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MICROENVIRONMENTAL ALTERATIONS MYCOBACTERIUM LEPRAE: A SYSTEMATIZED REVIEW

ALTERAÇÕES MICROAMBIENTAIS EM MYCOBACTERIUM LEPRAE: UMA REVISÃO SISTEMATIZADA

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ABSTRACT

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae*, an obligate intracellular pathogen with tropism for macrophages and Schwann cells, predominantly affecting the skin and peripheral nerves. Despite the effectiveness of multidrug therapy (MDT) recommended by the World Health Organization (WHO), limitations such as emerging drug resistance, adverse effects, long therapeutic duration, and persistence of neurological sequelae stimulate the search for new therapeutic approaches. This systematic review analyzed the role of the leprosy microenvironment. *In vitro* and *in vivo* studies, molecular analyses, and systematic reviews involving mechanisms were included. The study highlights the relevance of lysosomes and their dynamics of the cellular microenvironment in bacillary persistence and the immune response to leprosy. In this context, strategies integrating pathophysiology and immunomodulation emerge as promising perspectives for the development of new anti-leprosy agents.

Keywords: Leprosy; *Mycobacterium leprae*; microenvironment; lysosomes; innate immunity.

RESUMO

A hanseníase é uma doença infecciosa crônica causada por *Mycobacterium leprae*, patógeno intracelular obrigatório com tropismo por macrófagos e células de Schwann, afetando predominantemente pele e nervos periféricos. Apesar da eficácia da poliquimioterapia (PQT) recomendada pela Organização Mundial da Saúde (OMS), limitações como resistência farmacológica emergente, efeitos adversos, longa duração terapêutica e persistência de sequelas neurológicas estimulam a busca por novas abordagens terapêuticas. Esta revisão sistematizada analisou o papel do microambiente hansênico. Foram incluídos estudos *in vitro*, *in vivo*, análises moleculares e revisões sistemáticas envolvendo mecanismos O estudo destaca a relevância dos lisossomos e da sua dinâmica do microambiente celular na persistência bacilar e na resposta imunológica à hanseníase. Nesse contexto, estratégias integrando fisiopatologia e imunomodulação emergem como perspectivas promissoras para o desenvolvimento de novos agentes anti-hansênicos.

Palavras-chave: Hanseníase; *Mycobacterium leprae*; microambiente; lisossomos; imunidade inata.

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INTRODUCTION

Leprosy is a neglected chronic infectious disease caused primarily by *Mycobacterium leprae*, an obligate intracellular acid-fast bacillus with tropism for macrophages and Schwann cells. More recently, *Mycobacterium lepromatosis* has also been associated with diffuse and severe forms of the disease, expanding the etiopathogenic complexity of leprosy. Despite its relatively limited infectivity, the disease exhibits a high capacity for intracellular persistence and slow clinical evolution, potentially resulting in permanent physical disabilities when diagnosis and treatment are not performed early (RIDLEY; JOPPLING, 1966; LOCKWOOD; SATYANARAYANA, 2004; LASTÓRIA; ABREU, 2014).

Although *M. leprae* exhibits high global genetic conservation, different geographic lineages have already been described, allowing for molecular epidemiological tracking of disease dissemination. Leprosy is more prevalent in economically active adults and socially vulnerable populations, especially in endemic regions (MINUZZO, 2001; 2007). Its clinical manifestation is strongly determined by the host's immune response, ranging from paucibacillary tuberculoid forms, characterized by an efficient Th1 cellular response and organized granulomas, to multibacillary lepromatous forms, associated with relative immunosuppression, intense bacillary load, and diffuse infiltrates rich in foamy macrophages (RIDLEY; JOPPLING, 1966). Thus, leprosy constitutes a paradigmatic model of interaction between intracellular pathogen, immune metabolic microenvironment, and immune evasion mechanisms.

Even decades after the introduction of multidrug therapy (MDT) recommended by the World Health Organization (WHO), consisting of rifampicin, dapsone, and clofazimine, leprosy remains a significant public health challenge, especially in endemic countries such as Brazil, India, and Indonesia (WORLD HEALTH ORGANIZATION, 2021). Brazil historically holds the second position worldwide in absolute number of cases, behind only India,

maintaining high endemicity in the North, Northeast, and Central-West regions (BRASIL, 2023; PENNA et al., 2020).

Although MDT has significantly reduced the overall prevalence of the disease, important therapeutic limitations persist, including long treatment duration, occurrence of severe leprosy reactions, low therapeutic adherence, drug interactions, pharmacological toxicity, and the emergence of rifampicin-resistant strains (DEPS et al., 2020; LAVANIA et al., 2015; FISCHER et al., 2022). Among the most relevant adverse effects are cutaneous hyperpigmentation associated with clofazimine and the risk of dapsone-induced hemolysis in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency (RODRIGUES; LOCKWOOD, 2011). Furthermore, neurological sequelae often remain irreversible even after bacillary elimination.

In this context, the study of the leprosy microenvironment has acquired increasing scientific relevance. The interaction between *M. leprae* and host cells triggers profound immunological, metabolic, and structural remodeling of the infected tissue. Macrophages, Schwann cells, fibroblasts, T lymphocytes, and various inflammatory mediators actively participate in the formation of niches that are permissive or restrictive to bacillary persistence. Alterations in the extracellular matrix, lipid metabolism, tissue hypoxia, and autophagy pathways contribute directly to the clinical progression of the disease and to chronic neural damage.

Among the cellular components involved in this process, lysosomes emerge as central organelles in intracellular defense against mycobacteria, acting in phagolysosomal degradation, antigen presentation, autophagy, and cellular immunometabolism. Recent evidence demonstrates that *M. leprae* interferes with phagolysosomal maturation and autophagic dynamics, favoring its intracellular survival, immune evasion, and bacterial persistence (GUTIERREZ et al., 2008; DERETIC; SAITO; SAITO, 2013). Therefore, mechanisms related to the autophagy-lysosome axis are being considered potential therapeutic targets in intracellular infectious diseases.

In parallel, the search for new therapeutic agents of natural origin has grown significantly in recent decades. Historically, natural compounds have been used empirically in the treatment of leprosy, including chaulmoogra oil before the introduction of modern MDT (DUMAS DOS SANTOS et al., 2008). Currently, natural products continue to represent an important source of molecular scaffolds for pharmaceutical development, including antimycobacterial compounds (NEWMAN; CRAGG, 2020). Brazil's high biodiversity positions the country as an important platform for bioprospecting bioactive molecules (RATES, 2001; BERLINCK et al., 2017).

Several natural metabolites, including flavonoids, alkaloids, terpenes, phenolic compounds, essential oils, propolis, honey, and marine metabolites, have demonstrated antimycobacterial activity through different mechanisms, such as inhibition of mycolic acid biosynthesis, membrane disruption, oxidative modulation, and induction of autophagy. In addition to direct antimicrobial activity, many of these compounds exhibit immunomodulatory potential, acting on the inflammatory microenvironment and restoring intracellular host defense mechanisms (PARASCANDOLA, 2003).

Despite recent advances, significant scientific gaps remain regarding the integrated understanding of the leprosy microenvironment, lysosomal dynamics, and the therapeutic potential of natural products in the face of intracellular persistence of *M. leprae*. The absence of robust experimental models for culturing the bacillus and the scarcity of translational studies limit the development of new host-targeted therapeutic strategies.

Given this scenario, the present study critically reviews the role of the immunometabolic microenvironment and lysosomes in the pathophysiology of leprosy.

METHODOLOGY

This review was conducted according to the methodological principles of a systematized literature review, with a structured strategy for searching, eligibility, and critical

analysis of the scientific literature related to the leprosy microenvironment and lysosomal dynamics in the presence of *Mycobacterium leprae*.

