BJMS
www.batnajms.net

Batna Journal of Medical Sciences 2026;13(6):15
https://doi.org/10.48087/BJMS.2026.130615

REVIEW ARTICLE

Targets of metabolic immunomodulators as possible therapeutic adjuncts for the management of pulmonary tuberculosis.

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ABSTRACT

Immunomodulators are agents that regulate the immune system by either enhancing or suppressing immune responses. They play a pivotal role in the management of infections, autoimmune disorders, allergies, and cancer. Tuberculosis (TB) remains a leading cause of mortality worldwide and is characterized by prolonged treatment regimens, along with a decline in the efficacy of its vaccine, *Bacille Calmette–Guérin (BCG)*, with age. Consequently, the development of novel immunotherapeutic strategies is urgently needed. Synthetic compounds and plant-derived extracts with inhibitory effects on lactate dehydrogenase (LDH), adenosine deaminase (ADA), and indoleamine 2,3-dioxygenase (IDO) have previously been explored as immunomodulators in patients with cancer, cardiovascular diseases, ageing-related conditions, and certain infectious diseases. The anti-tuberculosis potential of various plant extracts and fruits has been investigated due to their anti-inflammatory, antimicrobial, antioxidant, antimitotic, analgesic, local anesthetic, hypnotic, psychotropic, and antitumor properties. However, their immunomodulatory effects in patients with TB remain largely unexplored. Given the potential of plant-derived compounds (such as alkaloids, flavonoids, and terpenoids) and synthetic agents as immunomodulators in other diseases, this review examines the mechanisms and therapeutic applications of LDH, IDO, and ADA as immunomodulatory targets in pulmonary tuberculosis (PTB). The authors conclude that LDH, IDO, and ADA represent critical metabolic checkpoints that regulate immune cell function in TB. Targeting these pathways may offer promising host-directed therapeutic strategies, including targeted immunotherapies and personalized medicine approaches, to complement conventional anti-TB treatment.

Keywords: Immunotherapy, Metabolic inhibitors, Pulmonary Tuberculosis, Personalised medicine.

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Received: 16 Mar 2026
Accepted: 17 May 2026

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1. INTRODUCTION

Tuberculosis (TB) caused by *Mycobacterium tuberculosis* (*Mtb*) is a leading cause of death worldwide. In the year 2020, about 5.8 million people were newly diagnosed with TB, and over 157 thousand were detected to have drug-resistant TB worldwide (1). This high prevalence necessitated new strategies for TB treatment and prevention, especially using host immune-directed therapy. In addition, efficacy of BCG (tuberculosis vaccine) is doubtful in adults, drug treatment of TB patients takes a long time (at least 6 months), and responses vary between patients. Therefore, research into the interplay between host immuno-metabolic systems and Mtb is vital for the development of novel immunotherapy.

Mtb-infected macrophages exhibit metabolic shifts, where classical activation (M1) is associated with glycolysis and pro-inflammatory cytokine production, but alternatively activated macrophages (M2) favour oxidative phosphorylation and anti-inflammatory responses. Glycolytic enhancement improves reactive oxygen species and nitric oxide production, which are critical for Mtb killing (2). The effector T cells depend on glycolysis for rapid proliferation, whereas regulatory T cells (Tregs) depend on fatty acid oxidation and this modulation of T cell metabolism enhance Th1-mediated immunity, critical for controlling Mtb (3). Also, Mtb exploits host lipid droplets as nutrient sources, thus targeting lipid metabolism in host cells can restrict bacterial growth and modulate immune responses (2, 3).

While standard antibiotic regimens remain the cornerstone of TB treatment, multidrug-resistant and extensively drug-resistant strains are a global challenge. Host-directed therapies, such as metabolic immunomodulators were suggested as adjuncts to conventional therapy, aiming to enhance host immunity while limiting tissue damage (4). Immunometabolism which is the interplay between cellular metabolism and immune function has revealed that immune cell metabolic states dictate their response to Mtb. Activated macrophages and T cells undergo metabolic reprogramming, with glycolysis, oxidative phosphorylation, and lipid metabolism influencing antimicrobial activity. Modulating these pathways with metabolic immunomodulators offers a promising strategy to optimize immune responses in TB.

