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Nanotechnology-Enabled Biomaterials: Transforming Tuberculosis Management through Advanced Diagnosis, Targeted Drug Delivery, and Immunotherapy

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Abstract: Tuberculosis remains a formidable global health challenge, necessitating the development of innovative therapeutic strategies to combat this infectious disease. In recent years, nanotechnology has emerged as a promising field with great potential for revolutionizing TB treatment. This review presents an overview of the application of nanotechnology in diagnosis, drug delivery, and immunotherapy for TB. Nanotechnology offers new avenues for improved diagnosis of TB by enabling rapid and sensitive detection of *Mycobacterium tuberculosis* in clinical samples. Nanoparticle-based biosensors can enhance the sensitivity and specificity of TB diagnostics. Nanoscale platforms such as quantum dots, carbon nanotubes, and gold nanoparticles can detect Mtb-specific biomarkers, facilitating early and accurate diagnosis and prompt treatment initiation. Nano formulations, which include liposomes, polymeric nanoparticles, and solid lipid nanoparticles, enable targeted delivery of anti-TB drugs to the site of infection. These nanocarriers protect the drugs from degradation, improve their solubility, and prolong circulation time, resulting in enhanced drug bioavailability and improved therapeutic outcomes. Nanotechnology-based approaches have the potential to significantly transform TB treatment by revolutionizing diagnosis, drug delivery, and immunotherapy; harnessing the unique properties of nanomaterials and nanodevices enables precise and targeted interventions, overcoming several limitations associated with conventional approaches. As research in this field progresses, it is anticipated that nanotechnology will continue to play a pivotal role in the fight against tuberculosis, ultimately contributing to global efforts to control and eradicate this devastating disease.

Keywords: Mycobacterium tuberculosis; diagnosis; drug delivery; immunotherapy.

1. Introduction

The primary cause of infectious illness tuberculosis (TB) is *Mycobacterium tuberculosis*. Technical resources are supporting TB control, but its elimination is still a long way off. TB is a severe public health issue that is mostly a result of income inequality and poverty [1]. In 1993, The WHO (World Health Organization) claimed that tuberculosis (TB) is a worldwide emergency as a result of a sharp increase in cases, mostly in industrialized nations, which is the foremost cause of infection-related adult humanity. According to the WHO, M. tuberculosis infects one-third of the world's population [2]. The global epidemic is fueled by misdiagnosis and delayed diagnosis [3]. The WHO's (World Health Organization's)

extension of the DOTS (Directly Observed Treatment, Short-course), co-infection with HIV and multidrug resistance (MDR) TB, fundamentally necessitates the diagnostic instruments [4]. Using an effective delivery method for the drug that provides the medicine to the selected tissues without reducing its potency or efficacy is a good strategy for combating drug resistance. Thus, using nanoparticles can enhance the distribution of anti-TB medicines (ATDs) to the tissues that have been infected with mycobacteria, as well as the identification of certain mycobacterial strains.

A highly beneficial approach to addressing drug resistance involves implementing an efficient drug delivery system capable of precisely transporting medication to specific tissues while maintaining optimal potency and efficacy. Thus, using nanoparticles can enhance the distribution of anti-TB medicines (ATDs) to the tissues that have been infected with mycobacteria, as well as the identification of certain mycobacterial strains. The therapeutic index of medicine can be greatly increased, the endurable of harsh chemotherapeutics improved, and systemic adverse impact decreased using nanotechnology-based drug delivery systems. The utilization of nanoparticles and nanodevices, which have diameters between 1 and 100 nm, can provide advanced development to help medications more effectively accomplish their goal and has grown to be a significant multidisciplinary field of research in recent years. Many ailments, including those of the heart, lungs, Parkinson's, brain, and body, have been treated using nanostructures, including Alzheimer's and cancer [5–9].