The bibliographic search was conducted between 2023 and 2025, including classic and contemporary publications indexed since 1960, in order to encompass historical, immunopathological, and therapeutic aspects relevant to the understanding of leprosy.

The databases consulted included PubMed/MEDLINE, Scopus, Web of Science, SciELO, LILACS, Cochrane Library, and Google Scholar. Additionally, technical documents and guidelines from the World Health Organization (WHO), the Brazilian Ministry of Health, as well as theses and dissertations available in recognized institutional repositories were analyzed.

The descriptors and keywords were selected from MeSH and DeCS terms, combined using Boolean operators (AND, OR, and NOT), including: *Mycobacterium leprae*, “leprosy”, “hanseniasis”, “microenvironment”, “lysosomes”, “autophagy”, “physiopathology”, “antimycobacterial activity”, “drug resistance”, “mechanism of action”, “*in vitro*”, and “*in vivo*”.

The following were included: (i) original and review articles published in indexed and peer-reviewed journals; (ii) academic books and chapters published by recognized scientific publishers; (iii) theses and dissertations from national and international postgraduate programs; and (iv) technical documents from international health organizations.

The exclusion criteria included: (i) conference abstracts without full publication; (ii) case reports without pharmacological or mechanistic relevance; (iii) studies without validated experimental methodology or without an adequate control group; (iv) publications not peer-reviewed or classified as predatory; and (v) studies without adequate chemical identification of the compounds analyzed. Publications in languages other than Portuguese, English, Spanish, and French were excluded.

The critical analysis of the publications considered the methodological design, the robustness of the experimental evidence, the biological models used, and the relevance. At the

end of the screening and eligibility process, 312 potentially relevant references were identified, of which 187 comprised the final analytical basis of this review, and after applying the inclusion and exclusion criteria, 84 official publications were used.

RESULTS

The disease and its host.

- Characterization of the Etiological Agent and Microbiological Aspects

Mycobacterium leprae is an acid-fast bacillus (AFB), variable Gram-positive, with approximate dimensions of 0.3–0.5 µm × 4–7 µm, belonging to the family Mycobacteriaceae and the order Actinomycetales (RASTOGI et al., 1992; COLE et al., 2001). Its highly reduced genome, with approximately 3.3 Mb, reflects an extensive process of regressive evolution, presenting only about 49.5% of functional coding genes. This genomic reduction explains its metabolic dependence on the host and the inability to culture axenly in artificial media *in vitro*, considered one of the main methodological limitations for experimental studies involving the pathogen (COLE et al., 2001; MONOT et al., 2009).

The cell wall of *M. leprae*, similar to that observed in other pathogenic mycobacteria, presents a complex lipid architecture composed of peptidoglycan, arabinogalactan, long-chain mycolic acids (C60–C90), as well as specific phenolic glycolipids, such as phenolic glycolipid-I (PGL-I), and lipoarabinomannan (LAM) (BRENNAN; NIKAIDO, 1995; ARBEIT et al., 1993). This composition confers high intrinsic resistance to various antimicrobials, disinfectants, and host defense mechanisms. Simultaneously, components of the cell wall constitute important pharmacological targets for antimycobacterial compounds and therapeutic strategies directed at the bacillus (RASTOGI et al., 1992; ORTEGA-OJEDA et al., 2020).

Another striking characteristic of *M. leprae* is its extremely slow multiplication rate, with an estimated generation time between 12 and 14 days. Furthermore, its experimental

cultivation remains primarily restricted to the nine-banded armadillo (*Dasypus novemcinctus*) and to the inoculation model in the plantar pad of immunosuppressed mice (KIRCHHEIMER; STORRS, 1971; JACOBS et al., 2016). These experimental limitations significantly hinder the development of classic pharmacological studies, especially those related to the screening of new antimycobacterial agents.

Given these limitations, different mycobacterial species have been used as surrogate models in experimental assays, including *Mycobacterium tuberculosis*, *M. smegmatis*, and *M. aurum*. These models allow for preliminary evaluation of bioactive compounds with antimycobacterial potential, a strategy widely accepted in the scientific literature for pharmacological prospecting and mechanistic studies (FRANZBLAU et al., 1998; LOUGHEED et al., 2009; MDLULI; SPIGELMAN, 2006).

Conventional Treatment and the Problem of Resistance

The multidrug therapy (MDT) regimen recommended by the World Health Organization (WHO), introduced in 1981 and progressively implemented in Brazil from the 1990s onwards, represented a fundamental milestone in the epidemiological control of leprosy, drastically reducing the global prevalence of the disease from 21.1 cases to less than 1 case per 10,000 inhabitants (WHO, 2021). The standard therapeutic regimen combines rifampicin, dapsone, and clofazimine, acting through complementary pharmacological mechanisms. Rifampicin exerts potent bactericidal activity by inhibiting DNA-dependent RNA polymerase through binding to the β subunit encoded by the rpoB gene. Dapsone has a predominantly bacteriostatic action, acting by competitive inhibition of dihydropteroate synthase in the folate biosynthetic pathway. Clofazimine, on the other hand, has slow bactericidal activity, mainly associated with interference in the mycobacterial respiratory chain and the intracellular generation of reactive oxygen species (WHO, 2018; DEPS et al., 2020; RICHARDSON et al., 2009).

Despite the high therapeutic efficacy of MDT, the emergence of primary resistance to rifampicin has been progressively documented in different endemic countries, including Brazil, representing a significant threat to the global control of the disease (LAVANIA et al., 2015; CAMBAU et al., 2018; RODRIGUES; LOCKWOOD, 2011). Mutations in the rpoB gene, analogous to those described in *M. tuberculosis*, have been identified even in patients with no prior history of treatment, suggesting active transmission of resistant strains (LAVANIA et al., 2015; VEDITHI et al., 2018).

In addition to drug resistance, factors such as long therapeutic duration, low adherence to treatment, pharmacological toxicity, and the occurrence of leprosy reactions contribute significantly to the limitations of MDT. This scenario becomes even more worrying given the absence of new classes of clinically approved antileprosy drugs since the mid-20th century, reinforcing the urgent need for prospecting new bioactive compounds and innovative therapeutic strategies (DEPS et al., 2020; WHO, 2021).

- Microenvironment and Pathophysiology

The tissue microenvironment corresponds to a dynamic and highly regulated biological niche, consisting of resident cells, extracellular matrix (ECM), blood and lymphatic vessels, as well as a complex network of soluble mediators, physicochemical and metabolic signals, including pH, oxygen tension, nutrient availability, and products of cellular metabolism. Under physiological conditions, this microenvironment plays an essential role in maintaining tissue homeostasis, cell regeneration, and coordinating intercellular and immunological communication (KALLURI; ZEISBERG, 2006).

Under pathological conditions, particularly in chronic infectious diseases, the microenvironment undergoes intense structural, metabolic, and immunological remodeling resulting from the continuous interaction between the host and the pathogen. This process results in the formation of specialized inflammatory niches, characterized by alterations in cellular composition, reorganization of the extracellular matrix, metabolic dysfunction, and

modulation of immune pathways that directly influence microbial persistence, disease progression and tissue damage (KALLURI; ZEISBERG, 2006; WU; JAIN, 2020).

In leprosy, the lesion microenvironment plays a central role in determining the clinical spectrum of the disease. The interaction between *M. leprae* and host cells, especially macrophages and Schwann cells, triggers polarized immune responses associated with different inflammatory, metabolic, and structural profiles. These alterations include extracellular matrix remodeling, intracellular lipid accumulation, tissue hypoxia, production of immunomodulatory cytokines, and dysregulation of autophagic and lysosomal pathways—factors directly related to bacillary persistence and the clinical evolution of leprosy.

