse effects, and long treatment durations, highlighting the need for 'me-better' treatment regimens. Host-directed therapy (HDT) has gained recognition as a promising approach in TB treatment. It allows the repurposing of existing drugs approved for other conditions and aims to enhance the effectiveness of existing anti-TB therapies, minimize drug resistance, decrease treatment duration, and adverse effects. By modulating the host immune response, HDT ameliorates immunopathological damage and improves overall outcomes by promoting autophagy, antimicrobial peptide production, and other mechanisms. It holds promise for addressing the challenges posed by multiple and extensively drug-resistant *Mycobacterium tuberculosis* strains, which are increasingly difficult to treat using conventional therapies. This article reviews various HDT candidates, including repurposed drugs, explores their underlying mechanisms such as autophagy promotion and inflammation reduction, while emphasizing their potential to improve TB treatment outcomes and outlining future research directions.

Keywords *Mycobacterium tuberculosis*, Tuberculosis, Infectious diseases, Host response, Host-directed therapy

Introduction

Tuberculosis (TB) is a chronic infectious disease caused by *Mycobacterium tuberculosis* (*M.tb*) and is the second leading cause of death from infectious diseases worldwide, following coronavirus disease 2019. TB remains a global public health issue, posing a serious threat to human health. The World Health Organization 2022 report estimates 10.6 million new cases of TB and 1.6 million associated deaths [1]. Currently, the main treatment regimen for TB involves a multidrug chemotherapy administered for at least six months. However, this regimen often involves prolonged courses of multiple antibiotics, which can lead to poor patient compliance, the emergence of multidrug-resistant TB (MDR-TB), and adverse reactions [2]. Therefore, there is a pressing need to explore alternative therapeutic approaches.

Host immune response is critical to the pathogenesis of TB. As a novel therapeutic approach, host-directed therapy (HDT) has gained attention as an avenue for improving treatment outcomes of drug-resistant TB and is being increasingly explored as an adjunct TB treatment [3]. By focusing on the intricate interactions between *M.tb* and host immune cells, HDT exploits these metabolic relationships to bolster protective mechanisms against the pathogen. During TB infection, HDT modulates host cell functions, enhances protective immune responses, and improves the mycobacterial killing activities of host immune cells, working to eradicate or limit TB infection [4, 5]. Conversely, HDT also balances immune reactivity by reducing exacerbated inflammation and tissue damage associated with TB infection through precise regulation of the host immune system [6]. This approach eliminates *M.tb* through mechanisms that bypass the pathways commonly targeted by conventional anti-TB drugs, thereby reducing the risk of developing antibiotic resistance [5, 7]. This is particularly beneficial given the

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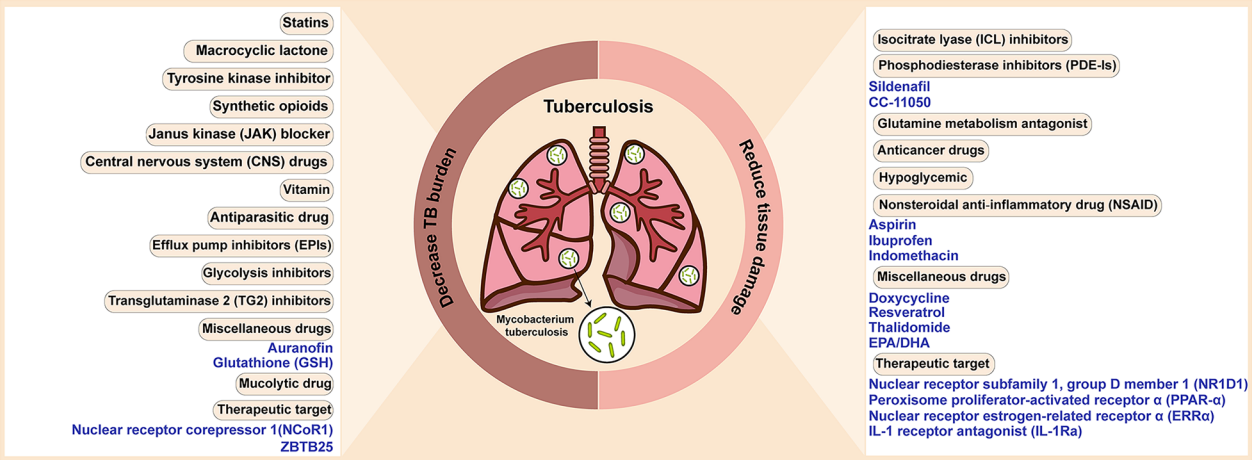

Fig. 1 Main current HDTs used in tuberculosis

rise of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis strains. This review focuses on a few drug candidates for HDT from two different perspectives: decreasing bacterial burden and mitigating pathological inflammatory responses (Fig. 1). Some of these drugs have been approved for the treatment of other diseases, such as simvastatin, everolimus, gefitinib and so on. In conducting our literature search, we aimed to comprehensively cover all significant HDT approaches for TB that have been reported over the years. While our search was not restricted to a specific time window, we focused on identifying key studies and advancements that have shaped the development of HDTs for TB. However, given the vast and evolving nature of the field, it is possible that some studies may not have been included. To ensure a thorough review, we utilized multiple databases, including PubMed, Scopus, and Web of Science, and employed broad search terms related to HDTs and TB. This approach allowed us to capture a wide range of studies, from early foundational work to recent clinical trials, providing a balanced overview of the field.

In addition, we have provided a partial list of these promising HDT agents and their targets of action (Table 1).

Promising candidates that decrease TB burden

Statins

Statins, specifically simvastatin and rosuvastatin, are widely used to lower circulating cholesterol levels and prevent coronary heart disease. These drugs exhibit anti-inflammatory and immunoregulatory properties while promoting cell autophagy and phagosome maturation by inhibiting the mammalian target of the rapamycin (mTOR) signaling pathway [8]. Autophagy, an intracellular process that catabolizes intracellular components through lysosomal degradation, plays a crucial role in the host defense against intracellular pathogens like *M.tb* [57] (Fig. 2). Macrophages are key immune cells that inhibit *M.tb* growth via autophagy and facilitate the presentation of antigens to other immune cells.

Preclinical studies in in vitro models have shown that simvastatin exerted its anti-tubercular activity through cholesterol-driven autophagy, which is mediated by the adenosine monophosphate-activated protein kinase (AMPK)–mammalian target of the rapamycin complex 1 (mTORC1)–TFEB axis [58] (Fig. 3). In human peripheral blood mononuclear cells (PBMCs), simvastatin significantly reduced *M.tb* growth and promoted apoptosis and autophagy [59]. Furthermore, statins like simvastatin, fluvastatin, and pravastatin improved the efficacy of anti-TB drugs in cell models. In animal models, pravastatin demonstrated strong adjuvant action in a mouse model of human-like necrotic TB lung granulomas [60]. These preclinical findings suggest that statins have potential as adjunctive therapies in TB treatment. In contrast, clinical trials have yielded mixed results. A phase IIA study of atorvastatin showed a significant reduction in mycobacterial load in the sputum of patients with pulmonary tuberculosis (PTB) [61], while another trial using rosuvastatin did not affect sputum culture conversion [62]. These results suggested that not all statins are equally effective in clinical settings, and further research into optimal dosing and specific statin classes is warranted.

