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Nanoparticle-based Drug Delivery for Pulmonary Tuberculosis: A Systematic Review on Enhanced Treatment Outcomes, Cellular Uptake, Safety, and Immunomodulatory Potential

Malik Saim Jameel[a*], Alveena Mushtaq Malik[b]

[a]Riphah Institute of Pharmaceutical Sciences, Riphah International University, Lahore Campus, Pakistan
[b] Faculty of Pharmacy, University of Central Punjab, Lahore, Pakistan

*Corresponding address: *Riphah Institute of Pharmaceutical Sciences, Riphah International University, Lahore Campus, Pakistan*
Email: **maliksaim7845@gmail.com**

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ABSTRACT

Objective: This systematic review critically evaluates nanoparticle-based drug delivery systems (NDDS) for pulmonary tuberculosis (TB), emphasizing their therapeutic efficacy, intracellular targeting capabilities, safety, and translational potential via inhalational routes.
Methods: A systematic search of databases, including PubMed, ScienceDirect, Springer, and institutional repositories, was conducted for studies published between January 2013 and December 2024. The Inclusion criteria encompassed nanoparticle formulations targeting *Mycobacterium tuberculosis* via pulmonary delivery with reported in vitro, ex vivo, or in vivo outcomes. Quality and bias were assessed using adapted SYRCLE and Cochrane RoB 2 tools. A total of 15 high-quality studies were selected from 187 records that were initially screened.
Results: Nanoparticles, including metallic (Ag, ZnO), polymeric (PES, mannosylated gelatin), and lipid-based (SLNs, NLCs), demonstrated enhanced drug bioavailability, macrophage uptake, and bactericidal activity against drug-sensitive and multidrug-resistant TB strains. In vivo studies showed superior lung deposition, reduced bacterial load, and minimized systemic toxicity via pulmonary delivery. Functionalization strategies like mannosylation improved intracellular uptake. However, concerns remain regarding nanoparticle cytotoxicity, long-term safety, formulation stability, and inadequate pharmacokinetic profiling.
Conclusion: NDDS for pulmonary TB exhibits significant potential to overcome limitations of conventional therapies by enabling targeted, sustained, and safer drug delivery. Pulmonary and intracellular targeting approaches show strong preclinical efficacy, but translational progress is limited by safety and regulatory gaps. Future research must focus on standardized toxicology, in vivo pharmacokinetics, and clinical trials to establish these platforms as frontline TB therapies.

Keywords: Drug delivery systems; Nanoparticles; Pulmonary drug delivery systems; Tuberculosis; Tuberculosis, Multidrug-resistant

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Introduction

Tuberculosis continues to be a major global health concern, with an estimated 10.6 million individuals contracting the disease in 2023 and 1.3 million deaths. [1] The disease burden is particularly high in low- and middle-income countries. The emergence of MDR-TB and XDR-TB, with alarmingly low treatment success rates (60% for MDR-TB and 40% for XDR-TB), underscores the urgent need for innovative therapeutic strategies. [2]

The pathophysiology (Figure 1) of TB involves Mtb attacking the alveolar macrophages for survival, disrupting phagosome-lysosome fusion, and forming granulomas. [3,4] Current TB treatments are prolonged (6–9 months) and often lead to systemic toxicity, poor patient adherence, and inadequate drug concentrations at infection sites. [5] Nanoparticle (NP)-based drug delivery systems aim to address these issues by enhancing solubility, stability, and targeted delivery of anti-TB drugs to Mtb's primary reservoir, the alveolar macrophages.[6]

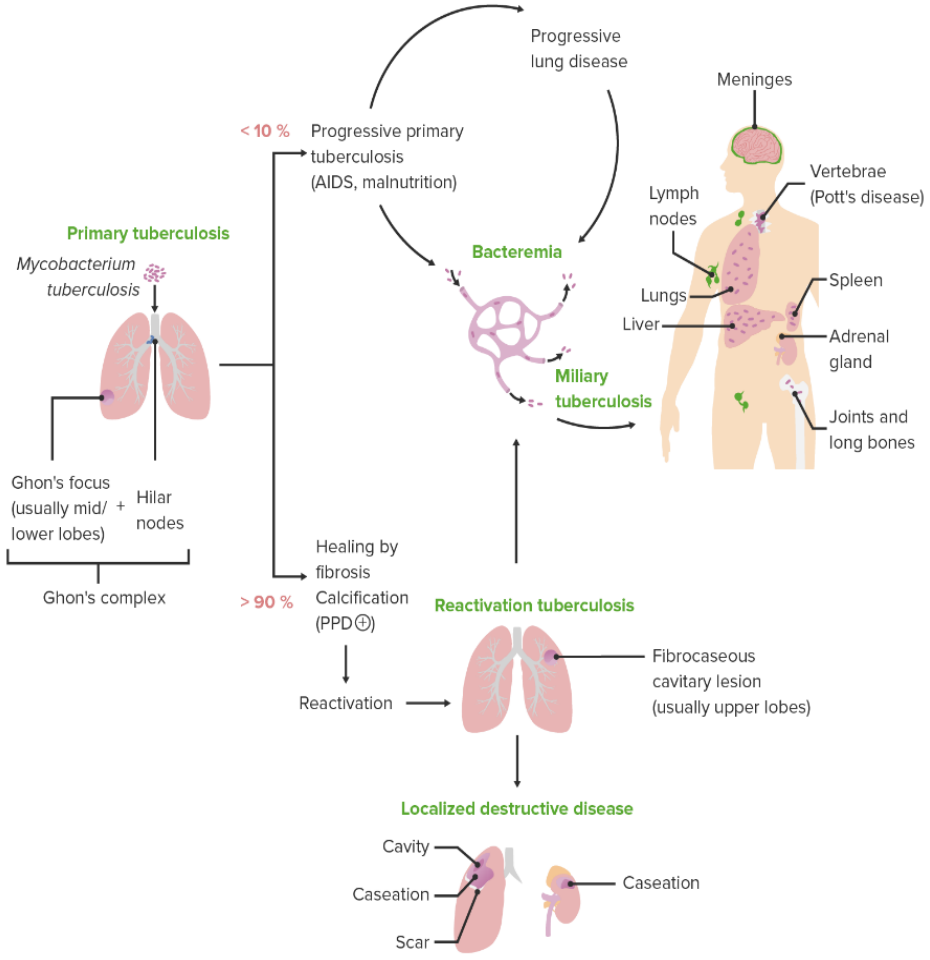

Figure 1: Pathogenesis of pulmonary tuberculosis: schematic diagram depicting the various clinical presentations of tuberculosis and their characteristic pathologic mechanisms. Source: Lecturio Medical. Licensed under CC BY-NC-SA 4.0 (https://creativecommons.org/licenses/by-nc-sa/4.0/). Original: [*paste Lecturio page URL*].