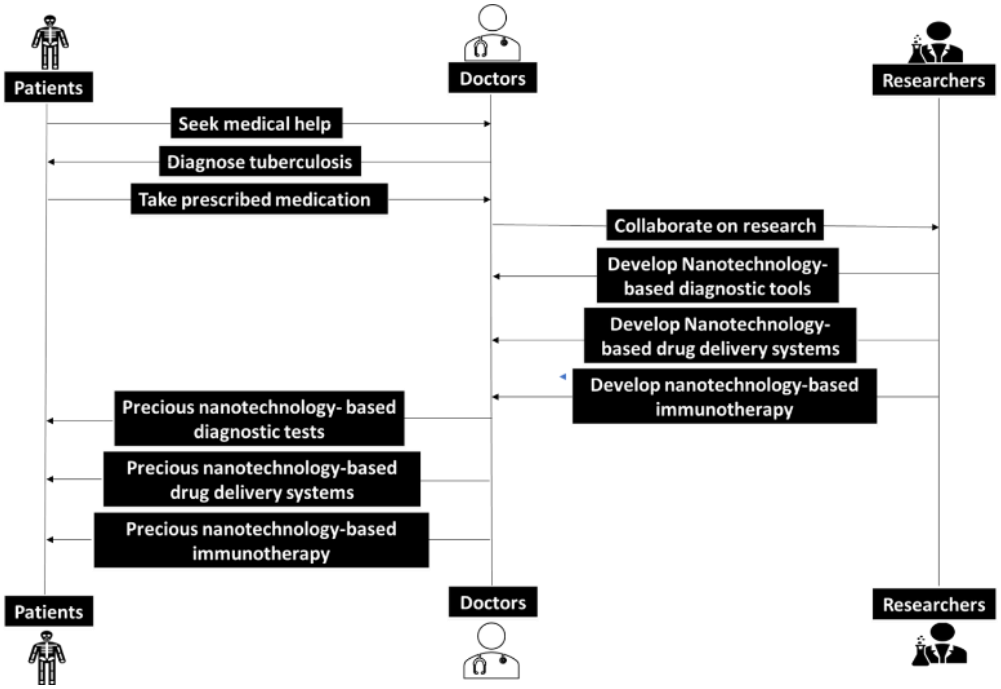

Figure 1. Revolutionizing diagnosis, drug delivery, and immunotherapy for tuberculosis.

The idea that someone who contracts the TB bacteria gets ill is untrue. Latent TB infection and TB illness are, therefore, two TB-related diseases. Broad-spectrum M. tuberculosis infection causes a very small percentage of individuals to acquire TB illness; nevertheless, HIV infection significantly raises the danger of acquiring TB and may serve as a triggering factor [10]. Additionally, the existence of immunosuppressive diseases such as malnutrition, alcoholism, diabetes, and chronic lung disease can be a cause [11]. The primary problem with the present TB chemotherapy is that the majority of molecules do not reach their targets and, as a result, linger in the body, generating negative aftereffects. This occurs whether the medicine is supplied orally or intravenously. Drugs have a limited therapeutic window due

to their quick clearance and short plasma half-life [12]. We need new TB therapies that can overcome these obstacles provided by antituberculosis medications to fight them and restore the success rate of tuberculosis therapy.

Earlier work was done in Australia to apply innovative tethered nanoparticles as an inexpensive, color-based test method for TB. A substitute study was done in India to use an optical biosensor for quick TB detection at a cheap cost of less than US$ 1 [4]. Because TB chemotherapy is complicated and calls for long-term administration of polydrug regimens, poor patient adherence to treatment is the single biggest cause of treatment failure [4]. Here, we examine the most recent developments in anti-TB medication delivery and anti-TB drug encapsulation, as well as the state-of-the-art nanotechnology-based diagnostic and therapeutic methods for treating tuberculosis (Figure 1).

2. Diagnostic Applications of Nanotechnology

The alternatives that are currently accessible are being expanded by nanotechnology, which will improve their effectiveness and sensitivity in identifying TB in the early stage of the disease. Polymerase chain reaction and other diagnostic procedures using nucleic acids are essential in this procedure. To increase the effectiveness of nanoparticles, they can be functionalized with different lectins and tagged with appropriate ligands—Uptake of PLG (Poly-DL-Lactide-co-Glycolide) nanoparticles [13,14].

