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Article Review

A Literature Review and Bibliometric Analysis of *Multidrug Therapy* (MDT) Resistance in *Mycobacterium leprae*

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Abstract

Background: Leprosy remains a global public health problem, and the emergence of resistance to *Multidrug Therapy* (MDT) poses a serious obstacle to eradication efforts.
Objective: This study aims to systematically review the mechanisms of resistance, the types of drugs involved, and the diagnostic approaches, while mapping research trends through bibliometric analysis.
Methods: The study was conducted using a *Systematic Literature Review* (SLR) method based on PRISMA guidelines with data sourced from Scopus for the 2015–2025 publication period. Of the 11,166 identified articles, only 16 met the inclusion criteria. Furthermore, a bibliometric analysis using the Bibliometrix R package on 2,214 publications was conducted to describe country scientific production, country production over time, co-occurrence, and word cloud.
Results: The results showed that gene mutations *rpoB*, *folP1*, and *gyrA*is a major determinant of resistance to rifampin, dapsone, and ofloxacin, while new mechanisms such as partial duplication *folP1* and compensatory mutations in *rpoC* indicates increasingly complex resistance patterns. India and Brazil contribute the most publications, in line with their high disease burden, while Indonesia's figures are relatively low despite being a major endemic country.
Conclusion: This study emphasizes that MDT resistance requires more precise strategies, including strengthening molecular surveillance, genetic-based diagnostics, and developing locally tailored therapeutic policies. Increased research capacity and international collaboration are also needed to accelerate the achievement of global leprosy elimination targets.

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INTRODUCTION

Leprosy (Hansen's disease) remains a global public health problem. The WHO reports that countries such as India, Brazil, and Indonesia are among the top three contributors to the world's leprosy burden.[1] This disease is caused by *Mycobacterium leprae*, an acid-fast bacillus that attacks the skin, peripheral nerves, and upper respiratory tract.[2,3] If not treated quickly and appropriately, this infection can cause permanent defects in the skin, nerves, eyes, motor system disorders, and strengthen the social stigma against sufferers.[4,5] Various treatment programs have been implemented, including the implementation of *MultiDrug Therapy* (MDT) consisting of rifampicin, dapsone, and clofazimine is effective in reducing the prevalence of leprosy globally, however cases of resistance to one or more MDT components have begun to be reported in various regions.[6]

Resistance to Multi Drug Therapy is a major challenge in leprosy control and elimination efforts. A recent meta-analysis study revealed a 10.18% increase in global drug resistance and increased after 2009.[7] Various molecular studies have identified genetic mutations associated with drug resistance, such as mutations in the gene *folP1* associated with resistance to dapsone, *rpoB* to rifampin, and *gyrA* to ofloxacin.[8,9] These mutations can alter the structure of the drug target in the bacterial body, thereby reducing the effectiveness of treatment, increasing the risk of relapse, and prolonging the period of infection. Interestingly, this mutation pattern shows quite wide geographic variation. In Indonesia, a new *gyrA* mutation was identified in the strain *M. Leprosy* from West Papua that are resistant to ofloxacin.

It is important to understand the impact of this mutation in order to develop new antimycobacterials that are not susceptible to resistance.[10] To address this challenge, researchers are exploring various strategies to identify new drug targets in *M. leprosy*, including in silico and in vitro studies, flux balance analysis, and gene expression profiling.[11] Although these mutations have been studied in various countries, a comprehensive understanding of the mechanisms, prevalence, and trends of multidrug resistance in *M. leprosy* remains fragmented. Furthermore, existing routine diagnostics and therapeutic strategies have not fully adapted to the genetic profile of resistance.

Recent research shows that genetic variation *Mycobacterium leprae* plays an important role in resistance to therapy.[12] *Technology Next-Generation Sequencing* (NGS) has improved the accuracy of genotype identification and detection of resistance-causing mutations.[8] Furthermore, the integration of immunological and genetic approaches is considered important for understanding leprosy pathogenesis and the immune response to gene variation.[13] However, these results are still scattered and have not been compiled into a comprehensive synthesis. Furthermore, there are not many studies that systematically analyze leprosy resistance. *Multi Drug Therapy* (MDT) on *Mycobacterium leprae*, both globally and regionally. Information about the research landscape in this field, such as topic trends, collaborative networks between researchers, and the geographic distribution of research, is also still not widely available. However, such mapping is important for identifying knowledge gaps, directing future research priorities, and supporting the development of more precise therapies.[14,15]

