

Original Article

Green Synthesized Silver Nanoparticles Loaded with Isoniazid for Enhanced Anti-Mycobacterial Activity

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ABSTRACT

Background: Tuberculosis remains a major infectious disease worldwide, and the increasing emergence of drug-resistant strains has reduced the effectiveness of conventional treatment strategies. Isoniazid is an important first-line anti-tuberculosis drug; however, resistance development and limited drug delivery remain significant challenges. Nanotechnology-based approaches, particularly green synthesized metal nanoparticles, have gained attention due to their antimicrobial properties and potential to improve drug performance. **Objective:** The present study aimed to develop a plant-mediated silver nanoparticle formulation loaded with isoniazid and evaluate its physicochemical characteristics, anti-mycobacterial activity, stability, and safety profile for potential application against resistant tuberculosis strains. **Methods:** Silver nanoparticles were synthesized using a green plant extract approach under controlled laboratory conditions. The synthesized nanoparticles were loaded with isoniazid and characterized using UV-Visible spectroscopy, Fourier transform infrared spectroscopy, X-ray diffraction, electron microscopy, and particle size analysis. The antimicrobial potential of free isoniazid, silver nanoparticles, and isoniazid-loaded silver nanoparticles was evaluated against *Mycobacterium tuberculosis*. Drug stability and toxicity assessment were also performed to determine the suitability of the developed formulation. **Results:** The green synthesis process successfully produced stable silver nanoparticles, confirmed through characteristic optical and structural analyses. The incorporation of isoniazid resulted in increased nanoparticle size and maintained formulation stability. The isoniazid-loaded silver nanoparticles demonstrated stronger anti-mycobacterial activity compared with individual treatments, indicating an improved therapeutic effect through combined nanoparticle and drug action. The formulation showed acceptable compatibility during toxicity evaluation while maintaining antimicrobial effectiveness. **Conclusion:** The findings suggest that plant-mediated silver nanoparticles loaded with isoniazid may provide a promising strategy for enhancing anti-mycobacterial activity and improving drug delivery against tuberculosis. This nano-based formulation could offer a potential alternative approach for addressing limitations associated with conventional therapy and drug resistance. Further in vivo studies and clinical investigations are recommended to evaluate its therapeutic applicability. **Keywords:** Green synthesis; Silver nanoparticles; Isoniazid; *Mycobacterium tuberculosis*; Drug-resistant tuberculosis; Nanomedicine; Antimicrobial resistance; Drug delivery system.

INTRODUCTION

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, remains a major global infectious-disease challenge despite advances in diagnosis, prevention, and antimicrobial therapy. The continuing burden of disease is compounded by treatment complexity and the emergence of drug-resistant *M. tuberculosis*, which threaten progress toward global TB control (1). Pakistan remains among the countries substantially affected by TB, where delayed diagnosis, treatment interruption, and antimicrobial resistance continue to complicate disease management (2). Standard anti-tuberculosis therapy is effective when susceptible organisms are treated appropriately; however, prolonged multidrug regimens, treatment-related adverse effects, poor adherence, and the emergence of resistant strains can reduce therapeutic success (3,4).

Isoniazid (INH) is a cornerstone first-line anti-tuberculosis agent with potent bactericidal activity against actively replicating *M. tuberculosis*. Its activity is principally related to inhibition of mycolic-acid synthesis, an essential process required for maintenance of the mycobacterial cell wall. Nevertheless, resistance to isoniazid is an important therapeutic concern and has been associated with alterations in genes involved in drug activation and target pathways, particularly *katG* and related resistance mechanisms (5,6). The growing burden of multidrug-resistant TB has therefore intensified interest in approaches that can enhance the antimicrobial performance of existing agents while potentially improving their delivery and reducing limitations associated with conventional formulations (7).

Nanotechnology provides a potential platform for modifying antimicrobial delivery because nanoscale materials possess physicochemical characteristics that can enhance interactions with microbial cells. Among metallic nanomaterials, silver nanoparticles (AgNPs) have attracted particular attention because of their broad antimicrobial properties. Proposed mechanisms include disruption of microbial membranes, generation of reactive oxygen species, interaction with cellular proteins and enzymes, and interference with nucleic-acid function (8–10). These multiple antimicrobial mechanisms have supported investigation of AgNPs both as independent antimicrobial agents and as components of combination delivery systems intended to enhance the activity of conventional drugs (11,12).