2.1. Quantum dots.

Semiconductor nanocrystals used in Nanotechnology (or "quantum dots") are not larger than 10nm and can produce a different color based on their size to overcome the limiting specificity of fluorescence or electronic microscopy to identify tuberculosis class B. These tiny probes can survive significantly more light emissions and excitation cycles than ordinary organic molecules without easily decomposing [13–15]. This study conducted a diagnosis of tuberculosis using quantum dots. The test involved mixing a sputum sample with quantum dots coated with antibodies to tuberculosis bacteria. If the bacteria were present in the sample, the quantum dots would bind to them and emit a fluorescent signal [16].

2.2. Imaging nanotechnology.

Targeted TB-bacilli molecules can be marked with artificial chromophores like fluorescent proteins or quantum dots to enable direct optical examination of intracellular signaling complexes, for instance, correlation imaging or confocal fluorescence microscopy [13]. This study uses magnetic nanoparticles for tuberculosis diagnosis. The nanoparticles were coated with antibodies to tuberculosis bacteria and were also magnetic. When the nanoparticles were mixed with a sputum sample from a patient with tuberculosis, they would bind to the bacteria and be attracted to a magnetic field. The study found that the nanoparticles could detect tuberculosis bacteria in sputum samples [17].

2.3. Noble metal nanoparticles.

This approach showed 94.7% reactivity and 99.6 percent accuracy for identifying Mycobacterium TB, whereas the *M. tuberculosis* complex was detected with 96.6 percent sensitivity and 98.9 percent specificity. It can identify rpoB mutations linked to drug resistance [14]. Noble metal nanoparticles, such as silver, gold, and platinum, have unique physical and

chemical characteristics that make them desirable for various biomedical applications, including drug delivery and antimicrobial therapies—their tiny size and high surface area-to-volume ratio permit efficient interactions with biological systems. Silver nanoparticles can enhance the effectiveness of TB treatment by boosting the antimicrobial action of existing therapies. It was found that silver nanoparticles, when used in combination with the antibiotic isoniazid, showed improved antibacterial activity against drug-resistant strains of M. tuberculosis. It was observed that the gold nanoparticles exhibited potent antimycobacterial effects, even at low concentrations, suggesting their potential as a novel therapeutic approach for TB treatment [18].

2.4. Protein chips (or proteomics).

Proteomics is useful for both the creation of drugs and the diagnosis of disease. Protein chips may be handled with small modular proteins from Tuberculosis bacteria that can accurately attached to proteins with specific biochemical or structural patterns [13]. The protein chip used in the study was designed to detect proteins tuberculosis produces, the bacteria that causes tuberculosis. The four proteins selected for the protein chip were Rv1860, RV3881c, Rv2031c, and Rv3803c. These proteins are known to be at greater expression levels in people with active tuberculosis than in people with latent TB infection [19].

2.5. Sparse cell detection.

This technique is developed depending on the special qualities of sparse cells, which are reflected in variations in internal Tuberculosis bacilli deformation. Sparse cells appear unusual and physiologically unique from the surrounding cells in typical environments. The task of finding a few cells and isolating them is quite difficult [13].

Other techniques include using immunofluorescence microscopy in conjunction with luminescence-based nanoparticles to detect Mycobacterium TB with incredibly high sensitivity and few false-positive results.[14]. The test for the presence of the Tuberculosis-bacilli genome is based on a brief test on the tuberculosis-bacilli deoxyribonucleic acid (DNA) segments embedded in a nano-gold particle. It forms a thick web of observable gold balls after binding to complementary DNA tentacles on many nanospheres, making identifying TB bacilli possible [13]. The capacity of nanostructured zinc-oxide films to identify genomic targets up to 100pM in clinical specimens and the lowered cost of automated sensitivity detection make nanofabricated devices appropriate for point-of-care applications in diagnosing Mycobacterium TB [14].