Based on this background, this study aims to systematically examine the resistance *Multi Drug Therapy* (MDT) on *Mycobacterium leprae.* This study focuses on resistance mechanisms, types of drugs affected, geographic and temporal distribution, and molecular approaches used in the literature. The analysis includes four main approaches, namely: (1) country scientific production to describe the countries with the highest number of publications; (2) country production over time to assess the dynamics of increasing or decreasing publication contributions in the last decade; (3) analysis co-occurrence keywords to identify the relationship between research themes and the focus of developing topics; and (4) word cloud to visualize the most dominant keywords used in the literature. Through this approach, the research is expected to produce a comprehensive scientific synthesis regarding *M. leprosy* resistance, while providing a basis for the development of genotype-based treatment strategies, more adaptive health policies, and more effective early detection and molecular surveillance systems

METHODS

This research uses an approach Systematic Literature *Review* (SLR) combined with bibliometric analysis to explore resistance *Multidrug Therapy* (MDT) on *Mycobacterium leprae*. The review was conducted in accordance with the PRISMA guidelines (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses*) to ensure transparency and replicability of the method.

Research Question

The following research questions were formulated to guide the review: (1) What are the mechanisms of resistance in Multidrug Therapy (MDT) that has been reported on *Mycobacterium leprae* in scientific literature? (2) What drugs are in Multidrug Therapy (MDT) most frequently associated with resistance? (3) What diagnostic or molecular approaches are used to detect resistance in *M. leprae*? (4) What are the research trends on *M. leprae* based on bibliometric analysis in the last decade?

Literature Search Strategy

A comprehensive literature search was conducted using the Scopus database as the primary source of bibliographic data. Scopus was selected due to its broad coverage of peer-reviewed journals in biomedical, microbiological, and public health research, as well as its compatibility with bibliometric analysis tools.

The search was performed using the following keyword strategy: “Mycobacterium leprae”, applied to the title, abstract, and keyword fields. The search was limited to articles published between 2015 and 2025 to capture recent developments in multidrug therapy (MDT) resistance research.

Inclusion criteria were defined as follows: (1) original research articles, (2) published in peer-reviewed scientific journals, (3) available in final publication form, (4) written in English, (5) open-access availability, and (6) relevance to multidrug resistance mechanisms, diagnostics, or therapeutic responses in *Mycobacterium leprae*.

Exclusion criteria included review articles, editorials, conference proceedings, non-scientific publications, articles published outside the specified time frame, non-English publications, and studies not directly related to MDT resistance in *M. leprae*.

No additional databases were included in order to maintain consistency and avoid data duplication in the bibliometric analysis. However, the authors acknowledge that restricting the search to a single database may limit the inclusion of some regional publications.

Study Selection and Screening Process

The study applied a two-level selection process to distinguish between articles included for bibliometric analysis and those selected for systematic qualitative synthesis.

For the bibliometric analysis, a total of 2,214 publications retrieved from the Scopus database between 2015 and 2025 were included without further content-based exclusion, as bibliometric analysis aims to capture the overall research landscape, publication trends, and thematic structures.

For the systematic literature review (SLR), a more stringent screening process was applied in accordance with the PRISMA guidelines. Initially, 11,166 records were identified from Scopus. Titles and abstracts were screened to assess relevance to multidrug therapy (MDT) resistance in *Mycobacterium leprae*. Articles that were clearly unrelated were excluded at this stage.

Subsequently, full-text screening was conducted on the remaining eligible articles based on predefined inclusion and exclusion criteria, including publication type, relevance to MDT resistance mechanisms, diagnostic approaches, and availability of full-text open-access articles in English. Reasons for exclusion at the full-text stage included irrelevance to resistance mechanisms, insufficient methodological detail, and lack of molecular or clinical resistance data.

Following this rigorous screening process, 16 articles were deemed eligible and included in the qualitative synthesis of resistance mechanisms. The detailed screening workflow and reasons for exclusion at each stage are illustrated in **Figure 1**.

Bibliometric Analysis

Bibliometric analysis was performed using data exported from Scopus in CSV format. Bibliometrix R package was used to visualize and analyze country scientific production, country production over time, co-occurrence, word cloud. The analysis focused on 2,214 publications from 2015 to 2025 to reflect the current research dynamics and identify emerging themes related to *Mycobacterium leprae*.

Data Extraction

This study adopted three main stages in the PRISMA framework, namely: identification, screening, and inclusion. In the identification stage, 11,166 articles were collected from database Scopus. Because no duplicate articles or records needed to be removed for technical or administrative reasons were found, all articles proceeded directly to the screening stage.