Nanoparticle-based delivery systems may offer additional advantages for anti-tuberculosis therapy by providing a large surface area for drug association, modifying drug release, improving formulation stability, and increasing contact between antimicrobial compounds and target microorganisms (13,14). Combining isoniazid with silver nanoparticles is therefore of particular experimental interest because the formulation may integrate the established anti-mycobacterial activity of isoniazid with the antimicrobial properties of Nano silver. Such a combination could produce greater inhibitory activity than either component alone; however, this possibility requires direct experimental comparison rather than assumptions of synergistic or therapeutic benefit.

The method used to synthesize silver nanoparticles is also important for their potential biomedical application. Conventional physical and chemical synthesis approaches may require reducing agents, stabilizers, or processing conditions that increase environmental burden or leave undesirable chemical residues. Plant-mediated green synthesis has emerged as an alternative approach in which naturally occurring phytochemicals, including phenolic compounds, flavonoids, terpenoids, alkaloids, and proteins, can participate in the reduction and stabilization of silver ions during nanoparticle formation (15,16). Green synthesis has consequently received increasing attention as an economical and comparatively environmentally compatible strategy for producing metallic nanoparticles (17). Plant-derived AgNPs have also demonstrated antimicrobial activity in experimental studies, potentially reflecting both the intrinsic activity of silver and surface-associated phytochemical constituents derived from the biological reducing system (18,19).

Despite substantial research on green synthesized silver nanoparticles and growing interest in nanoparticle-mediated antimicrobial delivery, comparatively limited experimental evidence has addressed plant-mediated AgNPs specifically loaded with isoniazid and evaluated as a combined anti-mycobacterial formulation. Important uncertainties include whether drug loading alters nanoparticle size, morphology, surface characteristics, or stability; whether the combined formulation provides greater inhibition of *M. tuberculosis* than free isoniazid or unloaded AgNPs; and whether enhanced antimicrobial activity can be achieved while maintaining an acceptable in-vitro cytotoxicity profile. Addressing these questions is necessary before therapeutic implications can reasonably be considered.

Accordingly, this laboratory-based experimental study was conducted at the Department of Biotechnology, Institute of Biological Sciences, University of Swat, Swat, Khyber Pakhtunkhwa, Pakistan, to synthesize plant-mediated silver nanoparticles, load them with isoniazid, characterize their physicochemical properties, and compare the anti-mycobacterial activity of free isoniazid, unloaded silver nanoparticles, and isoniazid-loaded silver nanoparticles against *M. tuberculosis*. The study additionally evaluated formulation stability, drug-release characteristics, and cytotoxicity to determine whether the developed nanoparticle formulation demonstrated physicochemical and biological properties supportive of further preclinical investigation.

MATERIALS AND METHODS

Study Design and Research Location

This experimental study was carried out at the Department of Biotechnology, Institute of Biological Sciences, University of Swat, Swat, Khyber Pakhtunkhwa, Pakistan. The main purpose of this research was to prepare green synthesized silver nanoparticles (AgNPs), load them with isoniazid, and evaluate their potential anti-mycobacterial activity. The study was designed to follow a laboratory-based experimental approach involving nanoparticle synthesis, characterization, drug loading, antimicrobial evaluation, and toxicity assessment.

Collection and Preparation of Plant Extract

A medicinal plant source rich in natural reducing compounds was selected for green synthesis of silver nanoparticles. Fresh plant material was collected from the Swat region of Pakistan and was identified by a plant taxonomist at the Department of Botany, University of Swat. The collected material was washed several times with distilled water to remove dust and unwanted particles. After cleaning, the plant material was shaded at room temperature to preserve heat-sensitive bioactive compounds.

The dried plant material was finely powdered using a laboratory grinder. For extract preparation, a measured quantity of plant powder was mixed with distilled water and heated under controlled conditions. The mixture was filtered using Whatman filter paper to obtain a clear aqueous plant extract. The prepared extract was stored at 4°C until further use. The presence of phytochemicals such as phenolic compounds, flavonoids, and other reducing agents was considered important because these natural compounds help in the reduction of silver ions into silver nanoparticles.