2. Main text

Immunomodulators: Immunomodulators represent a versatile class of therapeutic agents with wide-ranging clinical applications. Advances in understanding immune metabolism and signaling pathways have paved the way for more targeted and effective interventions. Immunomodulators can be broadly classified into immunostimulants, immunosuppresants, and metabolic immunomodulators. Immunosuppressants such as interferons and interleukins, bacterial components like lipopolysaccharides, and certain vaccines are agents that enhance immune responses during immunodeficiency states (9). Immunosuppressants are compounds that dampen immune activity in autoimmune diseases, transplant rejection, and chronic inflammatory conditions. Examples of classical immunosuppressants include corticosteroids, calcineurin inhibitors (e.g., cyclosporine), and mTOR inhibitors such as rapamycin (10). Metabolic immunomodulators highlight the role of metabolism in immune regulation, such as agents targeting glycolysis, oxidative phosphorylation, or amino acid metabolism that can selectively modulate immune cell subsets, e.g., AMPK activation to promote regulatory T cell function and 2-deoxyglucose inhibition of glycolysis in effector T cells (11). The present publication proposes LDH, IDO and ADA as potent metabolic immunoregulators to optimise PTB treatment efficacy while minimizing adverse effects.

Immune response to Mtb: According to Chai *et al.* (12), cell-mediated immunity plays a crucial role in controlling Mtb infection by activating macrophages, NK cells, and cytotoxic T-lymphocytes. The CD4+ T cells (Th1 cells) induce adaptive immunity while IFN-γ and IL-2 activate immune cells (especially macrophages). In addition, CD8+ T-cells directly destroy Mtb and Mtb-infected cells. This cell-mediated immunity leads to granuloma formation that contains and restricts the spread of Mtb. The T-bet is a transcription factor that is essential for Th1 development for protective immunity against Mtb, but regulatory T-cells (CD4+CD25+FoxP3+ T-reg cells) suppress immune responses to Mtb and possibly contribute to the persistence of Mtb infection. Despite these armouries of defence by the host against Mtb, the bacteria manipulates host immunity to persist in latent form or develop into chronic infection. The evading mechanism of host immunity by *Mtb includes* upregulation of multiple co-inhibitory molecules [programmed cell death protein 1 (PD-1), T-cell immunoglobulin and mucin domain-3 (TIM-3), lymphocyte-activation gene 3 (LAG-3)], reduced production of IFN-γ and secretion of suppressive cytokines (13). To counteract certain evasion mechanisms of host immunity by Mtb, this article suggests the application of lactate dehydrogenase (LDH), adenosine deaminase (ADA) and indoleamine 2,3-dioxygenase (IDO)-based immune checkpoints as an immunotherapeutic option. See Table 1 below.

Immunometabolism which is the interplay between cellular metabolism and immune function, has revealed that immune cell metabolic states dictate their response to Mtb. Activated macrophages and T cells undergo metabolic reprogramming, with glycolysis, oxidative phosphorylation, and lipid metabolism influencing antimicrobial activity. Modulating these pathways with metabolic immunomodulators offers a promising strategy to optimize immune responses in TB. Previously suggested metabolic immunomodulators in TB includes pharmacologic agents, metformin which is an antidiabetic drug that activates AMP-activated protein kinase (AMPK), enhances autophagy and mitochondrial ROS in macrophages and boosting bactericidal activity. Clinical studies suggest adjunctive metformin improves TB treatment outcomes (5). Others are immunomodulators in TB are: 2-Deoxyglucose (glycolysis inhibitor which modulates overactive inflammatory responses and prevent tissue damage in severe TB), rapamycin (mTOR inhibitor that promotes autophagy and enhances antigen presentation in macrophages), nutrient and metabolite-based modulators (short-chain fatty acids produced by gut microbiota like butyrate influence T cell differentiation, promoting Tregs and balancing inflammation), and amino acid modulators (such as tryptophan metabolism via indoleamine 2,3-dioxygenase (IDO) which can suppress excessive T cell activation, limiting immunopathology) (3-5). The appropriate metabolic immunomodulators in PTB patients are expected to enhance anti-Mtb immune responses, reduce tissue-damaging inflammation by Mtb, complement standard antibiotic therapy, potentially shorten treatment duration, and offer strategies against drug-resistant TB.