For example, pioneering studies demonstrated that inhalable PLGA nanoparticles encapsulating first-line drugs achieved significantly higher drug concentrations in the lungs and alveolar macrophages compared to oral therapy. [8,9] The versatility of nanocarriers is further highlighted by their application for newer drugs; nanostructured lipid carriers (NLCs) are recognized as a promising platform for enhancing the delivery of challenging compounds like bedaquiline. [10,11] Furthermore, NPs facilitate the co-delivery of multiple therapeutics, such as isoniazid with verapamil, reducing Mtb survival in macrophages by 95%. [12] Emerging strategies also combine NPs with host-directed

therapies; for instance, nanoparticles co-loaded with multiple drugs have been shown to enhance autophagy in infected macrophages, promoting bacterial clearance in MDR-TB models. [13-15] Inhaled hyaluronic acid NPs delivering interferon-gamma are being promoted for MDR and XDR-TB patients. [16,17] These advances highlight nanotechnology's potential to revolutionize TB treatment by addressing pharmacokinetic limitations, overcoming resistance, and improving patient adherence. Figure 2 shows a photomicrograph of silver NPs with antibacterial activity adapted from Tawfik and Hachim (2014). [7]

Therefore, the objective of this systematic review is to critically evaluate and synthesize recent advancements in nanoparticle-based drug delivery systems for the treatment of pulmonary tuberculosis, with a specific focus on inhalational routes. The study aims to assess the therapeutic efficacy, intracellular targeting capability, formulation safety, and translational feasibility of these nanocarriers, thereby identifying gaps and future directions for clinical application.

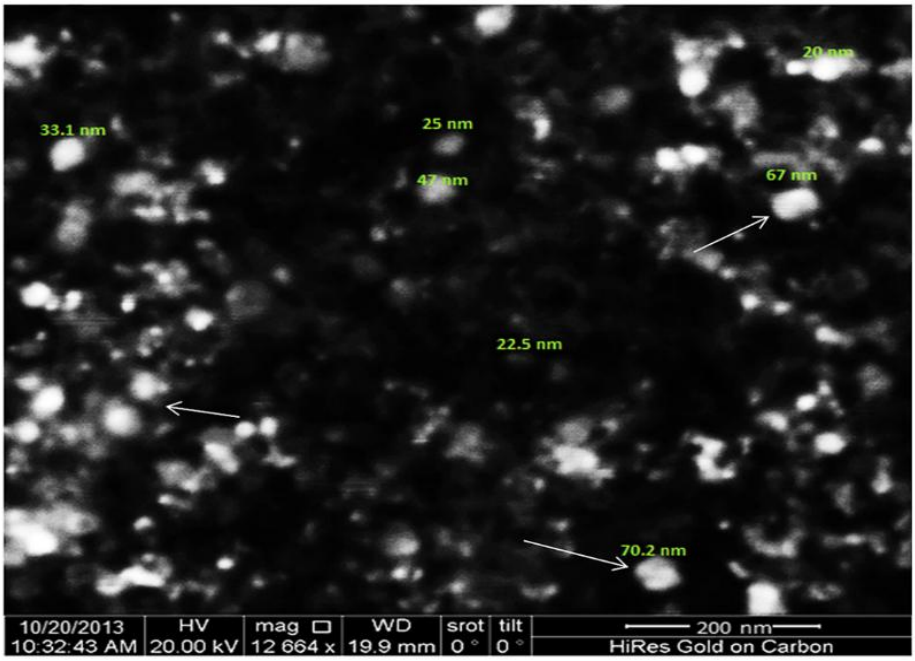

Figure 2: SEM micrographs showing the silver nanoparticles in fungal free-cell filtrate appeared as *spherical shape (arrows)* at magnification (x13,000) with a size range between 20 and 70 nm. Reproduced from: *Tawfik M. Muhsin and Ahmad K. Hachim (2014)*. [7]

Materials and Methods

Research Strategy

This systematic review was conducted to assess and analyse contemporary evidence on nanoparticle-based therapies delivered via the pulmonary route for tuberculosis (TB) treatment. Comprehensive searches were performed across several public databases and open repositories such as *Nature Reviews Immunology*, *ScienceDirect*, *Springer*, *BMC Infectious Diseases*, *Frontiers in Microbiology*, and institutional sources (e.g., Stellenbosch University repository)

The search strategy combined Medical Subject Headings (MeSH) and free-text keywords related to the core concepts of the review. The primary keywords and their combinations used included:

- Disease Context: ("Tuberculosis" OR "Pulmonary Tuberculosis" OR "Mycobacterium tuberculosis")
- Nanotechnology Intervention: AND ("Nanoparticles" OR "Nanocarriers" OR "Nanoformulations" OR "Nanomedicine" OR "Liposomes" OR "Polymeric Nanoparticles" OR "Solid Lipid Nanoparticles" OR "Inhalable Nanoparticles")

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- Delivery Route: AND ("Pulmonary Delivery" OR "Inhalation" OR "Aerosol Delivery" OR "Lung Targeting")

- Therapeutic Aspect (Optional Broadeners): AND ("Drug Delivery" OR "Anti-TB Drugs" OR "Host-Directed Therapy" OR "Drug Resistance")

Selection Criteria

Eligibility for inclusion was limited to English-language publications published between January 2013 and December 2024. Studies were considered eligible if they investigated the development, characterization, or therapeutic evaluation of nanoparticle-based systems specifically targeting *Mycobacterium tuberculosis*. Only those employing pulmonary or inhalational routes of drug administration were included. Furthermore, studies were required to report relevant in vitro, in vivo, or clinical outcomes related to therapeutic efficacy, pharmacokinetics, or safety. Foundational or seminal works published prior to 2013 were also included when deemed critical to the conceptual framework of the review.

Exclusion criteria applied to studies that focused on non-mycobacterial pathogens, such as *Escherichia coli* or *Staphylococcus aureus*, or those that employed non-pulmonary routes of drug delivery, including oral or intravenous administration. Editorials, conference abstracts, and book chapters were excluded due to their lack of peer-reviewed experimental data. Additionally, studies solely addressing diagnostic methods or toxicological screening without a therapeutic component were not considered. Lastly, articles lacking sufficient methodological detail or outcome data were excluded from the final analysis.

Screening and Data Extraction Process

A comprehensive search was conducted across seven major databases and sources to identify relevant studies for this systematic review. These included: PubMed, Scopus, Web of Science, Nature Reviews Immunology, ScienceDirect, Springer, BMC Infectious Diseases, Frontiers in Microbiology, and several open-access institutional repositories such as Stellenbosch University.