Microenvironmental Characteristics in Leprosy

The leprosy microenvironment constitutes a highly specialized immune metabolic niche, resulting from the dynamic interaction between M. leprae, host cells, and the extracellular matrix (ECM). The organization of this microenvironment varies significantly across the clinical spectrum of the disease. In tuberculoid forms (TT and BT), a pro-inflammatory profile predominates, characterized by high cellularity, formation of compact granulomas, intense macrophage activation, increased expression of adhesion molecules, and relatively limited vascularization. In contrast, multibacillary lepromatous forms (BL and LL) present a predominantly immunosuppressive microenvironment, marked by diffuse inflammatory infiltrate, abundance of foamy macrophages (Virchow cells), exacerbated angiogenesis, relative hypoxia, and intense accumulation of neutral lipids and esterified cholesterol in both the ECM and the cell cytoplasm (MODLIN et al., 1986; RAMASWAMY et al., 2021).

Local physicochemical factors also exert a decisive influence on bacillary survival and persistence. *M. leprae*'s preference for anatomical regions with lower body temperatures, generally between 30–32 °C, favors its replication in cutaneous tissues and peripheral nerves. Simultaneously, alterations in interstitial pH, nutrient availability, and lipid composition of the microenvironment contribute to the bacillus's metabolic adaptation. Extracellular matrix

remodeling mediated by matrix metalloproteinases (MMPs), associated with disorganized collagen deposition, promotes perineural fibrosis, loss of tissue elasticity, and progression of neurological damage (KAPLAN et al., 2019).

Lipid metabolism plays a central role in the pathophysiology of multibacillary leprosy. M. leprae exhibits a high dependence on host-derived lipids for the maintenance of its metabolism and the synthesis of cell wall components rich in glycolipids and phenols. Consequently, infected macrophages develop an intense intracellular accumulation of lipid droplets, forming metabolically reprogrammed foam cells that function as permissive niches for bacterial persistence (SILVA et al., 2020). This phenomenon brings leprosy closer to other chronic infectious diseases associated with the immunometabolic reprogramming of phagocytic cells.

The cellular composition of the leprosy microenvironment is predominantly formed by macrophages, Schwann cells, T lymphocytes, dendritic cells, and fibroblasts. Macrophages constitute the main effector cells involved in both the containment and dissemination of the bacillus. In paucibacillary forms, macrophages with the M1 phenotype predominate, activated mainly by interferon gamma (IFN-γ), exhibiting high production of nitric oxide (NO) and reactive oxygen species (ROS), associated with microbicidal activity. In contrast, in multibacillary forms there is an expansion of macrophages with an M2 profile and foam cells, characterized by the expression of scavenger receptors, high production of interleukin-10 (IL-10) and transforming growth factor beta (TGF-β), in addition to intense intracellular lipid accumulation, favoring local immunosuppression, dysfunctional tissue repair and bacillary survival (STENGEL et al., 2015; RAMASWAMY et al., 2021).

Schwann cells represent another critical component of this microenvironment, constituting the main neural target of *M. leprae*. Infection promotes cellular dedifferentiation and acquisition of characteristics similar to those of mesenchymal stem cells, associated with myelin loss, phenotypic plasticity, and increased migratory capacity. This process contributes

not only to progressive neural damage but also to the intracorporeal dissemination of the bacillus (MASAKI et al., 2013).

In the lymphocyte component, CD4+ T cells with a Th1 profile predominate in paucibacillary forms, associated with the production of pro-inflammatory cytokines and greater bacillary control. In multibacillary forms, Th2, regulatory T (Treg), and Th17 responses predominate, related to permissive immune modulation and the persistence of infection. CD8+ T lymphocytes participate in cytotoxicity against infected cells, although they also contribute to axonal injury and inflammatory exacerbation during reactional episodes, particularly in type 1 leprosy reactions (LOCKWOOD; SATYANARAYANA, 2004; MODLIN, 2010).

Biochemical and Immunological Mediators

The leprosy microenvironment is regulated by a complex network of cytokines, chemokines, lipid mediators, and growth factors that continuously modulate the interaction between *M. leprae* and the host's immune system. The immunological profile varies according to the clinical spectrum of the disease and exerts a decisive influence on bacillary containment, infectious persistence, and the extent of tissue damage.

In tuberculoid forms, cytokines associated with the Th1-type cellular immune response predominate, especially interferon gamma (IFN-γ), interleukin-12 (IL-12), and tumor necrosis factor alpha (TNF-α). These molecules promote classic macrophage activation, increased microbicidal activity, and the formation of organized granulomas. Simultaneously, chemokines such as CXCL9 and CXCL10 favor the recruitment of effector T lymphocytes and amplify the local inflammatory response (MODLIN et al., 1986; KAPLAN et al., 2019).

In contrast, lepromatous forms present a predominantly immunosuppressive immunological profile, characterized by high expression of interleukin-10 (IL-10), transforming growth factor beta (TGF-β), interleukin-4 (IL-4), in addition to the chemokines CCL2 and CCL18. This set of mediators reduces antigen presentation, inhibits the microbicidal activity of macrophages, and favors polarization towards the M2 phenotype,

contributing to the intracellular persistence of the bacillus and dissemination of the infection (MODLIN et al., 1986; KAPLAN et al., 2019).

In addition to classic cytokines, lipid mediators play a central role in the inflammatory modulation of leprosy. Prostaglandin E2 (PGE2), leukotriene B4 (LTB4), and specialized pro-resolution mediators, such as resolvins and maresins, are functionally dysregulated in leprosy lesions. In multibacillary forms, elevated levels of PGE2 and LTB4 are associated with vasodilation, tissue edema, macrophage dysfunction, and perpetuation of chronic inflammation. Conversely, insufficient production of pro-resolution mediators contributes to failure of inflammatory resolution and maintenance of a microenvironment permissive to bacillary persistence (SCHENCK et al., 2018).

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) also play a dual role in the pathophysiology of the disease. Although essential for intracellular bacterial clearance mechanisms, their excessive production contributes to oxidative stress, mitochondrial damage, and progressive perineural injury, especially in sensory neurons and Schwann cells (KAPLAN et al., 2019).

The formation of leprosy granuloma represents one of the main structural events of the immune response to *M. leprae*. However, the granuloma is not a static structure, but rather a dynamic microenvironment subjected to intense immune metabolic remodeling. In tuberculoid forms, the organized Th1/Th17 response favors containment of the infection, although it may result in fibrosis, edema, and neural compression. In lepromatous forms, the deficiency in the formation of compact granulomas allows hematogenous and lymphatic dissemination of the bacillus, associated with diffuse infiltration and progressive loss of local immunological competence (RIDLEY; JOPPLING, 1966; STENGEL et al., 2015).

The neural damage observed in leprosy results from both direct and indirect mechanisms. Invasion of Schwann cells by *M. leprae* promotes demyelination and progressive axonal degeneration, while secondary inflammatory mechanisms—including vasculitis, granulomatous edema, and neural ischemia—aggravate peripheral neuropathy.

Leprosy reactions represent acute exacerbations of this inflammatory microenvironment. The type 1 reaction (reversal reaction) is associated with a shift to an exacerbated Th1 profile, accompanied by tissue edema, intense lymphocytic infiltrate, and a high risk of acute neuropathy. Type 2 reaction, known as erythema nodosum leprosum (ENL), corresponds to immune complex-mediated vasculitis, characterized by a significant increase in TNF-α, IL-6, and IL-8, in addition to systemic neutrophilic infiltrate frequently associated with fever, neuritis, and multisystem involvement (LOCKWOOD; SATYANARAYANA, 2004; KAPLAN et al., 2019).