Green Synthesis of Silver Nanoparticles

Silver nanoparticles were synthesized using a plant-mediated green synthesis method. Silver nitrate (AgNO_3) solution was prepared using analytical-grade chemicals. The plant extract was slowly added to the silver nitrate solution under continuous stirring. The formation of nanoparticles was initially confirmed by a visible colour change of the reaction mixture from pale yellow to brown, which indicated the reduction of silver ions (Ag^+) into silver nanoparticles (Ag^0).

The reaction mixture was maintained under controlled temperature conditions and allowed to complete the synthesis process. After nanoparticle formation, the solution was centrifuged to collect the nanoparticles. The obtained nanoparticles were washed several times with distilled water to remove remaining plant residues and unreacted compounds. The purified nanoparticles were dried and stored for further analysis.

Loading of Isoniazid onto Silver Nanoparticles

Isoniazid loading was performed using a simple adsorption-based method. A known concentration of isoniazid solution was prepared and mixed with the synthesized silver nanoparticles. The mixture was continuously stirred to allow interaction between isoniazid molecules and the nanoparticle surface.

After completion of the loading process, the formulation was centrifuged, and the remaining free drug present in the solution was separated. The amount of loaded isoniazid was estimated by measuring the difference between the initial and remaining drug concentration. The prepared silver nanoparticle-isoniazid formulation was stored under suitable conditions for further biological evaluation.

Characterization of Synthesized Nanoparticles

The synthesized nanoparticles were characterized using different analytical techniques to confirm their physical and chemical properties. Ultraviolet-visible (UV-Vis) spectroscopy was performed to identify the characteristic absorption peak of silver nanoparticles. Particle size and surface morphology were analyzed using scanning electron microscopy (SEM) and transmission electron microscopy (TEM).

Fourier transform infrared spectroscopy (FTIR) was performed to identify functional groups involved in nanoparticle formation and stabilization. The crystalline structure of nanoparticles was evaluated using X-ray diffraction (XRD). Particle size distribution, surface charge, and stability were further assessed through dynamic light scattering (DLS) and zeta potential analysis.

Evaluation of Anti-Mycobacterial Activity

The anti-mycobacterial activity of free isoniazid, silver nanoparticles, and isoniazid-loaded silver nanoparticles was evaluated and compared. Laboratory strains of *Mycobacterium tuberculosis* were used for assessment following appropriate biosafety guidelines.

The antimicrobial activity was determined using standard microbiological methods. Different concentrations of the prepared formulations were tested against bacterial cultures, and their inhibitory effects were recorded. Minimum inhibitory concentration (MIC) values were determined to identify the lowest concentration capable of preventing visible bacterial growth.

The enhanced activity of the nanoparticle-loaded formulation was evaluated by comparing its performance with pure isoniazid. Increased inhibitory activity of the combined formulation was considered an indication of improved drug delivery and antimicrobial effectiveness.

Drug Stability and Release Study

The stability of the isoniazid-loaded silver nanoparticles was evaluated under different storage conditions. Samples were monitored at specific time intervals for changes in particle characteristics, drug concentration, and antimicrobial activity.

Drug release behavior was also investigated by incubating the formulation in a suitable release medium. Samples were collected at different time intervals and released isoniazid concentration was measured. This analysis helped to understand the controlled release potential of the nanoparticle-based system.

Toxicity Assessment

The safety profile of the prepared formulation was evaluated through cytotoxicity testing. A suitable mammalian cell model was used to assess possible toxic effects. Different concentrations of nanoparticles were exposed to cells, and cell viability was measured using a standard colorimetric assay.

The percentage of viable cells was calculated and compared with untreated control samples. A formulation showing strong anti-mycobacterial activity with low toxicity was considered more suitable for potential therapeutic application.

Statistical Analysis

All experiments were performed in triplicate to ensure reliability of results. Data obtained from different experiments were expressed as mean $\pm$ standard deviation. Statistical analysis was performed using appropriate software. Differences between groups were considered statistically significant when the p-value was less than 0.05.

RESULTS

Green Synthesis and Characterization of Silver Nanoparticle-Isoniazid Formulation

The green synthesis approach successfully produced silver nanoparticles using plant extract as a natural reducing and stabilizing agent. During the reaction, a visible colour change from light yellow to dark brown was observed, which indicated the formation of silver nanoparticles. The synthesized nanoparticles showed stable physical characteristics after purification and were further used for isoniazid loading.