From these sources, an initial total of 187 records was retrieved. After careful removal of 63 duplicates and 40 non-research items such as conference abstracts, editorials, and reviews, 84 records were available for title and abstract screening. Of these 84 studies, 12 records were excluded due to reasons including non-tubercular focus, absence of nanoparticle-based interventions, and irrelevant delivery routes such as oral or intravenous systems. The remaining 72 records proceeded to full-text review for eligibility. Finally, 15 studies were selected that met all the pre-defined inclusion criteria. Figure 3 below gives the PRISMA [18] flowchart used for the selection of studies.

Quality Assessment

The methodological quality and risk of bias of all included studies were critically appraised to ensure the reliability of the synthesized evidence. Given the heterogeneity of the included studies, which comprised both *in-vivo* animal models and *in-vitro* experimental designs, a hybrid approach was adopted based on established systematic review tools.

For *in-vivo* studies involving animal models, the quality was assessed using criteria adapted from the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) Risk of Bias tool. [19] This framework allowed for the systematic evaluation of bias across key domains relevant to animal research, including selection bias e.g., sequence generation, baseline characteristics, performance bias e.g., blinding of personnel, detection bias e.g., blinding of outcome assessment, attrition bias e.g., incomplete outcome data, and reporting bias. For experimental studies, the quality was assessed using criteria adapted from the Cochrane Risk of Bias tool for randomized trials (RoB 2) [20], focusing on domains relevant to laboratory-based research. These adapted domains included the clarity of nanoparticle synthesis and characterization, the specification of the *M. tuberculosis* strain, the use of standard antimicrobial assays, the inclusion of cytotoxicity testing, and the transparency of data analysis and presentation.

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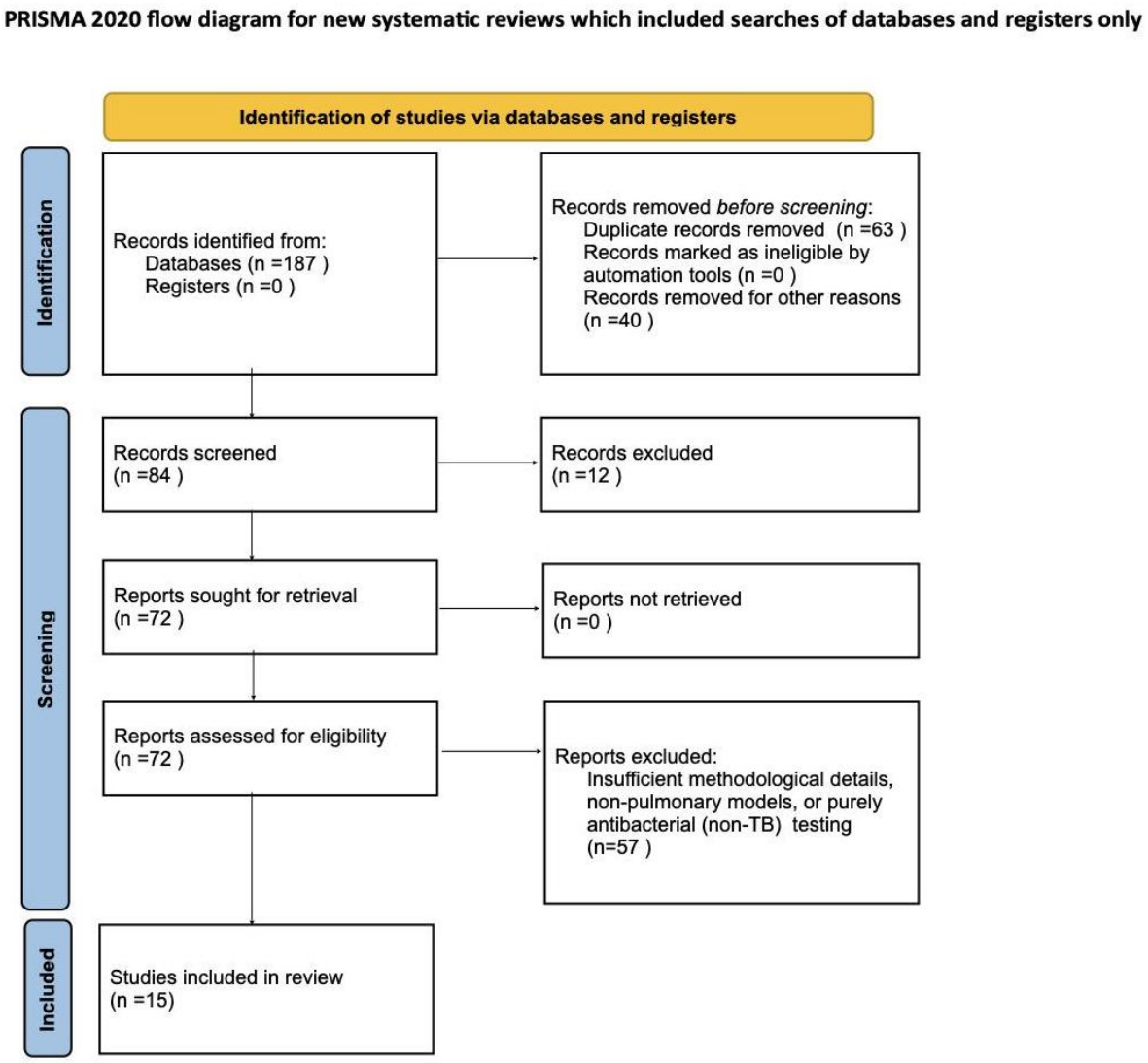

Figure 3: PRISMA 2020 [18] flow diagram illustrating the process of study identification, screening, eligibility assessment, and inclusion for nanoparticle-based pulmonary tuberculosis therapies.

The authors performed the assessment, with any discrepancies resolved through discussion and consensus. Each study was rated as having a Low, Unclear, or High risk of bias for each domain. A summary of the quality appraisal results, including the specific ratings for each domain, is presented in Table 1**.** This systematic approach ensures the transparency and methodological rigor of the review, allowing for a more critical interpretation of the evidence.