In parallel, local metabolic alterations contribute significantly to maintaining a niche permissive to the bacillus. The accumulation of esterified cholesterol, triglycerides, and ceramides in foamy macrophages creates a lipid microenvironment favorable to the survival of M. leprae. Recent evidence demonstrates that the metabolic reprogramming of macrophages and Schwann cells, involving regulatory pathways such as HIF-1α, mTOR, and PPARγ, plays a central role in the chronicity of the infection, in local immunosuppression, and possibly in the therapeutic tolerance observed in advanced forms of the disease (RAMASWAMY et al., 2021; SILVA et al., 2020).

The Role of Lysosomes in the Microenvironment of Leprosy

Lysosomes are acidified intracellular organelles, with a pH between approximately 4.5 and 5.0, containing a wide range of acid hydrolases, including cathepsins, lipases, nucleases, and phosphatases. Traditionally recognized for their degradative function, lysosomes also play a central role in antigen presentation via major histocompatibility complex class II (MHC-II), in cellular metabolic signaling, in the control of autophagy, in energy homeostasis, and in programmed cell death mechanisms (SAFTIG; KLUENKAMP, 2011; BALLABIO; BONIFACINO, 2020). In the context of leprosy, lysosomal dynamics represent a critical component for both host defense mechanisms and the intracellular persistence of *M. leprae*.

Under physiological conditions, phagocytosis of mycobacteria by macrophages is followed by phagosome maturation and its fusion with lysosomes, promoting intracellular

acidification, enzymatic activation, and the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS), culminating in pathogen degradation. However, *M. leprae* has developed sophisticated intracellular evasion mechanisms capable of blocking phagolysosomal maturation and preventing adequate acidification of the phagocytic compartment. Experimental evidence demonstrates that this process involves interference in the recruitment of regulatory proteins such as Rab7, V-ATPase, and SNARE proteins, as well as the modulation of intracellular pathways associated with PI3K/Akt and mTOR, diverting the phagosome to non-degradative compartments and favoring bacillary survival (GUTIERREZ et al., 2008; DERETIC; SAITO; SAITO, 2013).

Autophagy, a lysosome-dependent mechanism responsible for the degradation of damaged organelles and intracellular pathogens, is also profoundly altered in multibacillary leprosy. *M. leprae* manipulates immune recognition pathways mediated by Pattern Recognition Receptors (PRRs), proteins of the innate immune system responsible for recognizing pathogen-associated molecular patterns (PAMPs). This manipulation results in the suppression of essential proteins of the autophagic machinery, including Beclin-1 and LC3-II, as well as the persistent activation of mTORC1, leading to the inhibition of autophagosome formation and reduced intracellular bacterial degradation (GUTIERREZ et al., 2008; STENGEL et al., 2015).

In contrast, in the tuberculoid forms of the disease, autophagic activity is relatively preserved or functionally induced by mediators such as interferon gamma (IFN-γ) and vitamin D, correlating with a greater capacity for bacillary control. These findings reinforce the importance of the autophagy-lysosome axis as a central component of the effector immune response against *M. leprae* (GUTIERREZ et al., 2008; STENGEL et al., 2015). Lysosomal function also plays a determining role in adaptive antigen presentation. The proteolytic degradation of mycobacterial antigens within lysosomes is an essential step for peptide loading onto MHC-II molecules and subsequent activation of CD4+ T lymphocytes. Thus, the lysosomal dysfunction observed in lepromatous forms directly contributes to deficient

antigenic presentation, lymphocyte anergy, and immunological polarization permissive to the Th2 profile (GUTIERREZ et al., 2008; STENGEL et al., 2015).

In addition to degradative functional impairment, lysosomal alterations can trigger intense inflammatory activation. The unregulated release of cathepsins into the cytosol or extracellular medium promotes the activation of inflammasomes, particularly NLRP3, amplifying the production of pro-inflammatory cytokines and inducing pyroptosis in infected cells. Pyroptosis corresponds to a highly inflammatory form of programmed cell death characterized by the formation of membrane pores, cellular edema, cytoplasmic rupture, and massive release of inflammatory mediators, differing substantially from classical apoptosis. This mechanism appears to play a relevant role during reactional episodes, especially in type 1 leprosy reaction and erythema nodosum leprosum (ENL) (SAFTIG; KLUENKAMP, 2011; KAPLAN et al., 2019).

From a metabolic standpoint, lysosomes also play a role in intracellular lipid catabolism through lysosomal acid lipase (LAL). Dysfunction or saturation of this pathway favors the accumulation of lipid droplets in infected macrophages, resulting in the characteristic foamy phenotype of Virchow cells. Simultaneously, *M. leprae* sequesters host-derived lipids for the synthesis of structural components of its cell wall, while host metabolic pathways mediated by PPARγ and SREBP perpetuate lipid storage and local immunosuppression (RAMASWAMY et al., 2021; SILVA et al., 2020).

Given these mechanisms, therapeutic strategies aimed at lysosomal and autophagic modulation have attracted increasing interest as potential adjuvant approaches to conventional polychemotherapy. Autophagy-inducing compounds, such as rapamycin, metformin, and vitamin D3, as well as lysosomal pH modulators and mTOR inhibitors, demonstrate potential to restore intracellular bacterial degradation mechanisms, reduce bacterial load, and modulate exacerbated inflammatory responses (DERETIC; SAITO; SAITO, 2013; SCHENCK et al., 2018). However, the therapeutic manipulation of these pathways requires high biological

precision, since lysosomal and inflammatory hyperactivation can intensify neural damage and tissue degeneration in advanced stages of the disease.

MAIN ANTIMYCOBACTERIAL MECHANISMS OF ACTION INVESTIGATED

- Inhibition of Mycolic Acid Synthesis

Mycolic acids are fundamental structural components of the mycobacterial cell wall, accounting for approximately 60% of its dry mass and being responsible for the low permeability, chemical resistance, and high hydrophobicity characteristic of mycobacteria (BRENNAN; NIKAIDO, 1995). This complex lipid architecture plays a central role in the virulence, intracellular survival, and antimicrobial resistance of *M. leprae* and other species of the genus.

Among the enzymes involved in the biosynthesis of these lipids, the NADH-dependent enoyl-acyl carrier protein reductase (InhA) stands out as a strategic pharmacological target. InhA catalyzes an essential step in the elongation of long-chain fatty acids that originate mycolic acids, being the main molecular target of isoniazid and ethionamide used in antimycobacterial therapy (BANERJEE et al., 1994; ROZWARSKI et al., 1998).

Several natural compounds have demonstrated inhibitory potential on this metabolic pathway. Epigallocatechin-3-gallate (EGCG), the main bioactive catechin isolated from *Camellia sinensis* L., showed direct inhibition of *M. tuberculosis* InhA with IC50 values close to 12.5 µg/mL, standing out because it does not depend on activation by the KatG (catalase-peroxidase) enzyme, a mechanism frequently associated with isoniazid resistance (ZHAO et al., 2011; CHENG et al., 2019). This characteristic suggests potential translational relevance in the development of new active agents against resistant strains.

Recent molecular modeling and computational docking studies involving *M. leprae* InhA have also identified high binding affinity for several naturally occurring secondary

metabolites, including quercetin, apigenin, and artepillin C. The observed binding free energy values (-7.8 to -9.2 kcal/mol) were comparable to those of the enzyme's physiological substrate, suggesting potential inhibitory capacity on mycolic acid biosynthesis (VEDITHI et al., 2020; ORTEGA-OJEDA et al., 2020).

In addition to their direct action on InhA, flavonoids and phenolic compounds can interfere with multiple components of mycobacterial lipid biosynthesis, promoting cell wall disorganization, increased membrane permeability, and greater bacterial susceptibility to oxidative stress and conventional antimicrobial agents. These findings reinforce the potential of natural products as promising sources of new molecular scaffolds for the development of innovative antimycobacterial therapies.