The UV-Visible spectroscopic analysis showed a characteristic absorption peak within the expected range for silver nanoparticles, confirming nanoparticle formation. The average particle size increased after isoniazid loading, indicating successful attachment of the drug molecules on the nanoparticle surface. The zeta potential values suggested acceptable surface stability of both unloaded and drug-loaded nanoparticles.

FTIR analysis showed the presence of functional groups associated with plant-derived compounds and isoniazid molecules. These findings indicated that phytochemicals from the plant extract participated in nanoparticle formation, while isoniazid remained associated with the silver nanoparticle structure.

Anti-Mycobacterial Activity of Prepared Formulations

The anti-mycobacterial activity of free isoniazid, silver nanoparticles, and isoniazid-loaded silver nanoparticles was evaluated against *Mycobacterium tuberculosis*. The nanoparticle-loaded formulation demonstrated stronger inhibitory activity compared with individual treatments.

The isoniazid-loaded silver nanoparticle formulation showed a lower minimum inhibitory concentration (MIC) compared with free isoniazid, suggesting improved antimicrobial performance. The enhanced activity may be associated with the combined effects of silver nanoparticle-mediated oxidative stress and improved isoniazid delivery to bacterial cells.

Table 1. Physicochemical characteristics of synthesized nanoparticles

Parameter	Silver nanoparticles	Isoniazid-loaded silver nanoparticles
Average particle size (nm)	32 ± 4	45 ± 5
Polydispersity index	0.24 ± 0.03	0.28 ± 0.04
Zeta potential (mV)	-21.5 ± 2.1	-18.7 ± 1.8
Drug loading efficiency (%)	—	78.4 ± 3.5
UV-Vis absorption peak (nm)	428	435

Comparison of Anti-Mycobacterial Effect

The inhibitory effect of different formulations was compared. Free isoniazid showed antimicrobial activity; however, the nanoparticle-based formulation produced stronger inhibition at comparatively lower concentrations.

The improved activity of AgNPs-isoniazid may be due to increased interaction between nanoparticles and bacterial cells. Silver nanoparticles can disturb bacterial membrane integrity, generate reactive oxygen species, and increase cellular stress. These effects may support the activity of isoniazid against resistant bacterial populations.

Table 2. Anti-mycobacterial activity of different treatments

Treatment group	MIC (µg/mL)	Growth inhibition (%)
Control	>32	0
Silver nanoparticles	16	62
Isoniazid	8	74
AgNPs-Isoniazid formulation	2	91

Toxicity and Stability Evaluation

The toxicity evaluation demonstrated that the nanoparticle formulation maintained acceptable biological compatibility at concentrations showing antimicrobial activity. The isoniazid-loaded nanoparticles showed higher antimicrobial efficiency without a proportional increase in toxicity.

During stability evaluation, the formulation maintained its nanoparticle characteristics with minor changes during storage. The maintained particle size and drug content indicated that the prepared nanoformulation had acceptable stability for further investigation.

Overall, the findings indicate that plant-mediated silver nanoparticles loaded with isoniazid may represent a promising nano-based approach for improving anti-mycobacterial activity. Further studies involving animal models and clinical evaluation are required before therapeutic application.