Macrocyclic lactone

Rapamycin, a macrocyclic lactone isolated from *Streptomyces hygroscopicus*, is known for its immunosuppressive and antimicrobial properties due to its

Table 1 Emerging HDTs against TB

Therapeutic class	Candidates	Target	References
Statins	Simvastatin	Autophagy	[8]
Macrocyclic lactone	Everolimus	Inhibiting the mTOR pathway; Autophagy	[9]
Tyrosine kinase inhibitor	Gefitinib	Tyrosine-kinase inhibitors (TKI); Autophagy	[10, 11]
Synthetic opioids	Loperamide	Autophagy; LL37 expression	[12, 13]
Janus kinase (JAK) blocker	Tofacitinib	JAK blocker	[14]
Central nervous system (CNS) drugs	Fluoxetine	Selective serotonin reuptake inhibitor (SSRI)	[15]
Vitamin	Vitamin D	LL37 expression; Autophagy; Macrophage polarization	[16–18]
Antiparasitic drug	Nitazoxanide (NTZ)	Autophagy	[19–21]
Efflux pump inhibitors (EPIs)	Verapamil	EPI	[22]
Glycolysis inhibitors	2-deoxyglucose (2-DG)	Glucose uptake inhibitor	[23]
Transglutaminase 2 (TG2) inhibitors	Cystamine and cysteamine	Reducing agents	[24]
Miscellaneous drugs	Auranofin	Thioredoxin reductase (TrxR) inhibition	[25]
	Glutathione (GSH)	Th1 response regulation	[26]
Mucolytic drug	Ambroxol	Autophagy	[27]
Therapeutic target	Nuclear receptor corepressor 1 (NCOR1)	Autophagy	[28]
	Host transcriptional repressor protein zinc finger and BTB domain 25(ZBTB25)	Autophagy	[29]
Isocitrate lyase (ICL) inhibitors	Itaconate	ICL inhibitor	[30–32]
Phosphodiesterase inhibitors (PDE-Is)	Sildenafil	PDE-I	[33, 34]
	CC-11050	PDE-I	[35]
Glutamine metabolism antagonist	JHU083	Glutamine metabolism antagonist	[36]
Anticancer drugs	Bevacizumab (Avastin)	Anti-vascular endothelial growth factor (VEGF) antibody	[37]
Hypoglycemic	Metformin	Adenosine monophosphate–activated protein kinase (AMPK) activation; Autophagy	[38–40]
Nonsteroidal anti-inflammatory drug (NSAID)	Aspirin	Cyclooxygenase enzymes inhibitor	[41]
	Ibuprofen	Cyclooxygenase enzymes inhibitor	[42, 43]
	Indomethacin	Cyclooxygenase enzymes inhibitor	[44]
Miscellaneous drugs	Doxycycline	Matrix metalloproteinase (MMP) inhibitor	[45, 46]
	Resveratrol	Sirtuin (Sirt1) activation	[47, 48]
	Thalidomide	TNF-α inhibition	[49]
	EPA/DHA	Inflammation regulation	[50–52]
Therapeutic target	Nuclear receptor subfamily 1, group D member 1 (NR1D1)	Phagosome lysosome maturation	[53]
	Peroxisome proliferator-activated receptor α (PPAR-α)	Autophagy	[54]
	Nuclear receptor estrogen-related receptor α (ERRα)	Autophagy	[55]
	IL-1 receptor antagonist (IL-1Ra)	Blocking signaling	[56]

ability to inhibit the mTOR pathway, thereby promoting autophagy [63]. Specifically, rapamycin binds to FKBP12, forming a complex that inhibits mTORC1 activity. This inhibition relieves the suppression of ULK1, a key initiator of autophagy, leading to the formation of autophagosomes [64]. Preclinical studies in *M.tb*-infected mice have shown that rapamycin reduced pulmonary inflammation and caseating granulomas [65]. However, its application in clinical settings is restricted by high variability in absorption and

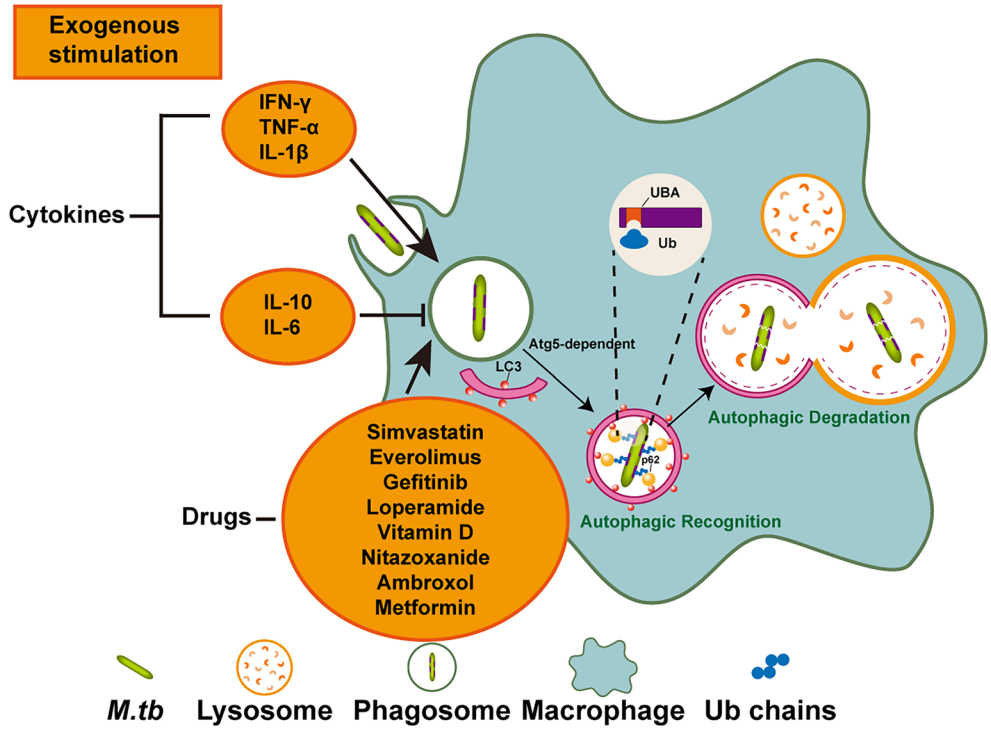

Fig. 2 Schematic representation of the correlation between autophagy induction and the anti-tuberculosis activity of indicated cytokines and pharmacological agents

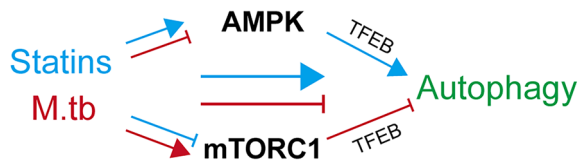

Fig. 3 Statins and *M.tb* infection exhibit opposing effects on AMPK, mTORC1, and autophagy. Statins suppress mTORC1 activity while activating AMPK, both of which cause enhanced nuclear translocation of TFEB, resulting in the expression of autophagy-related genes. *M.tb* produces opposite effects by activating mTORC1 and blocking AMPK, which prevents nuclear translocation of TFEB and inhibits autophagy

adverse reactions. Rapamycin's efficacy is further limited due to its metabolism via cytochrome P450 3A4 (Cyp3A4), which is induced by rifampin, complicating its use alongside standard TB treatments.