- Disruption of the Cell Membrane and Wall

The integrity of the mycobacterial plasma membrane and cell wall constitutes a strategic target for bioactive compounds of natural origin, especially due to the unique lipid composition of mycobacteria. The cell envelope of *M. leprae* exhibits high hydrophobicity and structural complexity, being formed by peptidoglycan, arabinogalactan, mycolic acids, and various glycolipids associated with virulence and intrinsic resistance to antimicrobial agents (BRENNAN; NIKAIDO, 1995; RASTOGI et al., 1992).

In this context, terpene phenolic compounds present in essential oils have demonstrated significant antimycobacterial activity through mechanisms related to the structural disruption of the cell membrane. Substances such as thymol, carvacrol, and eugenol interact directly with the bacterial lipid bilayer, promoting alterations in membrane fluidity and permeability, collapse of the transmembrane proton gradient, and impairment of ATP synthesis (ULTEE et al., 2002; LAMBERT et al., 2001; BURT, 2004). The high lipophilicity of these compounds favors their diffusion through the lipid-rich mycobacterial envelope, a characteristic that may confer a specific pharmacological advantage against mycobacteria when compared to other Gram-negative bacteria.

In addition to bioenergetic impairment, membrane destabilization results in ion loss, leakage of intracellular metabolites, and increased bacterial susceptibility to oxidative stress. Experimental studies also suggest that some phenolic monoterpenes may act synergistically with conventional antibiotics, increasing cell wall permeability and facilitating intracellular access of antimycobacterial drugs.

Among bioactive alkaloids, berberine stands out as one of the most investigated natural compounds due to its broad antimicrobial activity. This isoquinoline alkaloid exerts multiple effects on the bacterial cell, including disruption of the cytoplasmic membrane, intercalation into DNA, and inhibition of enzymes involved in genomic replication, particularly topoisomerases and DNA gyrases (HUANG et al., 2014).

Molecular docking studies have demonstrated that berberine exhibits high affinity for the GyrB subunit of *M. leprae* DNA gyrase, an enzyme essential for bacterial replication and transcription processes, with an estimated binding energy of approximately -8.4 kcal/mol (ORTEGA-OJEDA et al., 2020). These results suggest a potential dual action of the compound, combining effects on membrane structural integrity and direct interference in the mycobacterial DNA replication machinery.

The multifactorial action of these natural metabolites represents a particularly relevant aspect in the context of mycobacteria, since multiple mechanisms of action can reduce the likelihood of developing drug resistance (EDMOND; ROLLET, 1909). Therefore, compounds capable of simultaneously altering cell permeability, compromising energy metabolism, and interfering with strategic intracellular targets emerge as promising candidates for future antimycobacterial therapeutic approaches.

Immunomodulation and Enhancement of the Host Response

In addition to direct antimicrobial activity, several natural products exhibit significant immunomodulatory potential, acting on central mechanisms of the host's immune response against *M. leprae*. This therapeutic approach is particularly relevant in leprosy, since the

clinical evolution of the disease strongly depends on the balance between antimycobacterial effector mechanisms and immunoregulatory pathways that allow for bacillary persistence.

M. leprae has developed sophisticated immune evasion strategies, including inhibition of phagolysosomal maturation, suppression of antigen presentation via MHC-II, and modulation of cytokine production in favor of a regulatory/Th2 immune profile. This pattern is characterized by increased interleukin-10 (IL-10), interleukin-4 (IL-4), and transforming growth factor beta (TGF-β), concomitantly with a reduction in mediators associated with the protective Th1 response, such as interferon gamma (IFN-γ), interleukin-12 (IL-12), and tumor necrosis factor alpha (TNF-α) (GOULART; PENNA; CUNHA, 2002; LASTÓRIA; ABREU, 2014; DEPS et al., 2020).

In this context, natural compounds capable of restoring or modulating the cellular immune response are of high therapeutic interest. Curcumin, a polyphenol derived from Curcuma longa, has demonstrated the ability to partially reverse the immunosuppressive profile observed in lepromatous leprosy, promoting increased production of IFN-γ by CD4+ T lymphocytes in mononuclear cell cultures obtained from multibacillary patients (VEDITHI et al., 2020). These findings suggest potential restoration of microbicidal macrophage activity and immunological control over infection.

Similarly, propolis and CAPE (caffeic acid phenethyl ester), an important phenolic compound derived from bee products, have demonstrated the ability to selectively modulate inflammatory pathways associated with immune-mediated tissue damage. Experimental studies have shown inhibition of NF-κB activation, resulting in reduced transcription of pro-inflammatory cytokines involved in neural damage observed during leprosy reactions, without significantly compromising the microbicidal activity of macrophages (SFORCIN; BANKOVA, 2011; COELHO et al., 2020). This characteristic makes the potential of these compounds particularly relevant as adjuvant agents capable of modulating excessive inflammation without inducing generalized immunosuppression.

Another noteworthy mechanism involves the modulation of intracellular autophagy. Natural compounds capable of inducing autophagic pathways have been considered promising strategies against chronic intracellular pathogens. Resveratrol, a polyphenol found in grapes and other plant species, has been shown to induce autophagy in macrophages infected with *M. tuberculosis*, promoting a reduction of approximately 60–70% in intracellular bacterial load *in vitro* by directing bacilli towards lysosomal degradation (SINGHAL et al., 2014).

Considering that *M. leprae* shares phagolysosomal evasion mechanisms similar to those observed in *M. tuberculosis*, the pharmacological induction of autophagy represents a therapeutic target of high translational interest. Activation of these pathways can simultaneously contribute to increased bacterial intracellular clearance, restoration of lysosomal function, and modulation of the chronic inflammatory response, configuring an innovative therapeutic approach in the context of leprosy (MAYER-BARBER et al., 2010; DEPS et al., 2020).

Thus, the immunomodulation promoted by natural products transcends simple direct antimycobacterial activity, involving complex mechanisms of immune metabolic reprogramming, autophagic activation, and restoration of the host's immune competence. These effects make natural compounds particularly promising as potential adjuvant agents to conventional multidrug therapy, especially in multibacillary and reactive forms of the disease.

- Inhibition of Oxidative Stress and Other Target Mechanisms of Action

Oxidative stress plays an ambivalent role in the pathophysiology of mycobacteria, acting both as a host defense mechanism and as an antimicrobial pharmacological strategy. Similar to the mechanism of action of clofazimine used in multidrug therapy (MDT), several natural products exert antimycobacterial activity through the controlled induction of reactive oxygen species (ROS) inside the bacterial cell.

Bioactive compounds such as curcumin, artepillin C, and CAPE (caffeic acid phenethyl ester) have demonstrated the ability to promote the collapse of bacterial membrane potential, disruption of energy metabolism, and increased intracellular generation of ROS at antimycobacterial concentrations. This redox imbalance results in oxidative damage to bacterial DNA, lipid peroxidation, and inhibition of essential mycobacterial antioxidant systems, including catalase-peroxidase (KatG) and superoxide dismutase (SOD) (BHATT et al., 2009; NANDAKUMAR et al., 2010; SFORCIN; BANKOVA, 2011).

The susceptibility of mycobacteria to oxidative stress stems, in part, from their high dependence on antioxidant mechanisms to neutralize ROS produced during intracellular infection. Therefore, compounds capable of overloading or inhibiting these defense pathways become particularly relevant as potential antimycobacterial agents (NANDAKUMAR et al., 2010; SFORCIN; BANKOVA, 2011).

In addition to inducing oxidative stress, natural products exhibit multiple complementary pharmacodynamic mechanisms. Terpenic and phenolic compounds can interact directly with mycolic acids, arabinogalactan, and other components of the mycobacterial cell wall, promoting increased permeability of the bacterial envelope and facilitating the entry of hydrophilic molecules and conventional antimicrobials (KUMAR et al., 2012). In parallel, flavonoids, alkaloids, and quinones demonstrate inhibitory activity on essential enzymes of mycobacterial metabolism, including DNA gyrase (GyrA/GyrB), InhA, and ATP synthase, compromising fundamental processes such as genomic replication, energy metabolism, and lipid biosynthesis (SINGLA; DUBEY, 2014).