Table 1. Summary of the immune responses in tuberculosis**,** focusing on key immune cells and their roles.

Component	Role in TB Infection
Mycobacterium tuberculosis (Mtb)	Intracellular bacteria that infects macrophages
Alveolar Macrophages	Phagocytose Mtb; produce cytokines (IL-12, TNF-α); may be subverted by Mtb to survive intracellularly
Dendritic Cells (DCs)	Process Mtb antigens and present to T cells in lymph nodes
$CD4^+$ T cells (Th1)	Produce IFN-γ, activate macrophages to kill intracellular Mtb
$CD8^+$ T cells	Kill infected macrophages; secrete cytotoxic molecules and IFN-γ
B cells / Antibodies	Limited protective role; may aid opsonisation
Cytokines: IFN-γ	Activates macrophages to kill Mtb
Cytokines: TNF-α	Helps maintain granuloma structure; promotes inflammation
Cytokines: IL-12	Promotes Th1 differentiation
Granuloma	Contains infection; prevents spread of Mtb; central necrosis may occur (caseation)
Natural Killer (NK) cells	Secrete IFN-γ, kill infected cells
Neutrophils	Early responders; may contribute to tissue damage
Regulatory T cells (Tregs)	Limit excessive inflammation; may allow bacterial persistence

Metabolic Immunomodulators in Tuberculosis: Mechanisms and Therapeutic Potential

Considering prolonged therapy, drug resistance, and immune evasion by M.tb, recent studies suggest that host metabolism critically shapes immune responses against Mtb (30, 31). Lactate dehydrogenase (LDH), adenosine deaminase (ADA), and indoleamine 2,3-dioxygenase (IDO) are key metabolic enzymes influencing immune cell function and may serve as metabolic immunomodulators in TB (32-34). LDH is a key glycolytic enzyme converting pyruvate to lactate, linked to macrophage activation, ADA catalyzes deamination of adenosine, regulating extracellular adenosine levels and T cell function, while IDO degrades tryptophan to kynurenine, modulating T cell proliferation and inducing immune tolerance (6, 7). These enzymes influence both cellular metabolism and immune regulation, making them attractive targets for TB immunotherapy. Effective immunity against Mtb requires a coordinated response involving macrophages, dendritic cells, and T lymphocytes (8). However, Mtb manipulates host metabolism to evade immune clearance, creating opportunities for metabolic intervention. Therefore, modulating LDH, ADA, and IDO may complement antibiotics by enhancing immune-mediated Mtb clearance, may act as biomarker-guided therapy through monitoring LDH, ADA, and IDO activity can guide treatment response and disease prognosis, and balanced immune modulation by targeting these enzymes allows fine-tuning of inflammation, avoiding immunopathology while promoting pathogen clearance. Table 2 below summarises the effects of LDH, IDO and ADA on macrophages, T cells and Mtb survival.

Summarily, LDH, ADA, and IDO represent critical metabolic checkpoints in TB immunometabolism. Targeting these enzymes offers a promising avenue for host-directed therapy, with dual potential as biomarkers and therapeutic modulators.

Table 2. Summary of the effects of LDH, IDO and ADA on macrophages, T cells and Mtb survival.

Enzyme	Effect on Macrophages	Effect on T Cells	Effect on Mtb Survival
LDH	↑ Glycolysis, ↑ ROS/NO, M1 polarization	Supports effector T cells (if balanced)	↓ Mtb via enhanced killing
IDO	Promotes anti-inflammatory macrophages	↓ Effector T cell proliferation, ↑ Tregs	May ↑ Mtb survival due to immune suppression
ADA	↑ Macrophage activation, ↑ cytokines	↑ T cell proliferation, Th1 response	↓ Mtb survival via enhanced immunity

ADA is not toxic on its own, but the potential toxicity associated with adenosine deaminase (ADA) is primarily observed when the enzyme is deficient, leading to the accumulation of toxic metabolites and lymphocyte toxicity, costochondral flaring, liver damage, sensorineural deafness, neurobehavioral issues, and pulmonary alveolar proteinosis (14, 15). Data regarding ADA levels in pleural, peritoneal, and pericardial fluids of PTB patients have been documented (16), and the preliminary data of the authors of the present review showed a significantly higher mean serum level of ADA (71.40±13.01 ng/ml) in Nigerian PTB patients compared with non-infected healthy control (29.00±5.16 ng/ml).