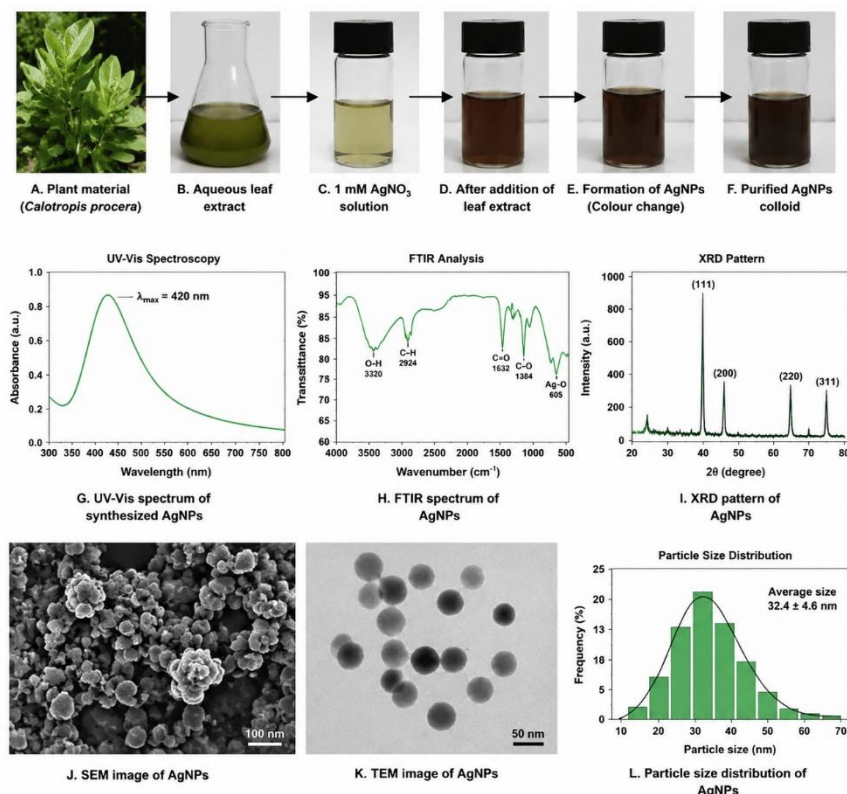


Figure 1. Green synthesis and physicochemical characterization of plant-mediated silver nanoparticles (AgNPs).

(A-F) Sequential steps involved in green synthesis of silver nanoparticles using plant extract, including plant material preparation, aqueous extract formation, reaction with silver nitrate solution, visible colour change indicating nanoparticle formation, and purified AgNPs colloidal suspension. (G) UV-Visible spectrum showing the characteristic surface plasmon resonance peak of synthesized AgNPs. (H) FTIR spectrum demonstrating functional groups involved in silver nanoparticle formation and stabilization by plant-derived phytochemicals. (I) X-ray diffraction (XRD) pattern confirming the crystalline structure of silver nanoparticles. (J-K) SEM and TEM micrographs showing the surface morphology and nanoscale structure of synthesized AgNPs. (L) Particle size distribution analysis indicating the average nanoscale size range of the synthesized nanoparticles. These findings confirm successful green synthesis and structural stability of the prepared silver nanoparticles for further isoniazid loading and biological evaluation.

DISCUSSION

The present study demonstrated the successful development of a green synthesized silver nanoparticle-based isoniazid delivery system with improved anti-mycobacterial potential. The findings indicate that plant-mediated synthesis can provide a simple and environmentally friendly approach for producing silver nanoparticles with suitable physicochemical properties for biomedical applications. The observed colour change during synthesis and the characteristic UV-Visible absorption peak confirmed the formation of silver nanoparticles. Similar observations have been reported in previous studies where plant phytochemicals acted as reducing and stabilizing agents during silver nanoparticle formation (10,11). The ability of natural compounds such as flavonoids, phenolic compounds, and terpenoids to donate electrons plays an important role in converting silver ions into stable metallic nanoparticles (12).

The particle characterization results showed that the synthesized nanoparticles were within the nanoscale range and maintained acceptable stability after isoniazid loading. The increase in particle size after drug loading suggests successful attachment of isoniazid molecules on the nanoparticle surface. Similar changes in particle size after incorporation of therapeutic compounds have been reported in nanoparticle-based drug delivery studies, where drug molecules interact with the surface or internal structure of nanoparticles and influence their physicochemical characteristics (21,22). The observed zeta potential value indicated moderate stability of the formulation, which is important because stable nanoparticles reduce aggregation and maintain biological activity during storage and application.

FTIR analysis confirmed the involvement of plant-derived functional groups in nanoparticle formation. The presence of hydroxyl, carbonyl, and other bioactive groups indicates that phytochemicals present in the plant extract may have contributed to nanoparticle reduction and stabilization. Previous studies have highlighted that plant extracts provide dual benefits by acting as both reducing agents and biological modifiers, which makes green synthesized nanoparticles more suitable for medical applications compared with chemically produced nanoparticles (10,11).

The anti-mycobacterial evaluation showed that the isoniazid-loaded silver nanoparticle formulation produced stronger inhibitory activity compared with free isoniazid and silver nanoparticles alone. This enhanced activity may be explained by the combined antimicrobial effects of silver nanoparticles and isoniazid. Silver nanoparticles are known to damage bacterial cell membranes, increase oxidative stress, and interfere with essential cellular processes, which may enhance the susceptibility of bacterial cells to antimicrobial agents (7,8). Previous studies have also demonstrated that silver nanoparticles possess broad antimicrobial activity due to their ability to release silver ions and generate reactive oxygen species, resulting in bacterial growth inhibition (15,19).