During the screening process, 11,166 articles were reviewed to assess their relevance to the field of study. A total of 383 articles were eliminated because they were not related to the main topic of resistance. Multidrug Therapy (MDT) on *Mycobacterium leprae*, leaving 10,783 articles that passed to the next stage. A total of 10,767 articles did not pass the selection because they did not meet the established inclusion criteria. The reasons for rejection included: articles published outside the 2015–2025 timeframe (n = 8,334), not being scientific articles (n = 764), not having been published in a final form (n = 5), not originating from a scientific journal source (n = 3), using a language other than English (n = 84), not available in a format open access (n = 550), and has no relevance to the focus of the study on resistance Multidrug Therapy (MDT) on *Mycobacterium leprae* (n = 1.028).

In the final stage, namely inclusion, the remaining 16 articles were deemed to meet the selection criteria and were included in this study. These selected articles were used as the primary basis for analyzing and answering research questions regarding resistance. Multidrug Therapy (MDT) on *Mycobacterium leprae*.

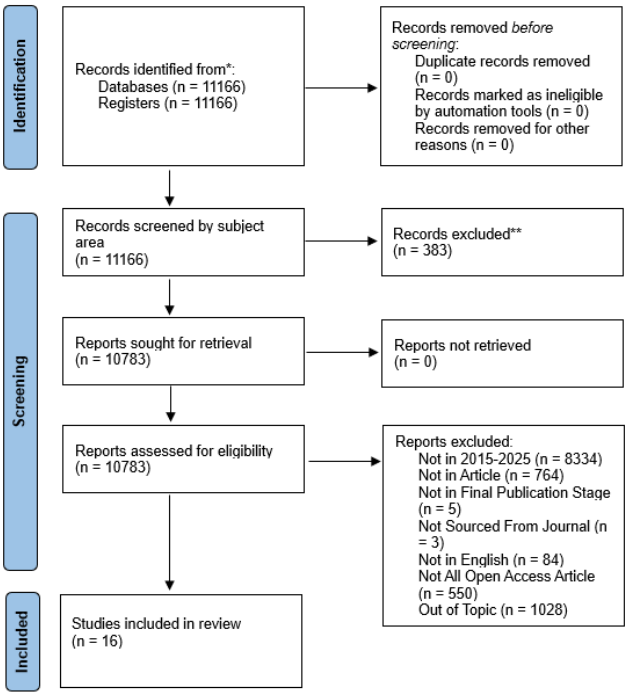

Figure 1. PRISMA Diagram Flow

RESULT AND DISCUSSION

Analysis of publication and citation distribution

The analysis of global scientific production in **Figure 2** shows the research landscape regarding *Mycobacterium leprae* highly concentrated and dominated by a handful of countries. India and Brazil clearly emerge as the most productive producers of research, visualized in the darkest blue on the map. This finding rationally correlates directly with the two countries' status as the highest contributors to leprosy cases in the world.[2] The high burden of the disease drives research urgency, the availability of abundant clinical data, and national health priorities, which collectively drive their scientific productivity.

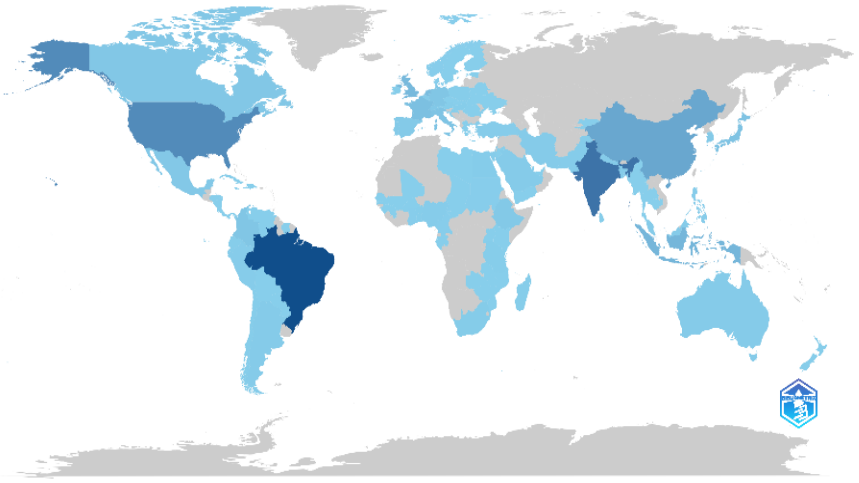

Figure 2. Country Scientific Production

Darker shades represent higher scientific production, and country labels are provided for major contributors. On the other hand, the United States also exhibits very high production, indicating that research leadership is driven not only by disease prevalence but also by strong research infrastructure capacity, funding availability, and international collaboration. The most significant finding from this map is the gap between disease burden and research output in several countries, including Indonesia. Despite being among the top three countries with the highest number of leprosy cases,[2] Indonesia's scientific output appears significantly lower than that of India and Brazil. This gap highlights potential

challenges in domestic research capacity and urges the strengthening of local research to develop evidence-based control strategies tailored to the local epidemiological context. This pattern confirms that the global leprosy research landscape is shaped by two main forces: endemic countries with a high disease burden, such as India, Brazil, and Indonesia and developed countries with superior scientific capacity.