3. Harnessing Nanoparticles for Antimycobacterial Drug Delivery

3.1. Liposomes.

A lipid bilayer membrane encloses an aqueous volume inside liposomes, which are concentric bilayered vesicles [20]. A British hematologist named Dr. Alec D. Banghamam unexpectedly discovered liposomes in 1961. A lipid-based membrane completely encloses an aqueous volume in a liposome, described as “simple tiny vesicles” [21]. They can encapsulate drugs that are both lipophilic and hydrophilic [22]. It may also be used to benignly encapsulate insoluble pharmaceuticals [23]. The compounds that are medicinally active, such as genetic

material, enzymes, vaccines, proteins, peptides, antifungals, cancer, diagnostics, immunomodulators, ophthalmology, etc., are delivered using liposomes as a carrier [24].

Additionally, liposomes are useful for loading lipid-soluble medicines onto the outer membrane and water-soluble medications into the interior aqueous compartment. High-entrapment efficiencies can be achieved by incorporating various medications into liposomes thanks to improvements in the techniques for creating and/or manipulating them [25]. The decomposing and release of the drug molecules to predetermined locations in a regulated way is represented by Liposomes [26]. Some studies were conducted that use liposomes to deliver CRISPR-Cas9 for tuberculosis treatment. A gene-editing technology, CRISPR-Cas9, can be used to target and destroy tuberculosis bacteria. The liposomes were loaded with CRISPR-Cas9 and then injected into mice with tuberculosis. The study found that the liposomes could deliver CRISPR-Cas9 to the bacteria and destroy them [27].

3.2. Solid lipid nanoparticles (SLNs).

Lipids that are solid at body temperature and 25°C combine with surfactants to generate SLN. Triglycerides, waxes, or a combination of glycerides are the lipids used in manufacturing SLN. The encapsulation effectiveness for these systems, which varies from 25 to 50 percent, falls when extremely identical lipids are used because they produce flawless crystals with good organization. Additionally, the drug may be ejected from the particle during storage during a polymorphic shift from the unstable form to the form. Due to their tiny size and biocompatibility, SLN's superior chemical and physical stability offers unstable pharmaceuticals more protection against degradation and the flexibility to be carried via different routes, including oral, parenteral, and cutaneous [28]. Controlled medication release is another benefit of these systems. By making water-soluble pharmaceuticals soluble in this solvent, SLNs can improve drug absorption [29–31]. The study was developed that the SLPs were loaded with imaging agents. The imaging agents were able to target the tuberculosis bacteria and emit a signal that a medical imaging device could detect. In a study, it was found that SLPs were effective in tracking the progression of TB infection [32].

3.3. Dendrimers.

Several atoms are arranged in long, repetitive chains in three dimensions to form dendrimers. These artificial nanoparticles have a diameter of 5–10nm. Regarding their shape and multifunctionality, they are particularly adaptable molecules. In a research review, Cheng *et al*. [33] have thoroughly explored the factors that influence drug delivery optimization for creating dendrimers, as well as their various combinations. These three areas may be connected to a wide variety of molecules, which accounts for the great functionality of these compounds. Since each of these areas serves a distinct purpose, it is possible to readily change qualities like solubility and thermal stability for various uses [34]. The shape of the transported pharmaceutical formulation is biochemically changed by using dendrimers in a different way, which facilitates its entrance into the target cells [35]. Dendrimers have been discovered in combination therapy approaches for TB. Researchers have investigated the co-delivery of multiple drugs using dendrimers to enhance treatment results and reduction of the development of drug resistance. Dendrimers can be functionalized with different drugs or drug combinations to enhance their effectiveness against TB [36].