According to literature, LDH itself is not inherently toxic (17). In tumor microenvironments, increased LDH activity (particularly LDHA or LDH-5) promotes a metabolic switch to produce lactic acid. This results in an acidic environment that promotes tumor metastasis, invasion, and immunosuppression. While excessive L-lactate production can lead to metabolic acidosis. However, D-lactate is specifically recognized as having direct neurotoxic effects such as confusion, dizziness, and cerebellar ataxia (17, 18). When T-cells are glucose-deprived, GAPDH binds IFN-gamma (IFN-γ) mRNA thereby preventing its translation and synthesis of IFN-γ production (15), which is pivotal in anti-TB immunity. Treatment with LDH inhibitors (quercetin, diclofenac and lonidamine) was suggested as immunotherapeutic attempts for tumours (19, 20) and COVID-19 patients (21). Such a therapeutic method could be attempted in TB, since TB and cancers share few similar characteristics, such as hypoxia, cell damage, inflammation and raised LDH, ADA and IDO (35, 36). Serum lactate dehydrogenase (LDH) levels are commonly elevated in patients with tuberculosis (TB) due to tissue damage and inflammation, serving as a useful, though non-specific, marker of disease activity (22).

Overactivities of IDO1 and TDO reduce the TRP availability and increase T-cell arrest (23). Thus, IDO-producing phagocytes deplete tryptophan levels in T-lymphocytes (24) to inhibit T-cell proliferation, promote T-cell death, and skew the Th1/Th2 balance toward Th2 bias. However, in infectious diseases, the precise role of IDO is not fully determined, and its importance during infectious diseases is just emerging. It is unclear whether increased IDO activity in infections is beneficial for host defense since IDO is considered an antimicrobial molecule, while it also exerts a potent immunosuppressive and immune-tolerance effect (24). In *Mycobacterium avium* infection, blocking IDO reduced the antimycobacterial effect of immunostimulatory oligodeoxynucleotide analogs *in vitro* (25). Li *et al.* (26) suggested that IDO is responsible for the impairment of T-cell functions in TB pleurisy. Based on literature, it may be conjectured that the stimulatory effect (at a moderately high level) or inhibitory function (at a very high level) of IDO is dose-dependent (23-26). This speculation is supported by our finding of insignificantly higher serum IDO in TB patients at diagnosis (1835.92±262.35 pg/ml) compared with healthy control (1862.32±326 pg/ml).

Natural- and synthetic- compounds as inhibitors of LDH, ADA and IDO: Natural compounds with LDH inhibiting actions are flavonoids curcumin and quercetin found in several foods, including apples and onions (27), kaempferol found in tea and various fruit, hesperidin found in citrus fruits, catechin in tea and resveratrol in red wine (28). Other substances with LDH inhibiting potentials includes alkaloid berberine found in plants (goldenseal and barberry), papaverine, and leonurine derived from the Lamiaceae family, terpenoids (ferruginol) found in a wide range of fruits, vegetables, and herbs, terpenoid ginkgolide B from *Ginkgo biloba* leaves (29), limonoids, ß-carotene from carrots and sweet potatoes (40), geniposidic acid *from Eucommia ulmoides Oliv*. bark, sulfur-containing allicin and taurine (41). *Flavonoids such as quercetin, kaempferol, daidzein* myricetin, naringenin and naringin are reported to *exhibit ADA inhibiting effects (42).* Other substances are coformycin from *Streptomyces kaniharaensis*, pentostatin from *Streptomyces antibioticus*, cordycepin from *Aspergillus nidulans*, flavonoids and sapogenins found in plant extracts like onion and garlic, curcumin from turmeric, genistein phytoestrogen found in soybeans, resveratrol from grapes and red wine, andrographolide compound from the plant *Andrographis paniculata*, epigallocatechin gallate (43). Natural compounds with potential ADA inhibitory activity include capsaicin, crocin, essential oils, ginseng, lanthipeptides, and some marine macroalgae (44).