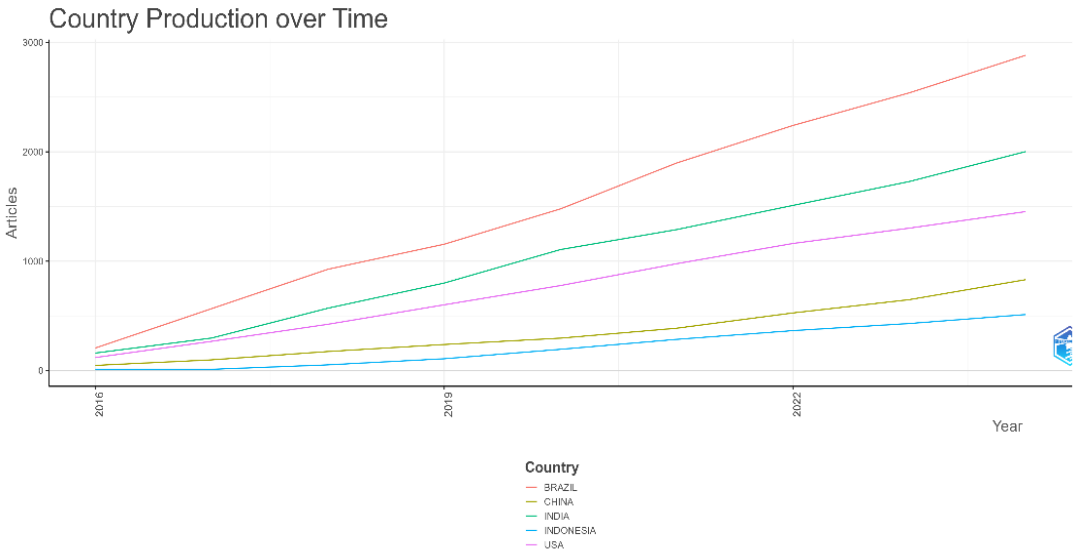

Figure 3. Country Production Over Time

Analysis of the dynamics of scientific production over the last decade in **Figure 3** demonstrates a strong and consistent upward trend in key countries, indicating sustained growth in research on *Mycobacterium leprae*. Brazil shows the steepest increase in publication output, reflected by the highest cumulative growth over the study period, confirming its position as a global research leader. India and the United States also exhibit robust and steady growth trajectories, ranking second and third respectively in terms of publication expansion. In contrast, China and Indonesia display more moderate growth rates, although both countries show a continuous upward trend across the decade. Overall, the temporal analysis highlights a clear acceleration of scientific output over time, suggesting increasing global research attention to leprosy, particularly in relation to drug resistance and clinical challenges.

Co-occurrence analysis of *Mycobacterium leprae*

Network map co-occurrence in **Figure 4** visually maps the thematic structure and inter-topic relationships in the literature of *Mycobacterium leprae.* This analysis reveals four main, interconnected research clusters. The blue cluster, which is the central and largest cluster, centers on fundamental keywords such as *"mycobacterium leprosy"*, *"leprosy"*, And *"human"*. The central position and large size of the nodes in this cluster confirm that the primary focus of the overall research is on the microbiological and pathological aspects of human leprosy.