3.4. Polymeric nanoparticles.

Polymeric nanoparticles are excellent applicants for drug delivery vehicles due to their high levels of biodegradability and biocompatibility. By choosing different surfactants, organic solvents, polymer lengths, and monomer dimensions, polymeric nanoparticles may be made with various features (drug release profile, zeta potential), making them structurally much more stable. Emblematic functional groups found in polymeric nanoparticles can be changed in accordance with the biological part of pharmaceuticals, which are the specific ligands. By structurally altering the surface of these nanoparticles with wheat gram agglutinin, researchers have increased the effectiveness of these particles [37]. Additionally, lectin-conjugated nanoparticles can significantly increase biorecognition and mucoadhesion of glycosylated visible structure on bacterial cell walls, leading to longer half-life serum [38]. Polymeric nanoparticles have also been explored for their immunomodulatory properties in TB treatment. Encapsulating immunomodulatory agents or antigens within nanoparticles can be targeted to immune cells and modulate the host immune response against M. tuberculosis. Recent studies have investigated polymeric nanoparticles as vaccine delivery systems for TB, aiming to enhance the protective immune response and develop long-lasting immunity [39].

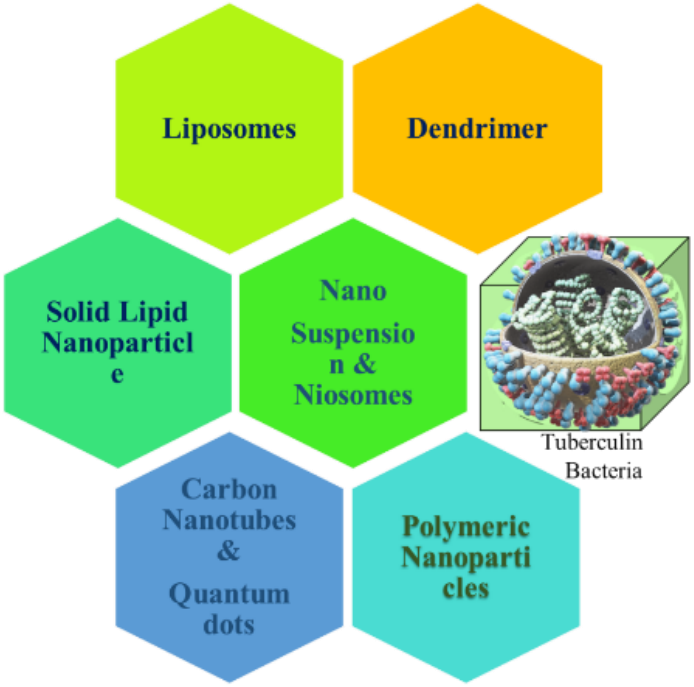

Figure 2. Different types of nanoparticles with tuberculosis.

Recently, various nanoparticles have been investigated for the treatment of TB, with all solid lipid nanoparticles (SLNs), liposomes, polymeric nanoparticles, dendrimers, and others (Table 1, Figure 2).

Table 1. Nanoparticles with Mtb drug, in-vitro studies, and targeted route.

Nanocarriers	Administration	Anti-TB drug	In-vitro studies	Reference
Polymeric nanoparticles	Oral	Moxifloxacin	Low plasma protein binding	[40]
Lipid nanoparticles	Intravenous	Bedaquiline (BDQ)	MIC values of BDQ, not modified after drug encapsulation	[41]
Nanocapsules	Respiratory	--------	No cytotoxic effects on HepG2, A549	[41]
Lipid-polymer hybrid NPs	Respiratory	Ciprofloxacin (CPX)	Deep lung deposition of the spray-dried drug-loaded nanocarriers	[42]
Liposomes	Intravenous	Clofazimine (CFM)	---------	[43]

4. Exploring Promising Advancments in Nanotechnological Interventions and Carrier such as Nano Drug Delivery Carriers

4.1. Nanosuspensions.

The microscale dispersion of colloidal particles is a popular definition of nanosuspension. It is typically used for medication delivery when it is only moderately dissolved in water and organic solvents. Using nanosuspension, several parameters may be adequately changed to fit a certain drug delivery mechanism, including drug dissolving velocity, charge distribution, and particle size [44]. Thus, in lowering bacterial burdens on the lungs of *M. avium*-infected mice, nanocrystalline clofazimine liver and spleen is just as efficient as liposomal clofazimine. This nanosuspension intravenous medication is a godsend for avoiding mycobacterial infections [45]. This method of medication administration offers enormous potential for the treatment of TB because ATD can result in substantial adverse effects.