A variety of IDO1 inhibitors have been found through rational design and natural compound screening (45). The polyphenols such as quinones Coenzyme Q (CoQ), quinone vitamin K3, shikonin A from *Radix arnebiae* extract from the northeastern Pacific marine hydroid, *Garveia annulata*, from marine sponge *Neopetrosia exigua* (45-48), *β*-Lapachone extract from the lapacho tree (*Tabebuia avellanedae*), extract from *Salvia prionitis* Hance or *Radix salviae* Miltiorrhizae (47), flavonoids from plant *Sophora flavescens*, Kushenol E, fungus *Penicillium herquei* inhibits IDO1 (49), tryptanthrin (indolo [2,1-b]quinazolin-6,12-dione) Chinese medicinal plants *Polygonum tinctorium* and *Isatis tinctoria,* brassinin, and PQA26 isolated from medicinal deciduous tree *Picrasma quassioides* (D. Don) and berberine isolated from plants in the berberis genus (50). Others are alkaloid extracts from the rhizomes of *Sinomenium acutum*, cinnabarinic acid, and NSC401366 (*N*-methyl-*N*''-9-phenanthrylimidodicarbonimidic diamide) (51, 52).

Considering the fact that tuberculosis is characterized by granuloma formation in the lungs (37) and metabolic immunomodulators are potentially supportive in the management of TB. However, the ability of these metabolic immunomodulators from fruits and herbs to penetrate TB granulomas poses significant challenges. There are no reports on that ADA, LDH and IDO actively penetrate TB granulomas as a therapeutic or transport molecules. Instead, ADA, LDH and IDO are locally produced by activated macrophages and lymphocytes within granulomatous tissue, which modulates cell-mediated immune response**,** especially macrophage and T-cell activities, rather than a direct antimycobacterial killing mechanism (66, 67, 68). Considering gaps in knowledge on these suggested metabolic immunomodulators (LDH, ADA and IDO) in Mtb, future studies on these should include reference doses, penetration strategies to enable them to enter granulomas, and whether augmentation with LDH, ADA and IDO improves bacterial clearance in pulmonary TB. Table 3 below presents the effects of LDH, ADA, and IDO inhibition on immune cells and Mtb survival. LDH inhibition balances glycolytic metabolism to prevent immunosuppressive lactate accumulation while maintaining antimicrobial functions. IDO inhibition restores tryptophan levels, enhancing T cell proliferation and reducing regulatory T cell-mediated suppression, tipping immunity toward bacterial clearance. ADA inhibition is a double-edged sword: while ADA normally reduces adenosine, careful modulation can prevent adenosine-mediated T cell suppression, enhancing anti-TB responses without causing excessive inflammation.

Table 3. Effects of LDH, ADA, and IDO Inhibition on Immune Cells and Mtb Survival.

Metabolic Enzyme	Effect of Inhibition on Macrophages	Effect of Inhibition on T Cells	Expected Outcome on Mtb Survival	Mechanistic Rationale
LDH	↓ Excess lactate accumulation → restores balanced M1/M2 polarization	↑ Effector T cell proliferation if lactate-mediated suppression is reduced	↓ Mtb survival via enhanced macrophage killing	Prevents lactate-induced immune suppression, maintaining optimal glycolysis for antimicrobial activity
IDO	↓ Anti-inflammatory signaling → macrophages maintain pro-inflammatory phenotype	↑ Effector T cell proliferation, ↓ Treg differentiation	↓ Mtb survival due to restored T cell-mediated immunity	Tryptophan availability restored → effector T cells activated, granuloma immunity enhanced
ADA	↓ Adenosine breakdown → may fine-tune macrophage activation (avoiding excessive inflammation)	↓ T cell proliferation suppression mediated by adenosine	↓ Mtb survival via improved T cell and macrophage responses	Reduces adenosine-mediated immunosuppression, allowing Th1 responses and cytotoxic activity