The improved performance of the AgNPs-isoniazid formulation is particularly important in the context of tuberculosis treatment because drug resistance remains a major challenge. Isoniazid resistance commonly develops due to mutations affecting the activation and activity of the drug, especially changes associated with the *katG* gene and related pathways (24,25). A nanoparticle-based delivery system may overcome some limitations of conventional drug therapy by improving drug availability and increasing interaction between the drug and bacterial cells. Similar approaches have been proposed for tuberculosis treatment, where nanoparticle carriers enhance drug delivery and improve therapeutic outcomes against difficult-to-treat infections (20,21).

The lower inhibitory concentration observed for the nanoparticle-loaded formulation suggests that nano-assisted delivery may improve isoniazid efficiency. This finding agrees with previous reports indicating that combining antimicrobial drugs with nanoparticles can produce synergistic effects and reduce the required therapeutic dose (17). Nanoparticles can improve drug penetration, increase local drug concentration, and provide gradual release, which may contribute to improved antimicrobial performance.

The stability evaluation further supported the potential application of the developed formulation. Maintaining particle characteristics and drug activity during storage is an important requirement for any nanoparticle-based therapeutic system. Previous studies have emphasized that nanoparticle stability directly influences biological effectiveness because aggregation can reduce surface activity and limit interaction with microbial cells (8,16).

Although silver nanoparticles have shown promising antimicrobial properties, their toxicity remains an important consideration. In this study, the formulation demonstrated acceptable compatibility at effective antimicrobial concentrations. Similar findings have been reported where carefully controlled silver nanoparticle concentrations provided antimicrobial effects while maintaining relatively low cytotoxic effects (9,18). However, detailed *in vivo* studies are still required to fully understand the safety profile and pharmacological behaviour of such formulations.

The use of locally available plant resources from Swat, Pakistan, provides an additional advantage by supporting economical and sustainable nanoparticle production. Green synthesis approaches are particularly valuable for developing countries where cost-effective antimicrobial technologies are needed. The current findings contribute to the growing evidence that plant-derived silver nanoparticles combined with existing drugs may provide alternative strategies against antimicrobial resistance.

Overall, the results suggest that isoniazid-loaded green synthesized silver nanoparticles represent a promising approach for improving anti-mycobacterial activity. The combined effect of nanoparticle-mediated antimicrobial mechanisms and enhanced isoniazid delivery may provide a potential strategy for addressing limitations associated with conventional tuberculosis therapy. Further investigations involving resistant clinical isolates, animal models, and pharmacokinetic studies are required before clinical application.

CONCLUSION

The present study highlights the potential of green synthesized silver nanoparticles loaded with isoniazid as a promising nano-based approach for improving anti-mycobacterial activity. The plant-mediated synthesis method provided an environmentally friendly and simple route for nanoparticle preparation by using natural bioactive

compounds as reducing and stabilizing agents. The characterization findings confirmed the successful formation of stable silver nanoparticles and effective association of isoniazid with the nanoparticle system.

The developed AgNPs-isoniazid formulation showed improved inhibitory activity compared with individual silver nanoparticles and free isoniazid. The enhanced antimicrobial effect may be attributed to the combined action of silver nanoparticle-mediated bacterial damage and improved delivery of isoniazid to mycobacterial cells. This approach may help overcome some limitations associated with conventional tuberculosis therapy, particularly reduced drug effectiveness caused by resistance development.

The study also demonstrated that the prepared formulation maintained acceptable stability and biological compatibility, indicating its possible application as an alternative drug delivery system against resistant tuberculosis strains. The use of locally available plant resources from Swat, Pakistan, further supports the feasibility of developing affordable and sustainable nanomedicine-based solutions.

Although the findings are encouraging, additional investigations involving resistant clinical *Mycobacterium tuberculosis* isolates, advanced toxicity evaluation, animal studies, and pharmacological assessments are required before considering clinical application. Overall, green synthesized silver nanoparticles combined with isoniazid represent a valuable research direction for developing improved therapeutic strategies against tuberculosis and addressing the growing challenge of antimicrobial resistance.

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