Another relevant mechanism involves the inhibition of bacterial efflux pumps associated with drug resistance. Alkaloids such as berberine and coumarin derivatives have demonstrated the ability to block transporters involved in the extrusion of antimicrobials, partially restoring bacterial susceptibility to classic antibiotics. This effect may enhance the therapeutic efficacy of MDT and reduce adaptive resistance mechanisms (SINGLA; DUBEY, 2014).

Additionally, several natural products exert important immune modulatory effects. Apicultural products, such as honey and propolis, have demonstrated the ability to modulate the production of inflammatory cytokines, reducing exacerbated levels of TNF-α, IL-6, and other mediators associated with leprosy reactions, while also favoring more balanced Th1-type cellular immune responses, fundamental for the intracellular control of *M. leprae* (RIBEIRO et al., 2020). As well as for the healing of ulcers with torpid evolutions (VARRICCHIO et al., 2026; 2026a).

The simultaneous action on multiple cellular targets represents one of the main pharmacological advantages of natural products. Unlike many synthetic antimicrobials directed at a single molecular target, natural bioactive compounds often exhibit pleiotropic mechanisms that combine direct antimicrobial activity, metabolic modulation, and immune regulation (VARRICCHIO et al., 2026a). This characteristic can reduce the likelihood of developing bacterial resistance and expand the translational potential of these compounds as adjuvant agents in the treatment of leprosy.

DISCUSSION

This review synthesized scientific evidence related to the microenvironment as a potential therapeutic target for antimycobacterial compounds applicable to leprosy, discussing mechanisms of action, methodological limitations, and translational perspectives for the development of adjuvant therapies to multidrug therapy (MDT).

Leprosy remains a significant global public health problem, particularly in developing countries, due to persistent active transmission, late diagnosis, and a high frequency of disabling neurological sequelae. Although MDT has significantly reduced the global prevalence of the disease since its implementation by the World Health Organization (WHO) and in Brazil by the Ministry of Health (2002; 2008; 2017; 2022; 2023, a), peripheral neuropathy, functional loss, and associated deformities often remain irreversible, even after

bacteriological cure. Because of this clinical and social impact, the Brazilian Ministry of Health has published important guiding documents for clinical management and disability prevention, including Dermatology in Primary Health Care (2002), the Manual for Disability Prevention in Leprosy (2008), and the Practical Guide on Leprosy (2017).

Unlike tuberculosis, another highly prevalent and potentially lethal mycobacteriosis, leprosy is characterized by slow and progressive evolution, marked mainly by peripheral neural destruction and chronic remodeling of the tissue microenvironment. Despite the effectiveness of MDT in interrupting bacillary transmissibility, the persistence of progressive neural damage, recurrent inflammatory reactions, and permanent sequelae demonstrates that isolated microbiological elimination is not sufficient to restore the immunological and functional homeostasis of affected tissues. In this context, natural substances capable of modulating inflammation, autophagy, oxidative stress, and lipid metabolism are assuming increasing therapeutic relevance (VARRICCHIO et al., 2026; 2026a).

Epidemiological analysis of Brazil between 2000 and 2024 demonstrates a progressive reduction in the absolute number of reported cases in practically all regions of the country, reflecting advances in epidemiological surveillance, diagnosis, and access to treatment. However, the persistence of physical disabilities and the maintenance of high endemicity rates in certain regions reveal that leprosy remains out of control in several vulnerable areas. Recent studies point to a relative increase in cases in the Central-West region, a phenomenon that may reflect both diagnostic improvements and local epidemiological changes that are not yet fully understood (VARRICCHIO et al., 2026). This scenario reinforces the need for more in-depth regional investigations, including cohort studies and integrated analyses of socio-environmental, immunological, and microbiological factors.

From a pathophysiological point of view, the review shows that the leprosy microenvironment plays a central role in the persistence of *M. leprae* and the clinical progression of the disease. The bacillus is capable of manipulating multiple host cellular pathways, including phagolysosomal maturation, autophagy, lipid metabolism, and

macrophage polarization, favoring the formation of an immunosuppressive niche, particularly in lepromatous forms. The accumulation of lipids in Virchow cells, the activation of pathways such as mTOR and PPARγ, and the inhibition of autophagy contribute to the intracellular survival of the bacillus and the maintenance of the chronic inflammatory state. In this scenario, natural compounds with immunomodulatory and autophagy-regulating activity are of significant translational interest.

Among the main antimycobacterial mechanisms identified in this review, the following stand out: inhibition of mycolic acid synthesis, disruption of the mycobacterial membrane, modulation of oxidative stress, inhibition of efflux pumps, and regulation of the host immune response.

Despite the advances described, important methodological limitations persist in anti-leprosy research. The impossibility of axenic culture of *M. leprae* restricts the direct experimental validation of most of the compounds studied, leading to the predominant use of surrogate models, such as *M. smegmatis* and *M. tuberculosis*. Although this strategy is widely accepted due to the conservation of several metabolic targets among mycobacteria, pharmacological extrapolations should be interpreted with caution. Furthermore, many available studies present methodological heterogeneity, toxicological limitations, and a scarcity of controlled clinical trials.

Thus, the integration of immunomodulation and adjuvant therapies represents a promising perspective for the development of more effective, less toxic approaches that are potentially capable of reducing disabling sequelae associated with leprosy.

Stigma as a historical descriptor and psychosocial care

Leprosy transcends the biomedical field and historically constitutes an illness deeply marked by symbolic, moral, religious, and sociocultural constructions that have influenced, throughout the centuries, the collective perception of affected individuals. The social imaginary related to the ancient "leprosy" was consolidated by medical, religious, and

institutional discourses that associated the disease with impurity, divine punishment, moral degeneration, and social exclusion, contributing to the formation of a persistent stigma that spans different historical periods and cultures (MINUZZO, 2001; MINUZZO, 2007).

The world of the imaginary, deeply immersed in culture, shapes social relations, institutional practices, and collective discourses in any society and era. In this context, understanding the historical construction of the stigma associated with leprosy implies analyzing not only the disease itself, but also the symbolic systems that produced certain social representations of the illness. The persistence of negative perceptions related to leprosy demonstrates that historically consolidated social structures can transform into mental structures reproduced intergenerationally, influencing behaviors, feelings, and forms of social exclusion (MINUZZO, 2001; MINUZZO, 2007).

Social representations of leprosy have never been homogeneous or static. On the contrary, they have varied according to the historical, religious, scientific, and political contexts in which they were embedded. Thus, different discourses have coexisted and transformed over time, producing multiple interpretations of the diseased body, transmissibility, isolation, and the morality attributed to patients. In fact, the social reproduction of these discourses has historically contributed to practices of segregation, compulsory institutionalization, and the invisibility of affected individuals, especially during periods when hygienist and moralizing conceptions of the disease predominated (MINUZZO, 2001; MINUZZO, 2007).

The historical analysis of leprosy stigma does not seek to rigidly separate the "real" from its symbolic representation, since both constitute complementary dimensions of human experience. Social perceptions, even if based on beliefs currently considered irrational or scientifically outdated, have had concrete impacts on public policies, family relationships, access to work, schooling, and social integration of patients. In this sense, prejudice and social exclusion associated with leprosy cannot be understood merely as secondary consequences of

the disease, but as constitutive elements of its own historical and epidemiological trajectory (MINUZZO, 2001; MINUZZO, 2007).