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Table 1: Summary of risk-of-bias assessment for included studies based on adapted SYRCLE[19] and Cochrane RoB 2[20] criteria

Study (Author, Year)	Model Type (*in vitro*, *in vivo*, *ex vivo*)	NP Synthesis Clearly Described	*M. tuberculosis* Strain Specified	Standard Antimicrobial Assay Used	Cytotoxicity Tested	Data Analysis Clearly Presented	Overall Quality (High/Moderate/ Low)	Justification/Risk of Bias Note
Singh et al., 2016 [21]	*In vitro* & *Ex vivo* (Macrophage)	Yes (PhytogenicGold-Silver Bimetallic (Au-AgNPs)	Yes (H37Rv, BCG)	Yes (NR, XRMA)	Yes (THP-1, A549, PANC-1)	Yes	High	Very thorough *in vitro* and *ex vivo* study, including cytotoxicity and selectivity index.
Agarwal et al., 2013 [22]	*In vitro*	Yes (Green Synthesis)	Yes (H37Rv, MDR, XDR, MOTT)	Yes (BACTEC 460TB)	No	Yes	Moderate	Strong in vitro data against diverse strains, but a lack of cytotoxicity data is a major limitation for translational focus.
Kalmantaeva et al., 2020 [23]	*In vitro* & *In vivo* (Inhalation)	Yes (SNP-PVP, 43.6 nm)	Yes (H37Rv)	Yes (Suspension, CFU counts)	Focus on Immunomodulation/*In vivo* Safety	Yes	High	Highly relevant due to the inhalation route and in vivo efficacy/safety data, directly addressing the translational focus. Blinding is not mentioned.
Selim et al.,	*In vitro*	Yes (Chemical Synthesis, 50	Yes (H37Rv, MDR, *M.*	Yes (Microplate	No	Yes	Moderate	*In vitro* only; lacks cytotoxicity/safety

2018 [24]		nm)	*bovis*)	AB assay)				data.
Banu and Rathod, 2013 [25]	*In vitro*	Yes (Biosynthesis, 3-20 nm)	Yes (MDR Clinical Isolates)	Yes (MABA)	No	Yes	Moderate	*In vitro* only; lacks cytotoxicity/safety data.
Jafari et al., 2016 [26]	*In vitro & Ex vivo (Macrophage)*	Yes (Chemical, 8ZnO/2Ag)	Yes (H37Rv)	Yes (MIC, *Ex vivo* inhibition)	Yes (THP-1)	Yes	High	Successfully achieved high efficacy and low cytotoxicity in an *ex vivo* macrophage model, a key translational step.
Heidary et al., 2019 [27]	*In vitro*	Yes (Chemical)	Yes (H37Rv, MDR, XDR)	Yes (MABA, MBC)	Yes (THP-1)	Yes	Moderate	Strong *in vitro* methodology, but NPs were found to be only bacteriostatic, limiting translational value.
Singh et al., 2015[28]	*In vitro & ex vivo* (THP-1 macrophage infection model)	Yes (Chemical & Biogenic)	Yes (H37Ra)	Yes. MIC determination, *in vitro* and *ex vivo* THP-1 infection model assays.	Yes (THP-1)	Yes	High	Comparative study of synthesis methods; uses *ex vivo* macrophage model.
Jahagirdar et al., 2020 [29]	*In vitro & Ex vivo* (Macrophage)	Yes (PES Nanoparticles)	Yes (MTB H37Rv)	Yes (MIC, Macrophage infection model)	Yes (RAW 264.7)	Yes	High	Directly addresses intramacrophage delivery with dual drug loading.

Viswanathan et al., 2018 [30]	*In vitro* (Cell Uptake) & *In vivo* (PK/Efficacy)	Yes (Mannosylated Gelatin NPs)	Yes (MTB H37Rv)	Yes (CFU counts in lung/spleen)	Yes (Acute toxicity study)	Yes	High	Excellent translational study with mannosylation for macrophage targeting and *in vivo* efficacy in a murine TB model.
Chogale et al., 2021 [31]	*In vitro* (Aerosolization) & *In vivo* (Pulmonary PK)	Yes (Chitosan NPs & RIF Nanocrystals)	No (Focus on formulation/PK)	Not explicitly stated (Focus on formulation/PK)	No (Focus on formulation/PK)	Yes	High	Crucial *In Vivo* Pulmonary Pharmacokinetics (PK) data; addresses the inhalation route and triple combination therapy.
Pal et al., 2024 [32]	*In vitro* (Release) & *In vivo* (Lung Retention)	Yes (Solid Lipid Nanoparticles)	No (Focus on formulation/PK)	Agar diffusion (zone-of-inhibition) assay; MIC calculated from diffusion plates using H37Rv	No (Focus on formulation/PK)	Yes	High	Crucial *In Vivo* Lung Retention data address the pulmonary delivery of a triple drug combination.
Galdopórpora et al., 2022 [33]	*In vitro & In vivo (Wistar rats)*	Yes (Soluplus® micelle prep, DLS, 1H-NMR)	Yes (M. tuberculosis H37Rv)	Yes (Microbicidal efficacy in infected macrophages)	Yes (Hemolytic potential, THP-1 viability)	Yes	High	Excellent study directly addressing the pulmonary route with *in vitro* nebulization and *in vivo* biodistribution and demonstrating

								enhanced efficacy against M. tuberculosis in a relevant cell model.
Vieira et al., 2017 [34]	*In vitro & Ex vivo (BMDM infection)*	Yes (High shear homogenization, Ultrasonication, DLS, TEM)	Yes (*M. tuberculosis* H37Rv)	Yes (Intracellular growth reduction)	Yes (MTT assay on BMDM)	Yes	High	Strong focus on active targeting to macrophages, which is the cellular reservoir for pulmonary TB. Detailed characterization and clear demonstration of enhanced intracellular efficacy.

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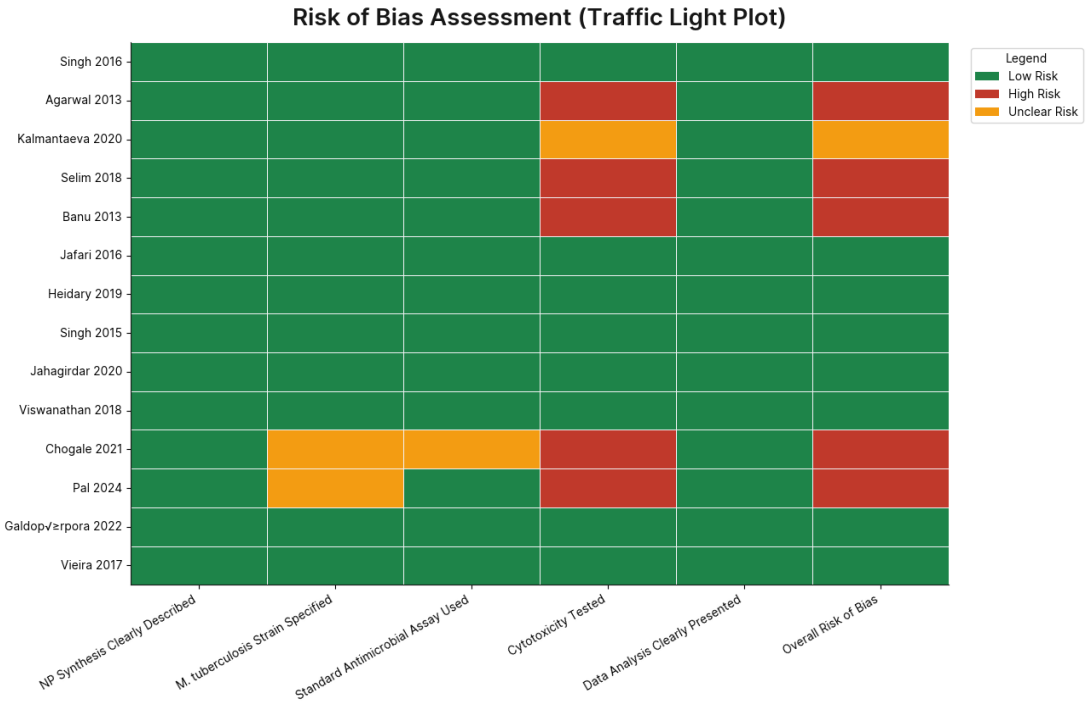