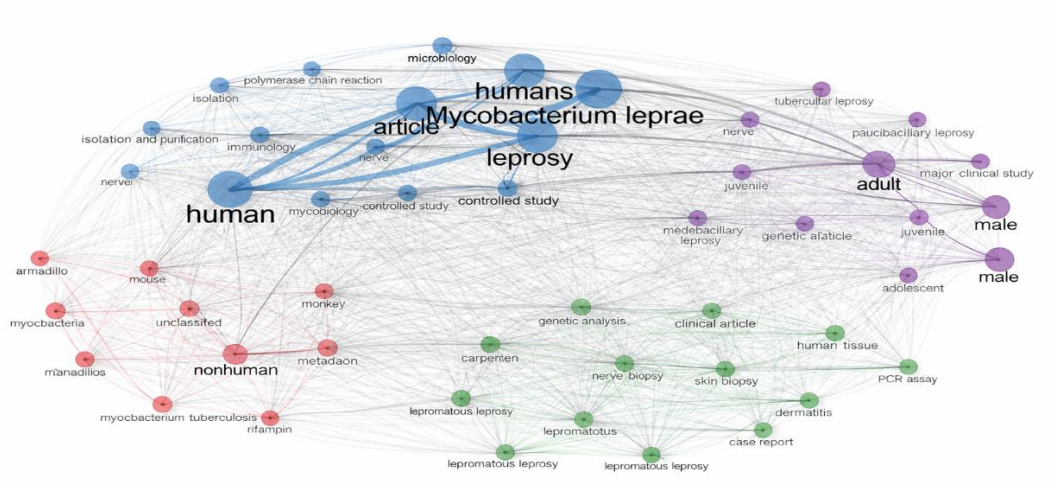

Figure 4. Co-occurrence

From this core, research expands into three more specific sub-areas. The green cluster at the bottom right clearly represents clinical and therapeutic research, characterized by strong associations between terms such as *"clinical article"*, *"dapsone"*, *"clofazimine"*, And *"skin biopsy"*. On the other hand, the red cluster at the bottom left highlights the basic and experimental research domains, with a focus on models' *"nonhuman"* or animals, as well as studies on *"immune response"* And *"metabolism"*. Finally, the purple cluster on the right depicts a focus on epidemiological and demographic research, linking keywords such as *"adult"*, *"male"*, And *"female"*.

This network structure logically demonstrates a highly organized leprosy research landscape. There is a core of fundamental research (blue) that serves as the foundation for three main branches: clinical investigations (green), basic research (red), and population studies (purple). The interconnectedness of these clusters indicates a logical flow of knowledge, where findings from basic research in animal models often inform human clinical studies, which are ultimately analyzed in the context of patient demographics.

Analysis of Published Articles

Table 1. Characteristics of Included Studies.

Study (Ref)	Country/Region	Study Design	Sample Type	Main Method	Target Genes	Focus of Study
16	France	Prospective surveillance	Clinical isolates	PCR + SNP genotyping	rpoB, folP1, gyrA	AMR surveillance
17	India	Observational	Patient samples	PCR sequencing	rpoB, gyrA, folP1	Ofloxacin resistance
18	Brazil	National surveillance	Clinical samples	PCR + sequencing	folP1, rpoB, gyrA	Dapsone resistance
19	Multi-country	Genomic study	Clinical isolates	Whole genome sequencing	Multiple genes	Phylogenomics & AMR
20	India	Genomic study	Isolates	WGS	rpoB, rpoC	Compensatory mutations
21	Multi-country	WHO surveillance	Clinical samples	PCR + microarray + WGS	rpoB, folP1, gyrA	Global AMR mapping
22	Comoros/Brazil	Molecular study	Biopsy samples	Deeplex sequencing	rpoB, folP1, gyrA	Novel resistance
23	Indonesia	Molecular docking	Patient samples	PCR + in silico	rpoB	Functional prediction
24	Indonesia	Clinical study	Patient samples	PCR sequencing	rpoB	Adherence vs resistance
25	Comoros	Deep sequencing	Community samples	Deeplex + qPCR	rpoB, folP1, gyrA	Prophylaxis impact
26	India/Nepal	Cohort study	Neuropathy patients	PCR sequencing	rpoB, folP1, gyrA	Primary resistance
27	India	Case report	Relapse patient	qPCR-HRM	rpoB, folP1, gyrA	MDR case
28	China	Molecular study	Clinical samples	Nested PCR	folP1, gyrA	Dapsone resistance
29	India	Clinical study	Suspected DR cases	PCR sequencing	rpoB	First evidence of RR
30	Brazil	Experimental study	Mouse footpad + patients	In vivo + sequencing	folP1, rpoB, gyrA	Transmission of MDR

Multidrug Therapy* (MDT) Resistance Mechanism in *Mycobacterium leprae

Table 2 presents a summary of the genetic mechanisms of multidrug therapy (MDT) resistance in *Mycobacterium leprae* across different countries. Resistance to MDT in *M. leprosy* is generally triggered by genetic mutations in the primary drug target. Mutations in the gene *rpoB* is a marker of rifampicin resistance, with amino acid substitutions such as S456L, S456F, and H451Y that alter the structure of RNA polymerase thereby reducing the effectiveness of drug binding.[16,17] In dapsone, dominant mutations are found in the gene *folP1* at codons 53 and 55.[18,19] Meanwhile, resistance to ofloxacin and fluoroquinolones is associated with mutations *gyrA* (A91V, G89C, G89A) that affect DNA gyrase as drug targets.[20–22]

In addition to these classical genes, several studies have identified new genes potentially involved in resistance. Benjak et al.[23] reported variations in *gyrB, ethA, fadD9,* and *ribD* which is associated with resistance to quinolones and alternative drugs. Jouet et al.[24] also discovered a new mechanism in the form of partial duplication in *folP1* and nonsense

mutations in *nth*, which has implications for DNA repair pathways. This confirms that resistance is not limited to classical point mutations but also involves complex genetic mechanisms and geographically variable evolutionary adaptations.