Everolimus, a derivative of rapamycin with better pharmacokinetics, has shown promising results in preclinical studies. At the cellular level, everolimus has been demonstrated to enhance autophagy by inhibiting PI3K/Akt/mTOR pathway. In in vitro granuloma models, everolimus not only controlled *M.tb* growth but also demonstrated an additive effect when combined with front-line anti-TB drugs like isoniazid and pyrazinamide. It modulates cytokine profiles and oxidative stress, further supporting its role in HDT [66]. Moving to clinical outcomes, a phase II trial investigating everolimus as an adjunctive therapy for TB showed that it was well tolerated and might enhance recovery of lung function, particularly in terms of FEV_1 [67]. While everolimus has shown promise in modulating the immune response and improving TB treatment outcomes, there are significant concerns about long-term use due to its immunosuppressive effects. Further research should assess the balance between its potential benefits and risks, particularly in patients with concurrent infections or immunocompromised states.

Tyrosine kinase inhibitor (TKI)

Imatinib, a TKI known for its antitumor activity, has shown promise in interfering with the entry and survival of *M.tb* in macrophages. Preclinical studies in *M.tb*-infected mice have demonstrated that imatinib decreased granulomatous lesions and bacterial load. It also demonstrated efficacy against antibiotic-resistant strains by promoting autophagy, potentially contributing to *M.tb* clearance and reducing the risk of drug-resistant diseases [68]. Another TKI, gefitinib (ZD1839, Iressa), which targets the epidermal growth factor receptor (EGFR), has

been shown to restrict *M.tb* replication in both macrophages as well as in the lungs of *M.tb*-infected mice by promoting the host autophagy pathway through the inhibition of the p38 MAPK signaling pathway activated by EGFR [10]. Additionally, gefitinib has also been shown to control *M.tb* growth in macrophages by enhancing lysosomal biogenesis and function through the inhibition of the signal transducer and activator of transcription 3 (STAT3) signaling pathway [11]. However, further clinical trials are necessary to evaluate the safety and efficacy of TKI as adjunctive therapies in TB treatment, with a focus on understanding how TKI might be safely integrated into clinical practice.

Synthetic opioids

Loperamide, a synthetic opioid routinely prescribed to treat diarrhea, demonstrates potential antimicrobial effects against *M.tb*. Preclinical studies in murine and human alveolar macrophages (AMs) have demonstrated that loperamide induced autophagy, enhancing its antimicrobial activity towards *M.tb* [12]. In addition, loperamide was found to reduce TNF-α levels and induce the production of antimicrobial peptides, such as bactericidal/permeability increasing protein and LL37, enhancing host's ability to fight against *M.tb* infections while protecting tissues from excessive inflammatory damage [13]. However, as an opioid, loperamide has potential side effects, including the risk of opioid dependence and gastrointestinal disturbances. Further clinical trials are necessary to determine the appropriate dosage, efficacy, and safety of loperamide in patients with PTB. Additionally, studies should explore whether loperamide's immunemodulating effects can be harnessed without inducing opioid-related side effects.

Janus kinase (JAK) blocker

Tofacitinib, a JAK blocker, accelerated bacterial elimination in a preclinical study when administered at high doses alongside standard TB chemotherapy in chronic *M.tb*-infected BALB/c mice. However, similar results were not observed in *M.tb*-infected C3HeB/FeJ mice with Ipr1 gene mutations. This difference may be attributed to the necrotic and hypoxic granulomatous lesions in C3HeB/FeJ mice, which could hinder the action of tofacitinib. These findings highlighted the importance of host factors such as granuloma structure and immune environment in determining the efficacy of JAK blockers [14]. However, the potential immunosuppressive effects of JAK inhibitors also pose challenges, particularly in immunocompromised individuals or those with concurrent infections. Further studies are warranted to investigate its effectiveness as an adjuvant treatment during the early stages of infection (approximately 3 weeks), prior to the onset of pathological necrosis.

Central nervous system (CNS) drugs

Dopamine and serotonin receptors mediate the immune responses to TB. Preclinical studies have shown that agonists or antagonists of these receptors activated autophagy, thereby enhancing the host's ability to eliminate *M.tb*. For example, the combination of fluoxetine (a 5-HT2C receptor antagonist) and bromocriptine (an agonist of type 2 dopamine receptors) was found to increase the release of proinflammatory cytokine (IL-6 and TNF-α) and stimulate autophagy in *M.tb*-infected macrophages [10, 15]. A synthetic fluoxetine analog (AM3e) also exhibited anti-TB efficacy against H37Rv strain [69]. While CNS drugs like sertraline (SRT) have shown promise in animal models, where their combination with front-line anti-TB drugs, improved early bactericidal activity, resolution of pulmonary pathology, and enhanced survival in mice infected with *M.tb* [70], clinical studies have raised concerns. For instance, a recent clinical trial on SRT as an adjunct regimen for asymptomatic cryptococcal antigenemia reported serious adverse events (psychosis, aggressive behavioral changes, and serotonin syndrome) [71]. Although CNS drugs may enhance TB treatment through immune modulation, their use as adjunctive therapies must be approached cautiously due to the risk of severe side effects. Further studies are necessary to determine the optimal dosage and treatment duration to ensure patient safety.

Vitamins

Vitamin D, a fat-soluble secosteroid hormone, plays a key role in combating *M.tb* by impairing bacterial growth and upregulating innate host responses [72]. Its active form, 1,25(OH)2D, regulates mucosal immunity, host defense, and inflammation by binding to the vitamin D receptor (VDR) in macrophages [73, 74], triggering the expression of the antimicrobial peptide cathelicidin (CAMP) (LL-37) and promoting autophagosome–lysosome fusion and maturation [16, 75]. Preclinical evidence shows that 1,25(OH)2D induces a shift from inflammatory (M1) to reparative (M2) macrophages, promoting the secretion of hydrogen peroxide, a critical factor for *M.tb* clearance [17, 18]. Clinical trials showed that cholecalciferol (vitamin D) supplementation, especially in patients with TB having 1,25(OH)2D deficiency, may augment standard anti-TB therapy (ATT) by accelerating sputum culture conversion and improving lesion absorption [7, 76]. However, other studies have reported mixed results, with some trials showing no significant impact on TB relapse or culture conversion [77, 78]. These findings underscore

the need for larger multicenter trials to fully assess the clinical utility of vitamin D as an adjunct therapy for TB.

Nitazoxanide (NTZ)

Nitazoxanide, an antiparasitic drug with notable antiviral and anti-inflammatory properties [79]. In preclinical studies, NTZ suppresses intracellular *M.tb* proliferation by inhibiting the enzymatic activity of human quinone oxidoreductase (NQO1), which in turn inhibits the mTORC1 pathway and induces autophagy [19]. In vivo studies demonstrated that NTZ, when combined with INH and rifabutin (RFB), successfully cleared all bacteria from the lungs and spleens of *M.tb*-infected mice and significantly restored tissue architecture[21]. However, a phase II clinical trial revealed that NTZ did not exhibit bactericidal activity against *M.tb* in drug-susceptible patients with PTB. This lack of efficacy may be attributed to the low plasma and sputum concentrations of NTZ and the high plasma protein binding of tizoxanide, the active metabolite of NTZ [80], highlighting the need for further pharmacokinetic optimization and clinical research to better understand its potential role in TB treatment.