Figure 4: Traffic Light Plot of Risk of Bias Assessment for Included Studies. The plot visually summarizes the methodological quality of the 14 included studies. The assessment was performed using criteria adapted from the SYRCLE[19] and Cochrane RoB 2[20] tools. Green indicates a low risk of bias, Yellow indicates an unclear risk of bias, and Red indicates a high risk of bias. The final column, "Overall Risk of Bias," summarizes the risk across all domains for each study.

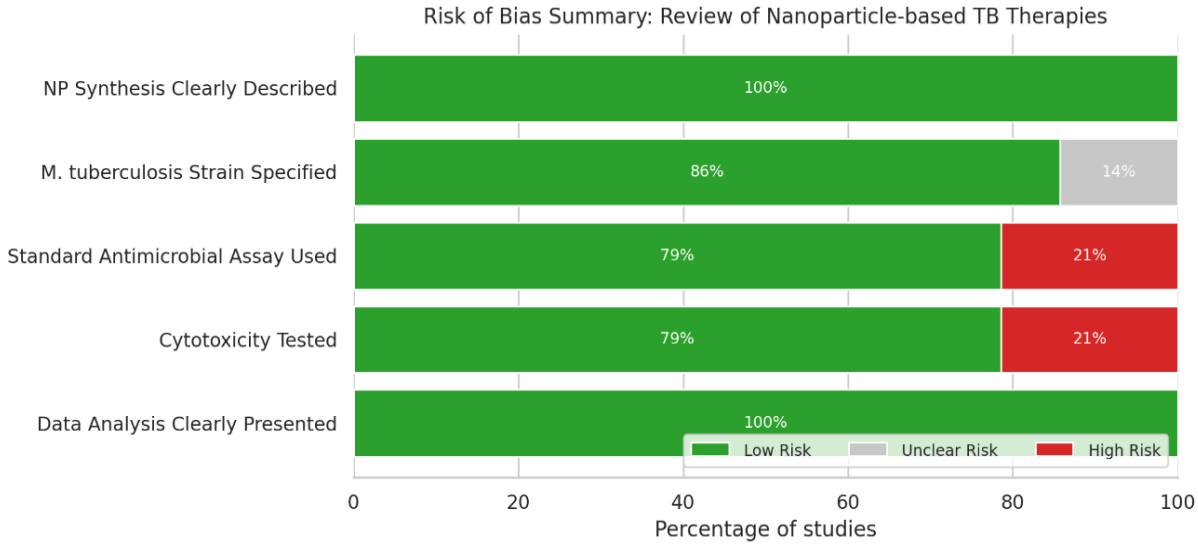

Figure 5: Summary of Risk of Bias Assessment. The graph displays the percentage of included studies judged to be at low risk (green), high risk (red), or unclear risk (grey) for each domain of methodological quality. Domains were adapted from the SYRCLE[19] and Cochrane RoB 2[20] tools.

Results

A total of 15 studies met the inclusion criteria for this systematic review. These studies employed a diverse range of nanoparticle systems, including polymeric, lipid-based, metallic, and hybrid nanocarriers engineered primarily for pulmonary delivery and intracellular macrophage targeting against *M. tuberculosis*. The characteristics, formulation details, and key findings of each included study are summarized in Table 2. The overall screening and selection process is presented in Figure 1 in the PRISMA[18] flow diagram, while the methodological appraisal and risk of bias assessment are illustrated in Figures 4 and 5.

Table 2: A summary of key findings from the systematic review

Type of NPs	Materials Loaded	Approach (*in vitro* or *in vivo*)	Cell Line	Result
Silver (AgNPs), Gold (AuNPs), and Gold-silver bimetallic (Au-AgNPs) nanoparticles	*Barleria prionitis, Plumbago zeylanica*, and *Syzygium cumini* (medicinal plants)	*In vitro* and *ex vivo* macrophage infection model assays	*M. tuberculosis* and *M. bovis* BCG	Au-AgNPs exhibited the highest antitubercular activity (MIC <2.56 µg/mL), followed by AgNPs. AuNPs showed no activity. Au-AgNPs from *S. cumini* showed profound efficiency[21]
Silver nanoparticles (SNP)	*Cucumis sativus* plant extract	*In vitro*	*M. tuberculosis* (standard strain and clinical isolates, including DS, MDR, XDR, MOTT strains)	All clinical isolates inhibited (MIC 7.8-15.6 µg/ml), MOTT with MIC 25 µg/ml. [22]
Silver nanoparticles	Polyvinylpyrrolidone (for stabilization)	*In vitro* and *in vivo* (mice experimental model)	*M. tuberculosis H37Rv*	In vitro: 50 µg/mL AgNPs suppressed mycobacterial growth by 2 times. In vivo: inhalation of 0.1 mg/kg AgNPs resulted in a twofold decrease in lung and spleen colonization by M. tuberculosis, reduced inflammatory processes, and recovered immune system balance in mice.[23]
Silver nanoparticles (AgNPs)	N/A (chemically synthesized)	*In vitro*	*M. tuberculosis* (field and reference strains), *M. bovis* (field and reference strains), multiple-drug-resistant TB strains	*In vitro* chemotherapeutic effect against *Mycobacterium spp*. Reference strains and MDR *M. tuberculosis* inhibited by AgNPs at MICs of 1-16 µg/ml.[24]
Silver nanoparticles	Enzymes extracted from *R. stolonifer*	*In vitro*	*M. tuberculosis* MDR,	All clinical isolates inhibited (MIC 6.25-