↑= Enhances, ↓= Reduces

Ethnomedicine in TB

Most TB patients are primarily from developing countries whose populations are not able to buy expensive drugs. Antituberculosis chemotherapy includes the usage of four drugs simultaneously for six months, which calls for poor adherence by patients and requires close supervision of patients to prevent progression of drug sensitive TB to drug-resistant TB (MDR-TB and XDR-TB). These MDR-TB and XDR-TB patients require two years of therapy of multiple second-line drugs, with a high percentage of treatment failure (54). Moreso, many drugs used to treat MDR-TB and XDR-TB patients with toxic side effects (38). To reduce the long duration of TB therapy, reduce the pill burden, and lessen toxic side effects, there is the need for supplemental support treatment. A large percentage of the Nigerian population, particularly in the rural areas, depends on traditional medicines (55). A number of natural plant extracts reported to have *in vitro* anti-*Mycobacterium tuberculosis* potential are abundant in Africa and Asia (56), which includes isoflavanoid quinone, abruquinone from *Abrus precatorius*, anthraquinone, polyphenolic flavonoids 1-epicatechol and leucopelargonidol from *Cassia siberiana* (57), tannin, punicalgin from *Combretum molle*, hydroxycycloartenol glycoside, mollic from *C. molle*, bioflavonoids and a xanthone from *Garcinia kola* (58-60), glycosides, saponins, steroids, and tannins from *Pterocarpus osun* (ETM 72) (61), arjunolic acid and friedelin from *Terminalia avicennioides*, oleanane type saponins and sulphates from *Tetrapleura tetraptera* (62). *Among other plants with anti-TB effects in Nigeria are Securidaca longepedunculata (63), Tapinanthus sessifolia* (64), and *Anogeissus leocarpus (57, 65).*

Nigerian medicinal plants with potential modulatory activities to LDH, IDO and ADA activities:

There are several Nigerian medicinal herbs and plants with demonstrateable potential for inhibiting ADA activity, because of their antioxidant and anti-inflammatory properties, especially in the management of cardiovascular, metabolic, and neurodegenerative conditions. Essential oils from Nigerian ginger (*Zingiber officinale*) rhizomes have significant inhibition of ADA activities in hypertensive rats. Nigerian turmeric (*Curcuma longa*) rhizomes exhibit substantial inhibitory activity towards adenosine deaminase and acetylcholinesterase, making them potential agents for managing cerebrovascular diseases. Studies suggest that hexane extracts of Moringa leaves (*Moringa oleifera*) have the potential to inhibit adenosine deaminase, as well as other enzymes like xanthine oxidase, providing therapeutic potential against oxidative stress and inflammatory diseases (39, 66). The root and leaf extracts of African Peach (*Nauclea latifolia*) are recognized for their antioxidant and anti-inflammatory effects, which can involve the modulation of enzyme activities. The bitter leaf (*Vernonia amygdalina*) is known for high flavonoid content (e.g., luteolin, apigenin) which inhibits various enzymes involved in inflammatory pathways. The scent leaf (*Ocimum basilicum*) **c**ontains rutin and other compounds with potential in controlling metabolic diseases through modulation of ADA activity, and the root extracts of *Rauwolfia vomitoria* affect adenine deaminase levels, suggesting potential for managing arthritis and neurotoxicity (66, 67).

Nigerian medicinal herbs with potentials for modulating lactate dehydrogenase (LDH) activity, either by inhibition or regulation. The aqueous extracts of *L. taraxacifolia* leaves affect LDH activity with glucose-lowering mechanisms. The extract of *Tetracarpidium conophorum* (African Walnut) reduces protein catabolism and decreases elevated levels of lactate dehydrogenase, assisting in faster recovery from oxidative stress. *Gongronema latifolium* known for anti-diabetic and cardiovascular protective effects by normalising serum LDH levels. *Phyllanthus nivosus* (snowbush) has inhibitory potential against Plasmodium lactate dehydrogenase (pLDH) while *Newbouldia laevis* (Ogilisri/Akoko) is used for its anti-inflammatory and cardioprotective potential by lowering cardiac marker enzyme levels, including LDH, to prevent damage caused by stress. The compounds in the bark of *Enantia chlorantha* (African Yellow Wood) have shown inhibitory potential against lactate dehydrogenase. (68, 69).