Efflux pump inhibitors (EPIs)

Verapamil, a calcium channel blocker used to treat hypertension, angina, and cardiac arrhythmia [81], has been identified as an EPI with potential application in TB therapy. Firstly, verapamil inhibits drug efflux pumps in *M.tb*, such as Rv1258c and Rv2686c, thereby increasing the intracellular concentration of anti-TB drugs like rifampicin and isoniazid. This not only enhances drug efficacy but also reduces the likelihood of drug resistance [82]. Secondly, Verapamil modulates host immune responses by promoting macrophage activation and increasing the production of reactive oxygen species (ROS) and nitric oxide (NO), which contribute to the killing of intracellular mycobacteria [83]. Additionally, Verapamil has been shown to reduce bacterial persistence, a major challenge in TB treatment, by enhancing drug accumulation and immune-mediated clearance [84]. In vitro studies demonstrated that verapamil, when combined with rifapentine, enhanced antimicrobial activity against *M.tb* in macrophages [85]. Animal models showed that verapamil accelerated bactericidal activity and achieved durable sterilization in infected mice [86]. However, verapamil's dual effects on drug metabolism, particularly its inhibition of CYP3A activity, raise concerns about potential interactions with essential TB drugs like rifampin, which is known to induce CYP3A enzymes [87]. Therefore, further clinical investigations are needed to determine the impact of verapamil on cardiac conduction, drug metabolism, and its potential as an adjunctive therapy for TB before regulatory agency clearance.

Glycolysis inhibitors

The Warburg effect, initially observed in cancer cells, refers to a metabolic state in which cells favor aerobic glycolysis over oxidative phosphorylation for ATP and macromolecule production. This phenomenon has also been observed in the immune cells during *M. marinum* infection. Preclinical studies demonstrated that pretreatment with 2-deoxyglucose (2-DG) induced autophagy and restricted the growth of *M. marinum* in zebrafish larvae, potentially enhancing host defenses against mycobacterial infections. However, post-infection treatment with 2-DG failed to inhibit bacterial replication and even promoted *M. marinum* growth in TNF-$\alpha^{-/-}$ zebrafish [23]. This was consistent with another study showing that 2-DG treatment of *M.tb*-infected macrophages enhanced *M.tb* growth [88]. While clinical studies have established that 2-DG can be safely administered to humans [89], its potential application in TB treatment is limited, particularly due to its effectiveness only when administered before infection. The potential of glycolysis inhibitors in post-infection TB therapy warrants further investigation, but current evidence suggests significant challenges in their use as therapeutic agents.

Transglutaminase 2 (TG2) inhibitors

Cystamine and cysteamine, as TG2 inhibitors, function as reducing agents that elevate the levels of glutathione and L-cysteine [90], thereby impacting cell metabolism. Preclinical studies demonstrated that these agents restricted *M.tb* growth in macrophages and suppressed host cell autophagy but did not exhibit direct bactericidal activity against *M.tb* cultures. In vitro models indicated that combining TG2 inhibitors with amikacin enhanced their antimicrobial activity in *M.tb*-infected macrophages and the granuloma-like structure ex vivo model [24]. These results showed that their combination with existing antibiotics like amikacin may offer potential, but clinical trials are essential to validate their efficacy and safety in TB patients.

Miscellaneous drugs

Auranofin

Auranofin, an orally administered anti-rheumatic drug, exhibits broad-spectrum antibacterial and antiviral activity in vitro. Preclinical studies indicated that it targeted the bacterial flavoenzyme TrxR, essential for *M.tb* survival by protecting against oxidative and nitrosative stress. By inhibiting TrxR, auranofin compromises *M.tb* defense mechanisms, especially in the

oxidative environment of macrophage phagosomes [91]. Despite showing efficacy in ex vivo whole blood cultures, auranofin did not affect sputum culture conversion in early clinical trials [25]. Its potential against acute and latent *M.tb* infections is still under investigation, and small-scale clinical trials may be necessary to assess its anti-TB efficacy either as a monotherapy or in combination with other anti-TB drugs.

Glutathione (GSH)

GSH, a naturally occurring antioxidant, plays a vital role in protecting cells from oxidative stress-induced damage, regulating DNA expression, detoxifying reactive metabolites, providing cysteine reservoirs, modulating apoptosis and antigen-presenting cell functions [92]. In vitro studies showed that H37Rv strain is sensitive to GSH, highlighting its potential for intracellular *M.tb* control [93]. Liposomal glutathione (L-GSH) supplementation was found to decrease the intracellular mycobacterial burden within in vitro granulomas derived from the PBMCs of patients with type 2 diabetes mellitus (T2DM) [26]. However, the small sample size and in vitro granuloma model used thus far do not fully replicate the complex granulomatous environments observed in PTB patients. Further small-scale clinical trials are needed to validate GSH's therapeutic effects in patients with TB.

Ambroxol (Amb)

Ambroxol, an active metabolite of bromhexine, is approved for the treatment of airway diseases in several countries. Preclinical studies have demonstrated that ambroxol enhanced the antimycobacterial activity of rifampicin against intracellular BCG [27], induced autophagy through the activation of TFEB both in vitro and in vivo models, promoted mycobacterial killing in macrophages. Moreover, it has been shown to potentiate rifampin's activity in a murine tuberculosis model [94]. However, the optimal dosage of Amb when co-administered with rifampin or vancomycin remains under investigation. Amb is metabolized by Cyp3A4, which is strongly induced by rifampicin in humans. High-dose Amb (1000 mg/day) has been used clinically to counteract rifampicin-induced Cyp3A4 activation and achieve sufficient Amb levels. However, this increased dose also resulted in higher levels of Cyp3A4-derived Amb metabolites, whose clinical implications remain unclear. Further clinical trials are needed to explore the interaction of Amb with other TB drugs and long-term impact on patients.

Therapeutic target

Nuclear receptor corepressor 1(NCoR1)

NCoR1 is a scaffolding protein that forms the foundation of a large corepressor complex responsible for suppressing the expression of genes involved in various biological processes [95]. The NCoR1 corepressor is involved in both autophagy and lysosome biosynthesis by fine-tuning ATP homeostasis via the AMPK–mTOR–TFEB signaling axis to control *M.tb* infection in myeloid cells. Preclinical studies have demonstrated that NCoR1 depletion, followed by treatment with rapamycin, anti-mycin-A, or metformin restored TFEB activity and LC3 levels, leading to improved clearance of *M.tb* [28]. Thus, NCoR1 is a promising therapeutic target for HDT in TB. However, it remains to be determined whether its beneficial effects are primarily mediated via the inhibition of direct PPARγ target genes, such as CD36, or through the PPARγ-mediated repression of proinflammatory transcription factors, such as NF-kB.