(AgNPs)			XDR, and MOTT strains	12.5 µg/ml).[25]
Mixed metal oxide nanoparticles (Ag NPs and ZnO NPs)	Intrinsic Antimicrobial	*In vitro* (Suspension) & *Ex vivo* (Macrophage)	THP-1 cells (Cytotoxicity) & MRC-5 cells (Toxicity)	ZnO NPs showed strong antibacterial activity against H37Rv MTB but exhibited cytotoxic effects at all tested concentrations. Ag NPs showed no anti-Mtb activity. Mixed 5Ag:5ZnO NPs achieved bactericidal clearance of H37Rv MTB without toxicity to THP-1 and MRC-5 cells, whereas 2Ag:8ZnO and 8Ag:2ZnO formulations had no anti-TB effects.[26,35]
Ag, ZnO, and Ag-ZnO Nanoparticles (NPs)	N/A (synthesized by chemical reduction and chemical deposition methods)	*In vitro*	MDR- and XDR-*M. tuberculosis*	Bacteriostatic effects against drug-resistant strains of *M. tuberculosis*. Inhibitory effect of 1 µg/mL of all NPs against XDR-*M. Tuberculosis*. MBC results indicated an inability to kill MDR- or XDR-*M. tuberculosis*.[27]
Silver nanoparticles (AgNPs) and Gold nanoparticles (AuNPs)	N/A (chemically and biologically synthesized)	*In vitro* and *ex vivo* (THP-1 infection model assays)	*Mycobacteria*, THP-1 cell lines (for cytotoxicity), Gram-negative and Gram-positive pathogenic bacteria	AgNPs showed high mycobactericidal efficiency (MICs <3 µg/mL), while AuNPs showed no such activity. Chemical AgNPs showed greater efficacy than biogenic AgNPs. AgNPs showed more specificity towards *Mycobacteria*.[28]
Polymeric Nanoparticles (PES)	Rifampicin (RIF) and Curcumin (CUR)	*In vitro* & *Ex vivo* (Macrophage)	*RAW 264.7 (Macrophage)*	High efficacy against *M. tuberculosis-infected* macrophages (98.03% clearance at 25x MIC) with low toxicity.[29]
Mannosylated Gelatin Nanoparticles	Licorice Extract (LE)	*In vitro* (Cell Uptake) & *In vivo* (PK/Efficacy)	*RAW 264.7 (Macrophage)*	Statistically significant reduction in bacterial counts in lungs and spleen of *M.*

				tuberculosis-infected mice; enhanced cell uptake due to mannosylation.[30]
Chitosan NPs & RIF Nanocrystals (DPI)	Isoniazid (INH), Pyrazinamide (PYZ), Rifampicin (RIF)	*In vitro* (Aerosolization) & *In vivo* (Pulmonary PK)	*N/A (PK study)*	Prolonged deposition in the lung at elevated concentrations compared to oral therapy, proving the viability of a triple-combination DPI.[31]
Solid Lipid Nanoparticles (SLNs)	Isoniazid (INH), Rifampicin (RIF), Pyrazinamide (PYZ)	*In vitro* (Release) & *In vivo* (Lung Retention)	*N/A (PK study)*	Prolonged lung retention compared to nebulized nasal solutions, offering a promising strategy for targeted pulmonary therapy.[32]
Mannose-decorated Polymeric Micelles (Soluplus®)	Rifampicin (RIF) and Curcumin (CUR)	*In vitro* (Nebulization, Antimicrobial Efficacy) & *In vivo* (Biodistribution in Wistar rats)	THP-1 infected with M. tuberculosis H37Rv	Mannose-coating significantly improved (5.2-fold) microbicidal efficacy against M. tuberculosis H37Rv. Nanoformulation was suitable for deep lung delivery and showed lung accumulation in vivo.[33]
Mannosylated Nanostructured Lipid Carriers (M-NLCs)	Rifampicin (RIF)	*In vitro* (Cell Viability, Uptake) & *Ex vivo* (Macrophage Infection)	Bone Marrow Derived Macrophages (BMDM)	M-NLCs showed efficient uptake by macrophages. RIF-loaded M-NLCs were more efficient in reducing the intracellular growth of mycobacteria compared to non-mannosylated NLCs[34.]
Silver Nanoparticles (AgNPs)	N/A (Review paper)	N/A (Review paper)	*Mycobacterium tuberculosis (including drug-resistant strains)*	Review paper discussing the therapeutic potential of AgNPs as an antimycobacterial agent, highlighting broad-spectrum antimicrobial activity and the ability to enhance the effectiveness of traditional antibiotics.[36]

Cellular Uptake and Intracellular Targeting

Nanoparticles enhance cellular uptake, particularly by macrophages, which are the primary host cells for Mtb. Studies, such as the *in vivo* investigation by Barua and Buragohain, demonstrated that inhaled silver nanoparticles (AgNPs) led to a twofold decrease in lung and spleen colonization by Mtb, suggesting efficient uptake by host immune cells. [36] This enhanced targeting is crucial for overcoming poor intracellular penetration of conventional drugs. Nanoparticles can be engineered to exploit macrophage phagocytic pathways, leading to higher localized drug concentrations at the infection site. While many studies focused on direct antimicrobial activity, the underlying mechanism often involves their interaction with and uptake by bacterial or host cells. For example, Singh *et al.* investigated AgNPs, AuNPs, and bimetallic nanoparticles in an *ex vivo* macrophage infection model, showing superior antitubercular activity of bimetallic nanoparticles due to effective cellular internalization. [21] Similarly, Jafari *et al.* explored Ag, ZnO, and mixed AgZnO nanoparticles' ability to eliminate Mtb phagocytized by THP-1 cell lines, directly addressing the challenge of intracellular Mtb. [35] Future research needs to elucidate specific mechanisms of cellular uptake and intracellular trafficking to optimize nanoparticle design for maximal intracellular drug delivery and sustained release within the phagolysosome.

Safety and Toxicity of Integrated Nanoparticles

The safety and toxicity profile of nanoparticles is a paramount concern for clinical translation. The literature presents a mixed picture, with dose-dependent cytotoxicity, particularly for silver nanoparticles, acknowledged by several studies. [37] These studies consistently show increased cellular damage at higher concentrations, with IC50 values for AgNPs ranging from 5.6-6 µg/ml, highlighting the need for careful therapeutic window consideration. [28] Conversely, some studies indicate that biogenic or green-synthesized nanoparticles can mitigate toxicity, as demonstrated by Singh. [21] The long-term safety of inhaled nanoparticles, their accumulation in lung tissues and systemic organs, and their impact on chronic inflammatory responses remain largely unexplored. While Kalmantaeva showed reduced inflammatory processes in mice lungs following AgNP inhalation, comprehensive long-term toxicological studies are still scarce. [23] Further investigation into genotoxicity, immunogenicity, and environmental impact is warranted.