Table 2. Genetic Mechanisms of *Multidrug Therapy* (MDT) Resistance in *Mycobacterium leprae* Across Different Countries

References	Country/Region	Mechanisms of Resistance	Drugs Associated
16	France & overseas territories	Mutations in *rpoB* (S456L, S456F), *folP1*(P55L, T53I/A),*gyrA*(A91V)	Rifampicin, Dapsone, Ofloxacin
20	India	Mutations in *rpoB*, *gyrA*, *folP1*	Rifampicin, Ofloxacin
18	Brazil	Mutations in *folP1* (codon 55), *rpoB*, *gyrA*	Dapsone, Rifampicin, Ofloxacin
23	Japan, China, Korea, Marshall Islands, Africa, Brazil, etc.	Mutations in *folP1* (codons 53, 55), *rpoB*, *gyrA*; novel variants in *gyrB*, *ethA*, *fadD9*, *ribD*	Dapsone, Rifampicin, Ofloxacin, Quinolones
25	India	*rpoB* mutations in RRDR; compensatory mutations in *rpoC*, *mmpL7*	Rifampicin, Dapsone, Ofloxacin
26	Multi-country (Brazil, India, Myanmar, Africa, Indonesia, etc.)	Mutations in *folP1*, *rpoB*, *gyrA*	Rifampicin, Dapsone, Ofloxacin, Clofazimine
20	India	*gyrA* mutation (A91V), *rpoB* mutation (S456L), *folP1* (codons 53, 55)	Ofloxacin, Rifampicin, Dapsone
24	Comoros, Brazil	Mutations in *rpoB*, *folP1*, *gyrA*, *gyrB*; nonsense mutation in *nth*; partial duplication of *folP1*	Rifampicin, Dapsone, Fluoroquinolones
17	Indonesia (Papua, West Papua, North Maluku)	*rpoB* mutations (T450A, S456L, H451Y)	Rifampicin, Dapsone, Clofazimine, Fluoroquinolones
27	Indonesia	*rpoB* mutations (codons 407–427, insertion 408–409)	Rifampicin, Dapsone, Clofazimine
28	Comoros	Mutations in *rpoB*, *ctpC*, *ctpI*, *folP1*, *gyrA*, *gyrB*; variation in *nth*	Rifampicin, Dapsone, Fluoroquinolones
21	India, Nepal	*rpoB* (Leu436Gln), *folP1*(Pro55Leu/Ser),*gyrA*(A91P, G89A/C)	Rifampicin, Dapsone, Ofloxacin
22	India	*rpoB* (T433I, D441Y), *gyrA* (G89C)	Rifampicin, Ofloxacin, Dapsone
19	China	*folP1* mutations (codons 53, 55), *gyrA*(A91V)	Dapsone, Ofloxacin, Rifampicin (no resistance), Clofazimine, Minocycline, Clarithromycin
29	India	*rpoB* mutation Glu442His	Rifampicin, Dapsone, Ofloxacin
30	Brazil	*folP1* (R100W), *rpoB*(L470Q),*gyrA*(L97F)	Rifampicin, Dapsone, Ofloxacin, Clofazimine (rare)

Multidrug Therapy (MDT) Drugs Associated with Resistance

The results of the study in **Table 1** show that resistance to *M. leprae* most frequently reported to rifampicin, dapsone, and ofloxacin, with variations in prevalence between countries. In France, mutations in the gene *rpoB* and *folP1* found in cases of rifampicin and dapsone resistance, especially in relapsed patients.[16] In Brazil, resistance to dapsone is the most dominant, although the overall prevalence is still low.[18] A multi-country study by Cambau et al. (2018) estimated the global prevalence of resistance to reach 8%, with a distribution of rifampicin (3.8%), dapsone (5.3%), and ofloxacin (1.3%), and there are cases of multi-drug resistance (MDR).

In India, ofloxacin resistance occupies a significant proportion with a prevalence reaching 12.5%, while mutations in *folP1* and *rpoB* is also frequently found.[20,22,29] From Indonesia, reports of rifampicin resistance due to mutations in *rpoB* quite prominent, especially in Papua, North Maluku, and Java.[17,27] MDR cases were also identified in India,[22] and Brazil,[30] indicating the transmission of primary resistance in the community. Thus, the pattern of drug resistance in *M. leprae* varies between regions, with rifampicin, dapsone, and ofloxacin remaining the hotspots for MDT failure in major endemic countries.