ZBTB25

ZBTB25, a host transcriptional repressor protein associated with the histone deacetylase 1 (silencing complex), has been identified as another potential target for HDT in TB. Preclinical evidence has shown that knockdown of ZBTB25 enhanced the release of lL-12p40 from infected macrophages. Treatment of macrophages with ZBTB inhibitors further induced autophagy and eliminated intracellular *M.tb* by enhancing JAK2 and STAT4 phosphorylation [29]. Additional research is necessary to determine the efficacy and safety of ZBTB inhibitors in clinical trials, as well as their potential in combination therapies with existing anti-TB drugs.

Promising candidates that reduce tissue damage

Tuberculoid granulomas (Fig. 4), the hallmark lesions of chronic TB, are well-organized, compact structure composed of differentiated macrophages, lymphocytes, and other immune cells [96, 97]. As granulomas mature, they develop fibrous walls and experience a significant decrease in the number of vessels penetrating the structure, which hampers the penetration of anti-TB drugs into the necrotic and hypoxic areas of the granuloma, where *M.tb* persists [98, 99]. The poor permeability of anti-TB drugs within granulomas, coupled with ineffective regulation of extracellular signaling, allows *M.tb* to adapt and develop drug resistance. In such environments, *M.tb* switches to fatty acid metabolism to enter a persistent state. HDT strategies can improve therapeutic outcomes by enhancing immune homeostasis during the formation and resolution of granulomas. By improving vascular perfusion within granulomas, HDT can increase

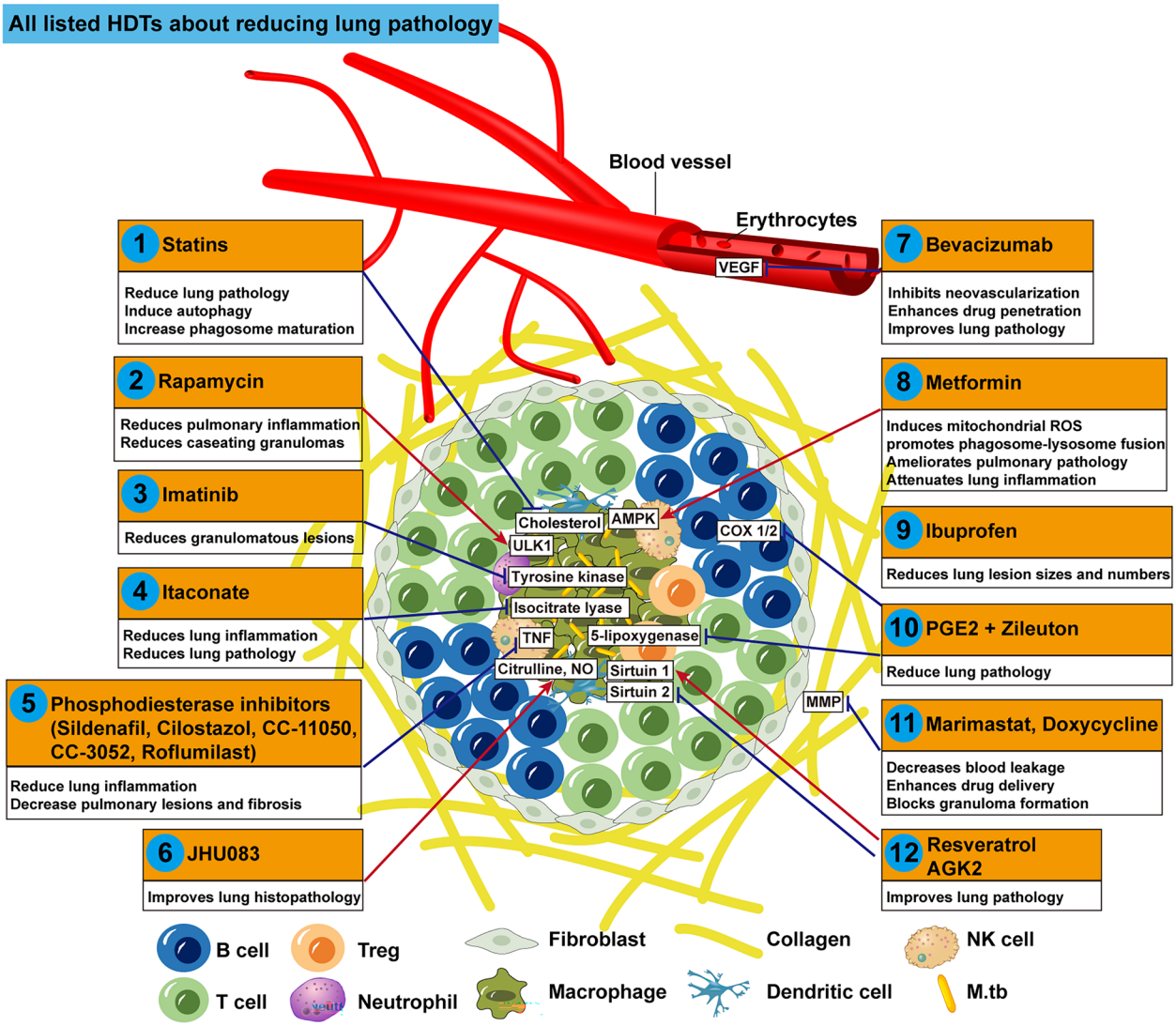

Fig. 4 The structure and main composition of granuloma and related drugs

the local concentration of antimicrobials, promote tissue repair, and enhance the clearance of latent mycobacteria by immune cells.

Isocitrate lyase (ICL) inhibitors

ICL plays a crucial role in mycobacterial glyoxylate and methyl isocitrate cycles, which are essential for *M.tb* survival, virulence [100], and antibiotic tolerance [101]. Preclinical studies demonstrated that itaconate, a structural analog of succinate, inhibits ICL through covalent interaction with the catalytic cysteine residues (Cys191 of ICL1 and Cys215 of ICL2) of *M.tb* [30]. Dimethyl itaconate activates innate immune defenses, maintains inflammatory homeostasis, activates STAT3 and autophagy, and exhibits strong antimycobacterial properties in both macrophages and in vivo models [102]. Additionally, itaconic acid promotes the pentose phosphate pathway, leading to ROS production, enhancing its anti-inflammatory and antibacterial properties [103]. In addition, Irg1-deficient phagocytes, which cannot produce itaconate, have shown increased susceptibility to *M.tb* infection, with infected mice exhibiting higher bacterial loads, reduced survival, exacerbated inflammation, extensive necrotizing granuloma formation and elevated neutrophil infiltration in the lungs [104, 105]. In summary, the development of pharmacological agents that promote itaconate production could potentially mitigate pathological inflammatory responses and prevent severe lung injury

associated with TB progression. But further research is needed to confirm these findings in clinical trials.