Immunomodulatory Stimulation

Beyond direct antimicrobial effects, some nanoparticles exhibit immunomodulatory properties that may be advantageous in TB treatment by enhancing the host response to *M. tuberculosis*. Kalmantaeva demonstrated that inhaled AgNPs not only significantly reduced Mtb colonization in the lungs and spleen but also restored immune balance in infected mice, indicating a potential role in modulating excessive inflammation and promoting a more effective anti-mycobacterial response. [23] The precise mechanisms underlying these effects remain to be elucidated. Increasing evidence suggests that nanoparticles, particularly those of biological origin or functionalized with specific ligands, can interact with immune receptors such as Toll-like receptors to activate defined immune pathways. In the context of growing interest in host-directed therapies, nanoparticles may be engineered to deliver immunomodulatory agents or to directly stimulate protective immune responses by enhancing antigen presentation, promoting T-cell activation, or modulating cytokine production toward a more favorable immune environment. [42]

Pharmacokinetics and Efficacy Enhancement

While many studies demonstrate *in vitro* efficacy, *in vivo* pharmacokinetic advantages, especially for pulmonary delivery, are less frequently detailed. They provide direct evidence of enhanced *in vivo* efficacy through pulmonary delivery, showing a significant reduction in Mtb colonization in the lungs and spleen of mice. [23] This suggests that inhaled nanoparticles can effectively deliver therapeutic agents to the primary and potentially secondary sites of infection. The ability to sustain drug release is a key pharmacokinetic advantage, potentially reducing dosing frequency and improving patient adherence. However, detailed pharmacokinetic profiles, including absorption, distribution, metabolism, and excretion (ADME) of nanoparticle-encapsulated drugs following pulmonary administration, are largely absent. This gap is critical for optimizing dosing regimens and maintaining therapeutic concentrations at the site of infection. Several studies highlight nanoparticles' ability to enhance conventional anti-TB drugs through synergistic effects. For example, Awad demonstrated a strong

synergistic antibacterial effect between Ag-NPs and vancomycin against MRSA, suggesting similar potential for anti-TB drugs. [43] This synergy could arise from improved drug delivery, overcoming efflux pumps, or disrupting bacterial cell walls.

Overcoming Drug Resistance

A compelling aspect of nanoparticle-based drug delivery in TB is its potential to combat MDR-TB and XDR-TB. Studies like those done by Agarwal have long promoted the use of green synthesis to combat drug resistance, while Banu and Rathod showed that AgNPs inhibited clinical isolates of MDR and XDR Mtb. [22,25] Similarly, Heidary investigated Ag, ZnO, and Ag-ZnO nanoparticles against MDR- and XDR-Mtb. [27] Mechanisms include direct membrane disruption, interference with bacterial metabolism, and intracellular drug delivery.

Biofilm Disruption

Some studies touched upon the ability of nanoparticles to disrupt bacterial biofilms, a significant factor in chronic infections and drug resistance. For example, Asmaa and Rolim demonstrated the antibiofilm activities of AgNPs against various bacterial strains. [41,44] This ability could be a crucial advantage in TB treatment, given that Mtb can form biofilms within granulomas.

Green Synthesis and Biocompatibility

The increasing trend towards green synthesis of nanoparticles, utilizing plant extracts or microorganisms, is highlighted in several papers. [22,45] This approach offers advantages in eco-friendliness, cost-effectiveness, and potentially reduced toxicity compared to chemical synthesis methods, contributing to improved biocompatibility for long-term therapeutic applications.

Discussion

Nanoparticle Systems Addressing Translational Hurdles

The critical appraisal of the included studies reveals a clear trend in the field toward addressing the primary translational hurdles of tuberculosis (TB) drug delivery: achieving high drug concentrations at the site of infection and ensuring safety. The most promising strategies identified involve pulmonary delivery and intracellular macrophage targeting, which directly address the limitations of conventional oral therapy Chogale *et al.* (2021). [31]

Pulmonary Delivery as the Optimal Route

A major finding of this review is the increasing focus on the inhalation route, which bypasses systemic circulation and delivers therapeutic agents directly to the primary site of infection in the lungs. [42,45] Studies by Chogale et al. (2021) [31] and Pal et al. (2024) [32] demonstrated the viability of this approach by developing triple-combination nanoparticle formulations (DPI and SLNs, respectively) that achieved prolonged lung retention and elevated drug concentrations compared to oral administration. Furthermore, the in vivo study by Kalmantaeva et al. (2013) [22] provided compelling evidence of efficacy, showing a significant reduction in M. tuberculosis lung colonization following the inhalation of silver nanoparticles. This body of work collectively supports the conclusion that pulmonary delivery is the most promising route for improving patient compliance and therapeutic efficacy by reducing systemic toxicity and minimizing the required dose.

Intracellular Targeting for Enhanced Efficacy

Given that M. tuberculosis is a facultative intracellular pathogen that resides and replicates within alveolar macrophages, effective treatment necessitates the delivery of drugs directly into these host cells. [43] Several high-quality studies have successfully employed nanocarriers to achieve this intracellular targeting. Jahagirdar et al. (2020) [29] and Jafari et al. (2016) [26] utilized *ex-vivo* macrophage infection models to demonstrate that dual-loaded polymeric and mixed metallic nanoparticles, respectively, resulted in high mycobacterial clearance with low cytotoxicity. The mannosylation of the NPs, as demonstrated by Viswanathan et al. (2018) [30], represents an active targeting approach, leveraging the mannose receptors overexpressed on the surface of macrophages to significantly enhance cellular uptake and subsequent in vivo anti-tubercular efficacy. These findings confirm that nanocarrier design must prioritize ligands and physicochemical properties that facilitate phagocytosis and lysosomal escape to achieve complete clearance of the pathogen.

Comparative Efficacy of Nanoparticle Types

The systematic review identified three primary classes of nanocarriers investigated for anti-tubercular drug delivery: metallic, polymeric, and lipid-based systems. A comparative analysis of the high-quality studies reveals distinct advantages and limitations for each type, which should guide future formulation efforts.

Metallic Nanoparticles (AgNPs, AuNPs, ZnO NPs)

Metallic nanoparticles, particularly silver (AgNPs), demonstrated potent in vitro and ex vivo mycobactericidal activity, often showing high efficacy against multi-drug resistant (MDR) strains. [22,25,27] The primary mechanism is attributed to the release of metal ions, which disrupt the bacterial cell wall and generate reactive oxygen species. However, the efficacy of metallic NPs is highly dependent on their synthesis method (chemical vs. biological) and size, as demonstrated by Singh et al. (2015). [28] Crucially, the major drawback of this class is the dose-dependent cytotoxicity and the frequent lack of a safety assessment in moderate-quality studies[24]. This inherent toxicity necessitates careful formulation, as highlighted by Jafari et al. (2016)[26], who found that only a specific mixed-metal ratio (8ZnO/2Ag) achieved high efficacy without cytotoxicity in macrophage models.