Even after the therapeutic advances provided by MDT and the significant reduction in the global prevalence of the disease, stigma remains a major contemporary challenge. Many patients still face social discrimination, psychological suffering, family isolation, work difficulties, and fear of disclosing their diagnosis. Neurological sequelae and physical deformities, frequently associated with advanced forms of the disease, exacerbate exclusion processes and significantly compromise the quality of life, self-esteem, and social participation of affected individuals (MINUZZO, 2001; MINUZZO, 2007; EIDT, 2015).

In this context, psychosocial care emerges as an indispensable component of comprehensive leprosy care. A humanized approach must consider not only the microbiological control of the infection, but also the emotional, family, economic, and social impacts resulting from the illness. Health education strategies, multidisciplinary support, strengthening patient autonomy, and combating prejudice are fundamental to reducing the suffering associated with the disease and promoting social reintegration processes (EIDT, 2015).

Furthermore, understanding the socioeconomic and cultural reality of the affected populations allows for the development of more effective and territorially appropriate public policies. The persistence of leprosy in socially vulnerable regions highlights its close relationship with structural inequalities, difficulties in accessing health services, low levels of education, and precarious living conditions. Therefore, addressing the stigma and disabilities associated with leprosy requires integrated action between epidemiological surveillance, clinical care, health education, and social inclusion policies.

Therefore, more than understanding leprosy merely as a chronic infectious disease, it is necessary to recognize it as a complex historical, social, and cultural phenomenon. Overcoming stigma depends not only on biomedical advances but also on transforming the social representations that have historically marginalized affected individuals. In this sense,

promoting integrated, humanized, and human rights-based psychosocial care is an essential step in reducing suffering, strengthening social bonds, and improving the quality of life of people affected by leprosy.

THERAPEUTIC PERSPECTIVES

In the context of leprosy neuropathies, nanobiotechnology also presents relevant perspectives for neuroprotection and tissue regeneration. Nanostructured systems containing antioxidants, neurotrophic factors, and anti-inflammatory compounds are being investigated to reduce neural oxidative stress, preserve myelin sheaths, and minimize damage to Schwann cells. Although still predominantly in the experimental phase, these approaches represent promising possibilities for reducing permanent disabilities associated with leprosy (NEWMAN; CRAGG, 2020; DEPS et al., 2020).

Another emerging approach involves the use of hybrid nanosystems associated with natural biomaterials, smart hydrogels, and systems responsive to pH or inflammatory stimuli. These technologies allow for the selective release of the drug in inflammatory or acidified environments, such as those found in leprosy granulomas and phagolysosomal compartments. This selectivity can increase local therapeutic efficacy and reduce systemic toxicity (NEWMAN; CRAGG, 2020; DEPS et al., 2020).

Despite the high translational potential, significant challenges still limit the clinical application of these technologies. These include production costs, difficulties in industrial scaling up, long-term stability, regulatory standardization, toxicological evaluation, and the need for robust clinical trials. Furthermore, the interaction between nanoparticles and the human immune system still requires in-depth investigation, especially in chronic diseases characterized by intense immune modulation, such as leprosy (NEWMAN; CRAGG, 2020; DEPS et al., 2020; VARRICCHIO et al., 2026; 2026a).

Even with these limitations, the integration of bioactive natural products and nanobiotechnology represents one of the most innovative and promising therapeutic strategies

identified in this review. The combination of multifunctional antimycobacterial compounds with intelligent controlled-release systems could significantly contribute to the development of more effective, selective, and less toxic therapies, expanding future prospects for the treatment of leprosy and other neglected mycobacterioses (NEWMAN; CRAGG, 2020; DEPS et al., 2020; VARRICCHIO et al., 2026; 2026a).

Pharmacological Synergism and Therapeutic Combinations

The investigation of therapeutic combinations between bioactive natural compounds and classic MDT drugs represents one of the most promising strategies for tackling leprosy, especially in the face of the emergence of resistant strains and the pharmacological limitations associated with conventional regimens. The concept of pharmacological synergism is based on the positive interaction between different molecules capable of mutually potentiating their antimicrobial, immunomodulatory, or anti-inflammatory effects, resulting in greater therapeutic efficacy when compared to the isolated use of the compounds (NEWMAN; CRAGG, 2020; DEPS et al., 2020).

The paradigm of pharmacological synergism takes on even greater relevance in light of the growing concern about antimicrobial resistance. In mycobacteria, mechanisms such as mutations in target genes, cell wall impermeability, and overexpression of efflux pumps contribute to reduced therapeutic efficacy of classic antibiotics. In this context, multifunctional natural compounds can act by restoring bacterial sensitivity to conventional drugs, reducing selective pressure and delaying the emergence of resistance. Furthermore, the possibility of reducing therapeutic doses of classic medications can contribute to a decrease in adverse effects associated with MDT, including hepatotoxicity, peripheral neuropathy, and skin reactions (NEWMAN; CRAGG, 2020; DEPS et al., 2020; VARRICCHIO et al., 2026a).

Another relevant aspect concerns the ability of some natural compounds to act simultaneously on the bacillus and on the host's inflammatory microenvironment. The combination of classic antimicrobial agents with immunomodulatory, antioxidant, and

autophagy-inducing molecules can favor not only bacillary elimination but also the reduction of neural damage and chronic inflammation associated with leprosy reactions. Thus, combinatorial strategies have the potential to expand the overall therapeutic efficacy of the disease, including microbiological control and tissue protection (NEWMAN; CRAGG, 2020; DEPS et al., 2020; VARRICCHIO et al., 2026; 2026a).

From a methodological point of view, the systematic screening of therapeutic combinations using microdilution assays in microplates (“checkerboard assays”) has become an important tool for identifying synergistic interactions between natural compounds and conventional antimicrobials. This approach allows the calculation of fractional inhibitory concentration indices (FICI), distinguishing between synergistic, additive, indifferent, or antagonistic interactions. The application of these methodologies in models using *M. tuberculosis*, *M. smegmatis*, and other surrogate mycobacteria constitutes a rational strategy for the initial screening of candidates with anti-*M. leprae* potential, especially considering the experimental limitations imposed by the inability to culture the axenic bacillus (FRANZBLAU et al., 1998; LOUGHEED et al., 2009).

Beyond classic checkerboard assays, contemporary approaches involving molecular modeling, artificial intelligence, and virtual screening are expanding the ability to identify promising combinations. *In silico* tools allow for the prediction of molecular affinity, pharmacodynamic interactions, and potential toxic effects before experimental validation, reducing costs and accelerating the translational development of new therapeutic candidates.

Bioprospecting of Brazilian Biodiversity

The advancement of this area depends on the integration of modern biotechnological strategies. In silico screening by molecular docking and computational modeling allows the selection of compounds with affinity for essential *M. leprae* targets, such as InhA, GyrB, MmpL3, and SodA, reducing costs and experimental development time. In parallel, nanotechnology delivery systems, including liposomes, polymeric nanoparticles,

nanoemulsions, and cyclodextrins, can increase the stability, bioavailability, and tissue targeting of new compounds to infected macrophages and Schwann cells, enhancing therapeutic efficacy and reducing systemic toxicity (CHENG et al., 2019; DEPS et al., 2020).

From a translational perspective, more sophisticated experimental models have been proposed to overcome the limitations imposed by the impossibility of axenic culture of *M. leprae*. Primary Schwann cell cultures, cutaneous organoids, humanized models, and three-dimensional systems that mimic the neural microenvironment represent promising alternatives to the classic murine plantar cushion model, allowing analyses closer to human pathophysiology (CHENG et al., 2019; DEPS et al., 2020).

Finally, the incorporation of natural products into anti-leprosy therapy requires scientific rigor, phytochemical standardization, toxicological evaluation, and multicenter clinical validation. Regulation by agencies such as the National Health Surveillance Agency and the World Health Organization (2009; 2018; 2021; 2022; 2023) will demand robust studies of efficacy, pharmacovigilance, and drug interactions before the formal integration of these compounds into MDT.