Phosphodiesterase inhibitors (PDE-Is)

Phosphodiesterases (PDEs) regulate the concentration of cyclic adenosine monophosphate (cAMP), a key second messenger in both eukaryotic and prokaryotic systems [106]. *M.tb* manipulates cAMP signaling pathways within infected macrophages, thereby influencing its survival [107]. Preclinical studies have showed that PDE inhibitors, such as sildenafil and cilostazol, can decrease tissue pathology, accelerate bacterial clearance, and reduce the time to lung sterilization in *M.tb*-infected mice when used in combination with standard TB therapy [33]. PDE4 inhibitors, including CC-11050, CC-3052, and roflumilast, when combined with INH, have been shown to reduce the lung bacillary burden, lung pathology, and fibrosis, as well as the size and number of lung granulomas in *M.tb*-infected rabbits and in both acute and chronic TB mouse models [35, 108, 109]. A phase 2 clinical trial demonstrated that CC-11050 and everolimus were safe and well tolerated as TB adjuvant treatments and enhanced recovery of lung function (FEV_1), which correlates with reduced all-cause mortality [67]. However, contrasting data from other studies showed that the addition of PDE4i rolipram to standard TB treatment accelerated mortality, increased the bacterial burden, and did not reduce the time to bacterial clearance in the lungs of a mouse model of TB [34], raising concerns about the general applicability of PDE-Is. Therefore, understanding the differential impacts of various PDE-Is and their long-term outcomes is essential before widespread clinical use.

Glutamine metabolism antagonist

Glutamine metabolism is crucial for T-cell cytokine production and M1-like polarization of macrophages in the proinflammatory response against *M.tb* infection [110]. Glutamine also serves as a key carbon and nitrogen source for *M.tb*-infected macrophages [111], supporting the pathogen's metabolic demands. The glutamine metabolism antagonist, JHU083, has been shown to inhibit *M.tb* replication both in vitro and in vivo, improving survival, reducing lung bacterial burden, and improving lung histopathology. These effects are achieved by reducing immunosuppressive myeloid cells, increasing effector T cells, and enhancing the production of citrulline and NO. However, in *M.tb*-infected immunocompromised mice, JHU083 showed reduced therapeutic efficacy [36]. This suggests that its benefits may be limited in patients with weakened immune systems, such as those co-infected with HIV. Therefore, further clinical trials are needed to assess its potential as an immunotherapeutic agent against TB, particularly in diverse patient populations with varying immune statuses.

Anticancer drugs

Polena et al. demonstrated that blocking vascular endothelial growth factor (VEGF) signaling with antibodies against VEGF or VEGFR-2 reduced *M.tb* transmission to the lung, spleen, and liver in *M.tb*-infected mice [112]. In line with this, bevacizumab (Avastin), a humanized monoclonal antibody against VEGF commonly used in cancer treatment, has demonstrated potential in the context of TB. In *M. marinum*-infected zebrafish, targeting VEGFR signaling improved the therapeutic effect of rifampicin [113]. Additionally, a preclinical study using a rabbit TB model showed that bevacizumab inhibited neovascularization, enhanced drug penetration into granulomas, improved lung pathology, and increased oxygenation, suggesting its potential to enhance the effectiveness of the current TB regimens [37]. However, larger multicenter randomized controlled trials are required to formulate guidelines for the clinical use of bevacizumab in treating tubercular granulomas. VEGF-A, which binds to VEGFR1, functions as an effective chemokine for macrophages. According to Harding et al., suppressing VEGF-A reduced granulomatous inflammation by interfering the recruitment of monocytes to infected tissues [114]. This suppression could potentially improve the survival of mice infected with virulent *M.tb,* while maintaining host defense. Thus, VEGF-A presents a potential target for therapeutic interventions in TB therapy.

Metformin

Metformin, a first-line drug for patients with T2DM [115], is known to activate AMPK [38], a key metabolic regulator. AMPK promotes autophagy by inhibiting mTOR, a potent negative regulator of autophagy, or by activating unc-51-like kinase 1, which is essential for autophagy initiation [39, 40]. Furthermore, the AMPK/PPAR γ coactivator-1 α (PGC1α) pathway upregulates autophagy-related genes, thereby promoting autophagy and phagosome fusion in macrophages during *M.tb* infection [116]. In vitro research found that metformin activated a novel galectin-directed ubiquitin signal transduction system in response to lysosomal membrane damage, induces autophagy, and facilitates the elimination of *M.tb* from macrophages [117]. Additionally, metformin inhibits *M.tb* growth, induces mitochondrial ROS production, promotes phagosome–lysosome fusion in vitro, ameliorates pulmonary pathology, attenuates chronic inflammation, augments immunity, and improves the therapeutic effect of the standard anti-TB regimen in *M.tb*-infected mice. In clinical studies, metformin therapy was associated with improved clinical outcomes,

including reduced TB severity, and a lower incidence of latent TB infection (LTBI) [118]. Retrospective studies also suggested that metformin decreased the risk of TB incidence [119, 120], cavitary TB [118], and mortality associated with diabetes mellitus during TB treatment [121]. Additionally, metformin has been shown to improve sputum culture conversion and lower the relapse rate of patients with TB-DM [122]. However, in one study, the use of a low dosage of metformin in combination with conventional ATT did not accelerate sputum culture conversion, which could be attributed to insufficient dosing [123]. Despite this, the role of metformin in reducing inflammation and improving overall outcomes makes it a promising adjunctive therapy in HDT for TB. Further prospective clinical trials are needed to determine whether the initial use of metformin can effectively prevent TB infection after exposure or simply mitigate the progression from LTBI to active disease. These studies should also aim to establish the optimal dose when metformin is used alongside current TB therapies, as well as its potential role in shortening treatment duration and enhancing prophylactic control of TB.

Nonsteroidal anti-inflammatory drug (NSAID)

Aspirin

Aspirin, a commonly used NSAID, primarily works by inhibiting cyclooxygenase (COX) enzymes, particularly COX-1 and COX-2, which in turn blocks thromboxane A 2 synthesis [124]. A study conducted on *M.tb*-infected mice showed that the co-administration of aspirin and pyrazinamide enhanced the efficacy of pyrazinamide during the early stage of TB treatment [42]. Additionally, a phase 2, randomized placebo-controlled trial showed that aspirin reduced stroke and death in HIV-uninfected adults with TB meningitis (Table 2) [41]. However, given the widespread use of aspirin, which may overlap with anti-TB treatment, it is necessary to determine their potential interaction in vivo. Initial assessment should be conducted using animal models, followed by larger studies involving children and adults. In addition, long-term TB treatment studies in mice, evaluating the effects of aspirin in combination with pyrazinamide and other TB drugs are needed to determine the potential role of aspirin in reducing TB treatment and preventing relapse.

Ibuprofen

Ibuprofen, another commonly used NSAID, inhibits COX-1 and COX-2 [125], both of which are involved in the synthesis of prostaglandin E 2 (PGE_2) in macrophages [126]. COX inhibition has been shown to enhance nitric oxide synthase (iNOS), TNF-α and IFN-γ expression and reduce mycobacterial loads by inhibiting the expressions of the PGE_2 [127]. However, PGE2 is known to play a dual role, as it can both suppress the immune response against *M.tb* and protect the host from excessive inflammation, suggesting that NSAIDs should be exercised with caution for TB treatment [128]. In some studies, the 5-lipoxygenase inhibitor zileuton, when co-administered with PGE2, reduced pulmonary bacterial burden and pathology and prevented acute death in *M.tb*-infected mice deficient in both IL1R1 and IFNAR1 [129]. Early animal studies also reported that ibuprofen enhanced the mycobactericidal effect of pyrazinamide in *M.tb*-infected mice [42], reducing the size and number of lung lesions, decreasing bacterial load, and prolonging survival of C3HeB/FeJ mice, which are particularly vulnerable to TB [43]. However, the combination of ibuprofen with standard chemotherapy has not yet been evaluated. Additionally, some studies have raised concerns, as ibuprofen treatment can increase the bacterial load and decrease survival in CB6F1 mice following high-dose aerosol infection [130]. Therefore, further animal experiments and clinical trials are needed to evaluate the effects of ibuprofen on both active and latent TB.