Diagnostic/Molecular Approaches to Detect Resistance in *M. leprae*

Table 3 summarizes the diagnostic and molecular approaches used to detect MDT resistance in *Mycobacterium leprae*, including PCR-based methods, sequencing approaches, and whole-genome sequencing. The most widely used molecular methods are conventional PCR and Sanger Sequencing to detect specific mutations in target genes (*rpoB, folP1, gyrA*).[23,29] Nested PCR And SNP genotyping is also used to increase sensitivity, especially in detecting minor

mutations in bacterial populations.[19] WHO Global Surveillance utilizes a combination of PCR, microarrays, *High-Resolution Melting* (HRM), to *Whole-Genome Sequencing* (WGS) for global resistance mapping.[26]

Table 3. Diagnostic and Molecular Approaches for Detecting MDT Resistance in *Mycobacterium leprae*

References	Diagnostic/Molecular Methods	Target Genes	Type of Evidence	Key Findings
16	PCR, SNP genotyping, Genotype LepraeDR	*rpoB*, *folP1*, *gyrA*	Genetic mutations	18 cases (11.3%) resistant; mostly dapsone (13), rifampicin (3), ofloxacin (2). Higher in relapse (25.7%) than new cases (7%). First AMR study in Europe.
20	PCR sequencing	*rpoB*, *gyrA*, *folP1*	Genetic mutations, clinical relapse	44.4% resistant cases; rifampicin resistance in 33.3% MI-positive. Morphological index suggested as early indicator.
18	PCR + direct sequencing	*folP1*, *rpoB*, *gyrA*	Genetic mutations	Resistance in 16/1183 patients (1.3%); majority relapse/treatment failure; mostly dapsone resistance. MDT is still effective.
23	Whole-genome sequencing (Illumina HiSeq/MiSeq)	*folP1*, *rpoB*, *gyrA*, *gyrB*, *ethA*, *fadD9*, *ribD*	Genetic mutations, WGS	Identified new resistance-associated mutations, ancestral strains from Far East. AMR linked to genomic diversity.
25	PCR sequencing + WGS (Illumina)	*rpoB*, *rpoC*, *mmpL7*	Genetic mutations, lab data	Rifampicin resistance is influenced by compensatory mutations. WGS revealed >11,000 variants.
26	PCR sequencing, micro-array, WGS, HRM	*folP1*, *rpoB*, *gyrA*	Genetic mutations	Global resistance ~8.0%; Rifampicin 3.8%, Dapsone 5.3%, Ofloxacin 1.3%. MDR: 20 cases (rifampicin+dapsone), 4 cases (ofloxacin+dapsone).
20	PCR + Sanger sequencing	*gyrA*, *rpoB*, *folP1*	Genetic mutations	Resistance in 16.9% patients; highest for ofloxacin (12.5%). Above global average.
24	Deep sequencing (Deeplex Myc-Lep), PCR, WGS	*rpoB*, *folP1*, *gyrA*, *gyrB*, *nth*	Genetic mutations (SNPs, VNTR)	New resistance mechanism identified (partial duplication in *folP1*). Assay highly sensitive (LOD 80–3000 genomes).
17	PCR + DNA sequencing, molecular docking	*rpoB*	Genetic mutations, in silico	T450A did not affect resistance; S456L and H451Y increased resistance potential.
27	PCR sequencing (Dual Cycle Terminator Kits)	*rpoB*	Genetic mutations	Resistance higher in poor adherence (29%) vs adherent patients (11%). Odds ratio 11.2.
28	Deep sequencing + qPCR	*rpoB*, *folP1*, *gyrA*, *nth*	Genetic mutations (deep sequencing)	All isolates sensitive to MDT drugs; prophylactic rifampicin did not induce resistance.
21	PCR + sequencing	*rpoB*, *folP1*, *gyrA*	Genetic mutations	Resistance in 7.8% samples: Ofloxacin 6.4%, Dapsone 2.6%, Rifampicin 1.3%. Includes primary resistance.
22	qPCR-HRM + sequencing	*rpoB*, *folP1*, *gyrA*	Genetic mutations, clinical relapse	Relapse case confirmed MDR (rifampicin+ofloxacin). Improved with alternative regimen.
19	Nested PCR + SNP genotyping	*folP1*, *gyrA*	Genetic mutations	25% samples resistant to dapsone. One MDR case (dapsone+ofloxacin). No rifampicin resistance.
29	PCR + sequencing	*rpoB*	Genetic mutation, clinical failure	First evidence of rifampicin resistance in Eastern India (2/50 patients).
30	In vivo mouse footpad test + sequencing	*folP1*, *rpoB*, *gyrA*	Genetic mutations, in vivo testing	16/37 resistant; MDR in 12 patients (8 relapses, 4 new). Evidence of primary transmission in families.