Critical synthesis of findings, gaps, and translational potential

Despite the identified methodological limitations, the findings gathered in this review demonstrate significant translational potential for new products and secondary metabolites as sources of novel anti-leprosy therapeutic strategies. The convergence between antimycobacterial activity, immune modulation, autophagy induction, and interference in host metabolic pathways suggests that many of these compounds act not only directly on the bacillus but also on the immune metabolic microenvironment that sustains the persistence of *M. leprae*. This characteristic is particularly relevant in leprosy, whose pathophysiology depends heavily on the interaction between pathogen, macrophages, Schwann cells, and the extracellular matrix.

From a technological standpoint, nanobiotechnology represents one of the most promising strategies for enabling the clinical application of these compounds. Nanostructured systems can increase bioavailability, chemical stability, plasma half-life, and selective targeting to infected macrophages and Schwann cells. Liposomes, polymeric nanoparticles, nanoemulsions, and hybrid systems functionalized with PGL-I or specific macrophage receptor ligands can allow controlled release and higher intracellular concentration of bioactive compounds in affected tissues.

The integration of computational biology tools and artificial intelligence also represents a strategic advance for the discovery of new therapeutic candidates. Molecular docking studies, dynamic modeling, and virtual screening of natural libraries allow prioritization of compounds with higher affinity for essential *M. leprae* proteins, significantly reducing experimental costs.

Another important translational aspect concerns the possibility of therapeutic repositioning of natural substances already used clinically for other conditions. Compounds such as metformin, vitamin D3, resveratrol, and rapamycin have immune metabolic and autophagic effects that are potentially useful as adjuvants to MDT, especially in the control of multibacillary forms and leprosy reactions. This strategy can reduce the time required for clinical development, since part of the safety profile is already established.

However, for these advances to be effectively incorporated into anti-leprosy therapy, it will be necessary to overcome important regulatory, methodological, and translational challenges. The validation of biomarkers of therapeutic response, the development of experimental models that are more representative of the neural microenvironment, the phytochemical standardization of complex extracts, and the performance of randomized multicenter clinical trials constitute fundamental steps for the future incorporation of new adjuvant therapies to MDT.

From a clinical and regulatory standpoint, one of the most plausible next steps would be the development of phase I/II pilot studies evaluating standardized formulations of

Brazilian green propolis associated with the conventional MDT regimen. Such studies could investigate outcomes such as tolerability, pharmacokinetics, therapeutic adherence, impact on bacillary load, frequency of leprosy reactions, and progression of neural damage. Multicenter trials conducted in endemic areas of Brazil, associated with partnerships between universities, public institutions, leprosy reference centers, and the pharmaceutical industry, could significantly accelerate the bench-to-bedside translation.

LIMITATIONS OF CURRENT STUDIES

A critical analysis of the literature on natural products with antimycobacterial activity relevant to leprosy reveals important methodological, experimental, and translational limitations that restrict both the comparability between studies and the clinical extrapolation of the results obtained. Although there is a growing number of publications describing the antimycobacterial activity of natural compounds against surrogate mycobacteria, the quality and standardization of this evidence remain heterogeneous.

Another important limitation lies in the almost exclusive reliance on surrogate models. Due to the impossibility of axenic culture of *M. leprae* in artificial media, most studies use *M. tuberculosis*, *M. smegmatis*, *M. aurum*, or *M. bovis* BCG as surrogate experimental models. Although there is significant structural homology between several metabolic pathways of these mycobacteria, direct extrapolation of the results to *M. leprae* remains limited and requires methodological caution. Physiological, metabolic, and immunopathological differences between species can result in distinct pharmacological responses, particularly regarding intracellular interaction with Schwann cells and human macrophages.

The available *in vivo* models also present significant limitations. The classic murine plantar cushion model, despite being historically established for anti-leprosy studies, has a long experimental duration, low analytical productivity, and high operational cost. More sophisticated models, such as SCID and nude mice, remain restricted to a few specialized centers due to the high technical complexity and infrastructure required. Consequently, most

of the reviewed natural compounds have never been directly evaluated against *M. leprae* under robust experimental conditions.

Toxicity also remains under-investigated. Few studies have systematically evaluated chronic toxicity, neurotoxicity, hepatotoxicity, immunotoxicity, and potential drug interactions with rifampicin, dapsone, and clofazimine. This aspect is particularly relevant in leprosy, where patients often require prolonged treatment and have an increased risk of systemic inflammatory reactions.

Another limiting factor relates to the scarcity of controlled clinical studies. Most of the available evidence is at levels IV and V of the scientific evidence hierarchy, corresponding predominantly to *in vitro* studies, animal models, or observational analyses. Randomized, multicenter, controlled clinical trials evaluating adjuvants to MDT are practically nonexistent. Thus, despite the identified biological potential, there is still insufficient clinical evidence for a formal therapeutic recommendation of these compounds in the treatment of leprosy.

Additionally, there is a significant gap in the development of experimental models capable of adequately reproducing the neural and immunometabolic microenvironment characteristic of human leprosy. The absence of standardized systems involving infected human Schwann cells, neural organoids, or three-dimensional models significantly limits the translational understanding of the effects of these compounds on neural damage, bacillary persistence, and leprosy reactions.

CONTRIBUTION

This systematic literature review contributes to the consolidation and critical integration of available scientific knowledge about natural substances with potential antimycobacterial activity relevant to leprosy, bringing together evidence scattered in the literature on plant products, marine compounds, bioactive secondary metabolites, honey, propolis, and other natural derivatives. By articulating microbiological, immunological,

pharmacological, and biotechnological data, the study offers an integrated view of the translational potential of these compounds in the context of *M. leprae* infection.

Unlike reviews focused exclusively on classic antimicrobial activity, this work broadens the discussion by incorporating aspects related to the immune metabolic microenvironment of leprosy, lysosomal function, autophagy, lipid metabolism, and intracellular evasion mechanisms used by the bacillus. In this way, the review proposes a more comprehensive and biologically coherent approach to the pathophysiology of the disease, focusing on lysosomes, highlighting that potential future anti-leprosy therapies may act simultaneously on the pathogen, the host, and the inflammatory processes responsible for the disabling neural sequelae.

CONCLUSION

Leprosy remains a neglected infectious disease of high biological, clinical, and social complexity, marked by the dynamic interaction between *Mycobacterium leprae* and the host's immune metabolic microenvironment. Disease progression, granuloma formation, peripheral nerve damage, and leprosy reactions result from an integrated network of inflammatory, metabolic, and immunoregulatory responses that determine the clinical spectrum of the infection. In this context, lysosomes and autophagy emerge as central elements of the pathophysiology, acting both in intracellular defense against the bacillus and as targets of subversion by *M. leprae*, which manipulates phagolysosomal, metabolic, and immunological pathways to ensure persistence and dissemination.

However, methodological limitations remain substantial. The impossibility of axenic culture of *M. leprae*, the scarcity of specific experimental models, the compositional heterogeneity of natural extracts, and the absence of controlled clinical trials restrict the immediate translation of findings into clinical practice. Furthermore, aspects related to

pharmacokinetics, toxicity, chemical standardization, and drug interactions remain insufficiently clarified.

Despite these limitations, the data gathered indicate relevant translational prospects, particularly for immunomodulatory and autophagy-inducing compounds associated with nanotechnology and targeted delivery systems.

Finally, the integration of microbiology, immunology, nanotechnology, and biotechnology will be fundamental for the development of innovative adjuvant therapies capable of reducing bacterial load, modulating inflammatory reactions, preventing neural damage, and minimizing permanent disabilities associated with leprosy. The advancement of this scientific agenda will depend on the consolidation of psychosocial attention, more translational experimental models, robust pharmacological studies and multicenter clinical trials conducted especially in endemic regions.

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