Indomethacin

Indomethacin, an NSAID that participates in both innate and adaptive immunity [131], has been shown to reduce the proportion of *M.tb* antigen-triggered Tregs, reactions of *M.tb* specific cytokines, and proliferation of T cells in active TB. This suggests their potential use in regulating immune responses against TB infection [44]. Nevertheless, future clinical trials should be conducted to explore the in vivo effects of indomethacin in patients during various stages of *M.tb* infection.

Miscellaneous drugs

Matrix metalloproteinase (MMP) inhibitor

MMP is a proteolytic enzyme that degrades the extracellular matrix, including elastin and collagen [136]. Elevated MMP levels are associated with lung inflammation and granuloma necrosis in TB. Marimastat (BB-2516), a small molecule MMP inhibitor, has shown promise by enhancing the in vivo efficacy of INH and RFP, increasing the proportion of healthy blood vessels at the infection site, and enhancing drug delivery and retention [137]. In a human lung tissue model of TB granulomas, marimastat blocked both granuloma formation and mycobacterial growth [45]. Moreover, anti-MMP-9 antibody treatment in C3HeB/FeJ mice led to the development of hypoxic TB granulomas and cavitary lesions, resulting in a lower relapse rate, although this was not significantly different [138]. Doxycycline, another MMP inhibitor, effectively prevented collagen destruction induced by TB infection [46]. Promising results from a recent phase II clinical trial showed that adjunctive doxycycline with standard

Table 2 Clinical studies of host-directed therapeutics for tuberculosis

Study name	Phase	Results	Clinical trials.Gov Identifier*	References
A Pilot Study of Adjunctive Aspirin for the Treatment of HIV Negative Adults With Tuberculous Meningitis	II	The addition of aspirin to dexamethasone may improve outcomes from tuberculous meningitis (TBM)	NCT02237365	[41]
Treating Tuberculosis With the Lipid Lowering Drug Atorvastatin in Nigeria (ATORvastatin in Pulmonary Tuberculosis)	II	Atorvastatin is a safe additive to standard anti-TB regimen and leads to a significant reduction in mycobacterial load in the sputum	NCT04721795	[61]
Rosuvastatin Evaluation as a Tuberculosis Treatment Adjunct	II	Adjunctive rosuvastatin at 10 mg once per day was safe but did not produce substantive benefits on culture conversion in the overall study population	NCT04504851	[62]
TB Host-Directed Therapy	II	CC-11050 and everolimus were safe and reasonably well tolerated as adjunctive therapies for tuberculosis, and analysis of preliminary efficacy suggests they might also enhance the recovery of FEV_1	NCT02968927	[67]
A 14 Day Early Bactericidal Activity Study of Nitazoxanide for the Treatment of Tuberculosis	II	At the doses used, NTZ did not show bactericidal activity against M. tuberculosis	NCT02684240	[80]
Vitamin D Supplementation Effect In Children With Pulmonary Tuberculosis Treatment	Not applicable	Vitamin D is beneficial in improving fever and cough resolution, and improving nutritional status in children with pulmonary TB and vitamin D insufficiency	NCT05073965	[132]
Doxycycline in Human Pulmonary Tuberculosis	II	Adjunctive doxycycline with standard anti-TB treatment suppressed pathological MMP in PTB patients	NCT02774993	[133]
Clinical Trial of Phenylbutyrate and Vitamin D in Tuberculosis (TB)	II	Adjunct therapy with PBA + vitD3 or vitD3 or PBA to standard short-course therapy demonstrated beneficial effects towards clinical recovery and holds potential for host-directed-therapy in the treatment of TB	NCT01580007	[134]
Immune Reconstitution in Tuberculosis Disease	II	Daily supplementation with vitD3 + PBA may ameliorate clinical TB symptoms and disease-specific complications, while the intervention had no effect on bacterial clearance in sputum	NCT01698476	[135]

* Further details for trial with NCT numbers can be accessed at http://clinicaltrials.gov

anti-TB treatment may hold potential [132]. However, cipemastat, a selective MMP inhibitor, paradoxically increased cavitation, immunopathology, and mortality in a murine model of cavitary TB [139]. Further phase 3 clinical trials with larger sample sizes are needed to thoroughly assess the immunopathological effects of MMP inhibitors like doxycycline on TB.

Resveratrol

Sirtuin 1(Sirt1), an NAD-dependent deacetylase, inhibits apoptosis in mammalian cells. *M.tb* infection downregulates Sirt1 expression, which is crucial for negatively modulating inflammatory responses by inhibiting the activation of TAK1, MAPK and NF-κB pathways and reducing IL-6 and TNF-α levels. Resveratrol treatment reverses this effect [47] and demonstrates the ability to decrease bacterial burden and improve lung pathology in *Mabc*-infected mice and zebrafish by activating Sirt3 [140]. Furthermore, resveratrol inhibited both *M.tb*-induced early and later apoptosis in macrophages, thereby markedly inhibiting intracellular *M.tb* growth [48]. Moreover, Sirt2 enhances macrophage activation in response to *M.tb* infection. Inhibition of Sirt2 by AGK2 restricted both drug-sensitive and drug-resistant *M.tb* strains, enhanced the efficacy of isoniazid, reduced the bacillary burden and improved disease pathology in *M.tb*-infected mice [141]. Sirt7 restricts intracellular *M.tb* growth by enhancing NO release from macrophages and NO-dependent apoptosis [142]. However, further studies on different experimental models, such as non-human primates, and with a range of other chemical inhibitors of sirtuins are required to fully explore the potential of sirtuin inhibitors as HDT for TB.

Thalidomide

Thalidomide, originally used as a sedative, hypnotic, and antiemetic, could promote host immunity against *M.tb* infection by increasing cytokines production and T lymphocyte proliferation [143]. When combined with antibiotics, thalidomide lowered TNF-α levels, reduced leukocytosis, and alleviated brain pathology, resulting in markedly improved survival in a rabbit model of acute *M.tb* CNS infection [144]. Clinical studies have shown that the addition of thalidomide to the anti-TB treatment regimen resulted in substantial clinical and neuroradiological improvement, with a favorable safety profile and good tolerability in patients with tuberculous meningitis (TBM) [49]. However, owing to concerns about its teratogenic and potentially mutagenic effects, its use in TB treatment remains experimental and requires further investigation.

Omega-3 long-chain polyunsaturated fatty acids (n-3 LCPUFA)

N-3 LCPUFA, found in oily fish and supplements such as eicosapentaenoic acid and docosahexaenoic acid, are essential for numerous physiological and biochemical processes, especially in inflammation modulation. Studies have shown that adding n-3 LCPUFA to TB treatment regimens reduced *M.tb* burden [50], decreased systemic and lung inflammation [51], and enhanced weight in *M.tb*-infected C3HeB/FeJ mice with a sufficient n-3 LCPUFA status [52].