The latest development is the use of high-throughput sequencing technologies, such as Deeplex Myc-Lep,[24] which allows the simultaneous detection of SNPs, VNTRs, and novel resistance mechanisms with high sensitivity. WGS is also an increasingly adopted approach, as evidenced that have successfully identified new genetic variants outside of classical genes.[23,25] In Indonesia, simple PCR-based molecular methods are still dominant,[17,27] while in silico approaches such as molecular docking are also starting to be developed to predict the effects of mutations.[17] This indicates a gap in diagnostic technology between developed and developing countries, while also opening up opportunities for the development of rapid diagnostic methods that are more adaptive to field conditions in endemic areas.

Strengths and Limitations of the Study

This study has several strengths. First, it combines a systematic literature review based on PRISMA guidelines with bibliometric analysis, allowing both depth of evidence synthesis and a broader mapping of the research landscape. This dual approach increases the robustness and transparency of the findings. Second, the use of Scopus as a data source ensures coverage of high-quality, peer-reviewed publications over a ten-year period (2015–2025), capturing recent developments in MDT resistance research. Third, the integration of molecular, clinical, and bibliometric perspectives provides a comprehensive understanding of resistance mechanisms, diagnostic approaches, and global research trends in *Mycobacterium leprae*.

Despite these strengths, this study has some limitations. First, the systematic review included only 16 articles due to strict inclusion criteria, which may limit generalizability to all global research on MDT resistance. Second, the bibliometric analysis relied solely on Scopus, potentially excluding relevant studies indexed in other databases such as Web of Science or PubMed. Third, variations in study design, sample size, and molecular methods across included studies may introduce heterogeneity, making direct comparisons challenging. Finally, the co-occurrence and clustering analysis are based on author-provided keywords, which may not fully capture the complexity of each study's focus.

Considering both the strengths and limitations outlined above, the findings of this study should be interpreted as a comprehensive yet not exhaustive representation of current MDT resistance research in *Mycobacterium leprae*.

CONCLUSION

This study provides a structured and comprehensive synthesis of resistance to Multidrug Therapy (MDT) in *Mycobacterium leprae* based on four guiding research questions. First, regarding mechanisms of resistance (RQ1), the review confirms that MDT resistance is primarily driven by mutations in the rpoB, folP1, and gyrA genes, with additional compensatory and novel mutations emerging in several endemic regions, indicating increasing genetic complexity of resistance. Second, in relation to drugs most frequently associated with resistance (RQ2), rifampicin, dapsone, and ofloxacin were consistently identified as the most implicated agents, highlighting the need for continuous surveillance of their effectiveness in MDT regimens. Third, concerning diagnostic and molecular approaches (RQ3), the study reveals a transition from conventional PCR-based methods toward high-throughput sequencing and in silico analyses, although access to advanced diagnostics remains uneven across countries. Finally, based on bibliometric trends (RQ4), global research over the last decade shows growing attention to molecular resistance mechanisms, with dominant contributions from India and Brazil, alongside increasing interdisciplinary collaboration between microbiology, genomics, and clinical research. Overall, these findings emphasize that MDT resistance is an evolving challenge requiring routine molecular monitoring in endemic areas, improved access to modern diagnostic technologies, and stronger international collaboration to support evidence-based leprosy control strategies aligned with the global goal of "Towards Zero Leprosy."

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GENERATIVE AI DISCLOSURE STATEMENT

Portions of this manuscript were assisted by generative artificial intelligence tools. Claude AI was used to assist in generating the initial outline of the article, while Consensus AI was utilized to support the identification of relevant scholarly references and sentences from scientific literature. The authors reviewed, verified, and revised all AI-assisted outputs to ensure the accuracy, originality, and integrity of the final manuscript.

AUTHOR CONTRIBUTION STATEMENT

Sulthon Nurreza Setyawan: Conceptualization, Methodology, Study design, Literature search and screening, Data curation, Bibliometric analysis, Visualization, Writing Original draft preparation, Writing Review & Editing; **Syafri Musthofa**: Data curation, Literature screening, Writing Review & Editing; **Isnawati Isnawati**: Supervision, Validation, Conceptualization, Writing Review & Editing, Final approval of the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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