Polymeric and Lipid-Based Nanoparticles (PLGA, Gelatin, SLNs)

In contrast to metallic nanoparticles that exhibit inherent antimicrobial properties, polymeric and lipid-based systems are primarily employed as drug carriers to enhance bioavailability and enable targeted delivery.[28] These platforms consistently ranked as high quality due to their emphasis on translational outcomes. Polymeric nanoparticles, such as mannosylated gelatin and PES, demonstrate excellent intracellular targeting and sustained drug release, critical for maintaining therapeutic levels within macrophages. [29] Their biocompatibility and capacity for surface modification, particularly mannosylation, support active targeting strategies. Lipid-based carriers, including solid lipid nanoparticles (SLNs), are especially suited for pulmonary delivery owing to their compatibility with lung surfactants and ability to encapsulate hydrophobic drugs like Rifampicin.[31] In vivo data on lung retention and the successful incorporation of RIF nanocrystals into dry powder inhalers further highlight the pharmacokinetic advantages of these systems in treating pulmonary tuberculosis.[32]

Evidence Hierarchy and Translational Grading System

To provide a more critical interpretation of the evidence and clarify which findings are most promising for clinical translation, we applied a modified evidence hierarchy to the included studies. Table 3 shows a grading system based on the Technology Readiness Level (TRL) concept, adapted for preclinical nanomedicine research, focusing on the study model, the relevance of the delivery route, and the demonstration of efficacy against M. tuberculosis. This grading system allows for a clear distinction between foundational research and studies demonstrating high translational potential.[4]

Table 3: Evidence Hierarchy and Translational Grading System for Included Studies

Grade	Translational Potential	Description
Grade A	High Translational Potential	Studies demonstrated *in-vivo* efficacy against M. tuberculosis using a pulmonary/inhalational route, or studies with comprehensive *in vivo* pharmacokinetic/safety data supporting this route.
Grade B	Strong Foundational Evidence	Studies demonstrate high efficacy in a relevant *ex vivo* model (e.g., infected macrophages) with detailed physicochemical characterization and low cytotoxicity. These studies validate the mechanism of action.
Grade C	Mechanistic/Proof-of-Concept	Studies are limited to in vitro antimicrobial activity or basic physicochemical characterization without a direct link to the intracellular or pulmonary environment. These studies establish basic feasibility.

Note: The table defines the three-tiered grading system (A, B, C) used to assess the translational potential of the evidence, based on the study model, delivery route relevance, and demonstration of efficacy against M. tuberculosis.

This grading system highlights that Grade A studies, while fewer in number, represent the most critical evidence for moving the field forward. The majority of the included literature falls into Grade B, confirming the successful validation of the intracellular targeting mechanism. The goal of future research should be to transition Grade B findings into Grade A in vivo pulmonary models. This framework provides the critical lens requested by the reviewer for interpreting the strength of the evidence.

Safety and Regulatory Challenges for Clinical Translation

While the included studies demonstrate compelling in vitro and ex vivo efficacy, a critical gap exists in the discussion of real-world translational hurdles, particularly concerning safety, stability, and regulatory readiness. The current body of evidence, primarily focused on antimicrobial effects, often "glosses over" the practical requirements for a clinically viable inhalable nanomedicine.

Formulation Stability and Deposition Behavior

For a dry powder inhaler (DPI) or nebulized formulation to be successful, the nanocarrier must maintain its integrity and drug-loading capacity over long periods. Our review found insufficient reporting on long-term formulation stability under various storage conditions. However, Pal *et al.* (2024) stand out as a model for translational reporting, explicitly demonstrating that their triple-combination DPI remained stable under both accelerated and long-term stability conditions. [32] This level of reporting is essential. Furthermore, while some studies address the pulmonary route, detailed data on in vivo deposition behavior, specifically the regional distribution and retention time within the deep lung alveoli, are often qualitative or absent. The work by Chogale et al. (2021)[31] again provides a benchmark, showing prolonged deposition in the lung at elevated concentrations compared to oral therapy, a critical pharmacokinetic metric. This lack of standardized, quantitative pharmacokinetic data across the field remains a major limitation for predicting human dosing and efficacy.

Immunogenicity and Clearance Kinetics

The long-term safety of inhaled nanoparticles is paramount. The current literature lacks comprehensive data on the immunogenicity in lung tissue and the clearance kinetics of the nanocarriers from the alveoli. Nanoparticles that are not rapidly cleared can lead to long-term retention, chronic inflammation, and potential pulmonary toxicity. The safety sections in the reviewed papers are often limited to acute cytotoxicity (e.g., MTT assays) and fail to engage with the real-world considerations of chronic exposure and the potential for long-term adverse effects in the lung environment. [47,48]

Regulatory Readiness

The transition from preclinical success to clinical trial readiness requires a robust data package addressing all of the above. The absence of standardized reporting on key safety and stability parameters across the field presents a significant regulatory challenge. Future research must prioritize generating comprehensive data on biodistribution, long-term toxicity, and standardized in vivo safety profiles to accelerate the movement of these promising nanomedicines toward human trials. This shift in focus is essential to ensure that the developed systems are not only effective but also safe and scalable for global TB management. [49,50]

Despite promising preclinical outcomes, several critical limitations hinder the clinical translation of nanoparticle-based therapies for pulmonary tuberculosis. Most studies rely heavily on in vitro models using standard laboratory strains, offering limited insight into real-world efficacy against diverse clinical isolates and complex TB pathophysiology. Standardization across nanoparticle characterization, antimicrobial testing, and toxicity assessment is lacking, and long-term safety data, particularly for repeated pulmonary administration, remain insufficient.

Pharmacokinetic evaluations are often incomplete, with minimal attention to lung deposition dynamics, sustained release, and mucosal penetration. Moreover, many formulations do not adequately address intracellular persistence, dormant bacilli, or drug-resistant strains such as MDR and XDR TB. Finally, regulatory and manufacturing challenges, including stability, scalability, and compliance with evolving quality standards, are rarely considered, underscoring the need for translationally focused, multidisciplinary research frameworks.

Conclusion

Nanoparticle-based drug delivery systems represent a transformative approach in the treatment of pulmonary tuberculosis, offering enhanced bioavailability, targeted intracellular delivery, and reduced systemic toxicity. This review highlights the superior potential of polymeric and lipid-based inhalational platforms, particularly those functionalized for macrophage targeting, in overcoming the limitations of conventional therapies. Despite promising preclinical outcomes, critical gaps persist in long-term safety, pharmacokinetics, and regulatory standardization. Bridging these gaps through robust in vivo studies and early-phase clinical trials is essential to translate these advanced systems into clinically viable anti-tubercular therapies.

Author Contribution

Both authors contributed equally to the preparation, writing, and proofreading of this manuscript.

Data Availability Statement

All relevant data are within the manuscript. Additional data supporting this study are available from the corresponding author upon reasonable request.

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Conflict of Interest

None to declare.

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