Therapeutic target

Nuclear receptor

In *M.tb* infections, several nuclear receptor agonists have demonstrated encouraging results in enhancing host antimicrobial defense and autophagy. Overexpression of nuclear receptor subfamily 1, group D member 1 (NR1D1)/Rev-Erba, an orphan nuclear receptor, has been shown to enhance the antimycobacterial properties of macrophages and decrease the survival of *M.tb* by promoting phagosome–lysosome maturation through IL-10 repression in human macrophages[53]. Chandra et al. identified NR1D1 as a potential antimicrobial therapeutic target because it promotes autophagy and lysosomal biogenesis through positive regulation of TFEB expression. GSK4112, a synthetic agonist of NR1D1, also induced autophagy in human macrophages [145], supporting the involvement of NR1D1 in the clearance of *M.tb*. Another nuclear receptor, peroxisome proliferator-activated receptor α (PPAR-α), modulates gene expression related to inflammation and mediates antimycobacterial responses against *M.tb* infection by activating the expression of genes associated with autophagy, lysosomal function, and phagosomal maturation through lipid catabolism and upregulation of TFEB transcription[54]. Gemfibrozil (GEM), a PPAR-α activator, has been shown to decrease *Mabc* burden and inflammatory responses in vivo [146]. In addition, the oldest orphan nuclear receptor estrogen-related receptor α (ERRα), an important regulator of metabolic gene transcription and innate immune function, including those induced by toll-like receptor (TLR) and antimicrobial activities against intracellular bacterial infection [147], facilitated post-translational activation of autophagy by deacetylating various autophagy-related proteins, including ATG5, BECN1, and ATG7. Additionally, ERRα is regulated downstream of AMPK and is crucial for antimicrobial host defense against *M.tb* infection by promoting phagosome maturation and regulating excessive inflammation [55]. In summary, strategies targeting ERRα may offer novel therapeutic options for TB treatment.

IL-1 receptor antagonist (IL-1Ra)

IL-1Ra, encoded by *Il1rn*, binds to IL-1R1 without inducing signaling pathways and prevents the binding of IL-1α/β [148]. An intervention using an anti-IL-1Ra antibody in *M.tb*-infected B6.Sst1^s mice, designed to block IL-1Ra and restore IL-1 signaling, resulted in decreased bacterial burden in the lungs, maintained body weight, and reduced lung lesions in mice [56], suggesting that IL-1Ra might be a promising target for HDT during *M.tb* infection.

Furthermore, certain combination therapies involving HDT have also shown promising results. For instance, everolimus combined with oral L-GSH increased the levels of Th1 cytokines, including IFN-γ, TNF-α, and IL-2 and decreased intracellular *M. bovis* BCG infection in patients with T2DM [149]. The combination of phenylbutyrate (PBA) and 1,25-dihydroxyvitamin D3 ($1,25(OH)_2D3$) induces LL-37 expression in a lung epithelial cell line and enhances *M.tb* killing in human monocyte-derived macrophages through activation of autophagy and resolution of lung pathology [150]. Clinical trials have also demonstrated that therapy with PBA in combination with vitD3 can promote the clearances of *M.tb* from the respiratory tract, accelerate sputum culture conversion, reduce clinical symptoms, and promote favorable immunomodulation, thus improving treatment outcomes [146]. However, daily supplementation with vitD3 + PBA improved clinical TB symptoms and other complications but did not substantially affect bacterial clearance in sputum [147]. These mixed results underscore the need for further research to optimize HDT strategies.

Discussion

Currently, while traditional anti-tuberculosis therapies, such as the standard first-line regimen (isoniazid, rifampicin, pyrazinamide, and ethambutol), have been effective in treating drug-susceptible TB, they face significant challenges, including drug resistance, adverse effects, and prolonged treatment durations [1]. Consequently, researchers have explored innovative therapeutic approaches, including HDT. HDTs offer a complementary approach by targeting host immune responses to enhance bacterial clearance and reduce tissue damages. Recently, HDT drugs, used as adjuvants to conventional antidrug regimens, have provided new ideas and hopes, particularly for patients with TB with drug resistance or with various underlying diseases. Findings from a recent study indicate that HDT can reduce the course of therapy, lower the occurrence of drug resistance, and cure refractory tuberculosis. Several HDT drugs used in the treatment of TB, including statins, macrocyclic lactones, and TKI, have received approval by the US Food and Drug Administration for other clinical applications, underscoring their favorable safety profiles. In addition, while we have categorized HDTs into two broad groups based on their primary effects—(1) decreasing TB burden and (2) reducing tissue damage—it is important to note that some HDTs can simultaneously address both aspects. For example, metformin, a well-studied HDT agent, not only limits excessive inflammation and tissue damage by modulating immune responses but also promotes autophagy through mTOR inhibition, thereby enhancing the clearance of *M. tb* [118]. These dual-function HDTs highlight the potential for multifunctional therapies that target both bacterial survival and host immunopathology. However, for the sake of clarity and intuitive presentation, we have classified HDTs based on their dominant mechanism of action. This approach allows for a more structured discussion while acknowledging the multifaceted nature of some HDTs.

In terms of cost-effectiveness, traditional therapies are generally inexpensive but may incur higher long-term costs due to treatment failures, drug resistance, and management of adverse effects. On the other hand, HDTs, while potentially more expensive initially, could reduce overall healthcare costs by improving treatment efficacy, shortening therapy durations, and minimizing complications. Some HDTs, such as vitamin D, are also a practical and cost-effective solution. However, the widespread adoption of HDTs requires further validation through large-scale clinical trials to establish their efficacy, safety, and cost-effectiveness in diverse populations. By integrating HDTs with existing anti-TB regimens, it may be possible to achieve a more balanced and effective approach to TB management, particularly for drug-resistant and complicated cases.

With respect to safety, it is also crucial to thoroughly evaluate the safety profiles and potential adverse effects of HDTs. For instance, metformin, is generally well-tolerated but can cause gastrointestinal side effects (e.g., nausea, diarrhea) and, in rare cases, lactic acidosis, particularly in patients with renal impairment [118]. Similarly, vitamin D supplementation, although safe at recommended doses, can lead to hypercalcemia and hypercalciuria if administered in excess [151]. Other HDT agents, such as statins, are associated with muscle-related adverse effects (e.g., myopathy and rhabdomyolysis), especially at high doses or when used in combination with other medications metabolized by the cytochrome P450 system [152]. Additionally, immunomodulatory agents like tofacitinib, a JAK inhibitor, carry risks of increased susceptibility to infections, particularly in immunocompromised individuals, as well as potential cardiovascular and thromboembolic events [153].

Therefore, in the future, HDT research should focus on several key areas: (1) refining drug delivery systems to enhance the efficacy of HDT agents in the lungs; (2) conducting larger, multicenter clinical trials to determine optimal dosing and safety profiles; (3) investigating the potential for combination therapies to shorten TB treatment durations while minimizing side effects. Addressing these priorities will be critical for advancing HDT from preclinical promise to clinical reality, and (4) developing more robust and physiologically relevant in vitro assays and in vivo models that better recapitulate the complex host–pathogen interactions and immune responses observed in human TB.

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Declarations

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