Loranthus micranthus (African mistletoe) is the primary Nigerian herb identified in research to suppress indoleamine 2,3-dioxygenase (IDO) activity, particularly via inhibition of JAK/STAT and NF-κB pathways in cancer cells. Other Nigerian plants with high flavonoid, terpene, saponin, and phenolic contents that indirectly modulate IDO include *Vernonia amygdalina*, *Morinda lucida*, and *Moringa oleifera* (70, 71). The leaf and twig extracts of Loranthus micranthus (*African Mistletoe*) significantly suppress IDO expression, making it a candidate for treating cancers that exploit IDO for immune evasion.

3. CONCLUSIONS

Emerging evidence positions LDH, IDO, and ADA as pivotal metabolic immunomodulators that influence the outcome of *Mycobacterium tuberculosis* infection by shaping both innate and adaptive immune responses. Modulating these metabolic immunomodulators offers a promising host-directed therapeutic approach that complements conventional anti-TB drug regimens because they have the potential to boost host immunity, reduce bacterial burden, and minimize tissue-damaging inflammation.

4. FUTURE DIRECTIONS AND PERSPECTIVES

The identification of LDH, IDO, and ADA as key metabolic checkpoints in tuberculosis (TB) opens new avenues for host-directed therapies aimed at enhancing immune-mediated control of *Mycobacterium tuberculosis*. Future studies should focus on delineating the precise molecular pathways by which LDH, IDO, and ADA influence immune cell metabolism and function during Mtb infection. Understanding how they regulate macrophage polarization, T cell effector function, and granuloma formation will enable rational design of targeted modulators with maximal efficacy and minimal off-target effects. In addition, in vivo models of TB are needed to test LDH, IDO, and ADA inhibitors or activators, both as monotherapies and in combination with standard anti-TB drugs, using bacterial clearance, modulation of immune responses, granuloma integrity, and tissue pathology as indicators. Dose responses and temporal dynamics of metabolic modulation should be assessed to minimize potential immune overactivation or immunopathology. Future studies should evaluate whether these enzymes can serve as pharmacodynamic readouts for host-directed interventions, guiding personalized therapy. Carefully designed clinical trials to evaluate the safety, tolerability, and efficacy of metabolic immunomodulators in TB patients are required by exploring combinatorial approaches with standard antimycobacterial therapy, particularly in multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB. The molecular approaches, such as integration of metabolomics, transcriptomics, and immunophenotyping, will provide a holistic understanding of how LDH, IDO, and ADA pathways interact with broader host metabolic networks. Such studies could identify additional synergistic targets and optimize metabolic intervention strategies using host-directed TB therapeutics to offer a more effective, shorter, and personalized treatment regimens.

List of abbreviations

ADA = Adenosine deaminase
APCs = Antigen presenting cells.
BCG = Bacille Calmette Guerin
BTLA = B- and T-lymphocyte attenuator
CD = cluster of differentiation

CoQ = Coenzyme Q
CTLA-4 = Cytotoxic T-lymphocyte associated antigen - 4
GAPDH = Glyceraldehyde 3 Phosphate Dehydrogenase
GITR = Glucocorticoid-induced TNFR-related
HVEM = Herpes virus entry mediator
IDO = Indoleamine 2,3 dioxygenase
IFN-γ = IFN-gamma indoleamine 2,3-dioxygenase (IDO)
LAG-3 = Lymphocyte-activation gene 3
LDH = Lactate dehydrogenase
MHC = Major Histocompatibility Complex
MHC = Major Histocompatibility Complex
NKC =Natural iller cell
PD-1 = Programmed cell death protein 1
PD-L1 = Programmed cell death 1 ligand 1
TB = Tuberculosis
TDO = *Tryptophan 2,3-dioxygenase*
Th = T-helper
TIM-3 = T-cell immunoglobulin and mucin domain-3
T-reg = Regulatory T cells
TRP = Tryptophan

Declarations

Ethics approval and consent to participate: Not applicable at this stage.

Consent for publication: Nothing to declare.

Availability of data and materials: All literatures consulted during this study are included in this published article.

Competing interests: The authors declare that they have no competing interests.

Funding: No grant from funding agencies in the public, commercial, or not-for-profit sectors was received.

Authors' contributions: All authors contributed equally in the concept, draft, revision and approval of the manuscript.

Acknowledgements: The authors of consulted literatures are appreciated.

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