4.2. Carbon nanotubes.

They are tubes with cross-sectional diameters ranging from 1 to 100nm and lengths of several micrometers. They come in single-walled and multi-walled varieties. They have several uses and may be functionalized by attaching a variety of chemical moieties to their surface [46]. Carbon nanotubes exhibit metallic and nonmetallic behavior, greatly enhancing their biological value. Nucleic acids, proteins, and bioactive peptides can be linked to their surface to increase the accessibility of their carriers to cells and organs. Recent studies have explored the development and characterization of isoniazid-chitosan-carbon nanotubes for potential applications in tuberculosis (TB) treatment. In *in vitro* studies, the drug-loaded nanotubes have been optimized to inhibit the growth of Mycobacterium tuberculosis effectively [47].

4.3. Aerosolic nanoparticles.

Nanoparticle suspensions in the form of dry, powdery aerosols are known as aerosolic nanoparticles. They are employed in creating nanoparticles that may serve as molecules for medication delivery that may be breathed to treat lung infections that follow. Nanoparticles can be used quite well to treat TB, one of these respiratory illnesses with multidrug resistance [48]. Effective TB diagnosis and therapy with far less systemic toxicity will almost certainly be accomplished using aerosolic nanoparticles. Effective TB diagnosis and therapy with far less systemic toxicity will almost certainly be accomplished using aerosolic nanoparticles. Effective TB diagnosis and therapy with far less systemic toxicity will almost certainly be accomplished using aerosolic nanoparticles.

4.4. Quantum dots.

The average size of quantum dots is 10nm, and they might be made to glow in a range of colors depending on their size [49]. They emit a wide range of radiation, which spans various wavelengths; they can be particularly effective fluorophores. This makes it possible for an approximation of TB-infected cells to be done more quickly, precisely, and successfully [50].

4.5. Niosomes.

Niosomes are structurally similar to liposomes in that they are nanoscale and resemble nonionic sacs, but they also offer a few benefits over liposomes. These molecules can be stabilized by surfactants since they are amphipathic molecules [51]. Until now, isoniazid, rifampin, and pyrazinamide have been used as traditional ATDs in TB therapy employing niosomes. Using niosomal nanoparticles is extremely beneficial in assuring some essential factors for the best medication biodistribution in biological systems. With these aid, drug surface charges can be estimated using zeta potential technology, spectroscopic techniques can be used to calculate how much of the medication molecule is absorbed into the carrier, and transmission electron microscopy may be used to determine the particle size of the medication formulation. The drug can be delivered more effectively and smoothly to the necessary sites [52]. Their usage has substantially improved specific-site medication administration, pointedly decreased the general toxicity of medication administered, and made the therapy more widely available for diseases like TB [53]. A recent study was conducted where they developed and characterized D-Cycloserine and ethionamide dual dual-loaded-drug self-assembled niosomes for handling multidrug-resistant tuberculosis [54].

4.6. Nanoemulsions.

With the aid of surfactant molecules, two immiscible liquids may be joined to form stable thermodynamic mixtures known as nanoemulsions that behave as a single phase [55,56]. In an influential review article, Ahmed *et al*. [57] have thoroughly described how rifampicin-based nanoemulsions are used to treat tuberculosis. They have clarified key design elements, including viscosity, solubility, and the capacity for chemical interaction, enabling nanoemulsions to be designed as optimum drug delivery vehicles. At modest doses, it has been used successfully to destroy TB bacteria, and there is barely any chance of toxicity or adverse effects [58]. A recent study was conducted where they developed a nanoemulsion rifampicin-loaded cationic with precise surface modification using polymyxin B and chitosan. The researchers aimed to enhance the effectiveness of the preparation developed for treating ocular tuberculosis [59].

5. Enabling Technology

As a result, medication delivery based on nanotechnology has emerged as a game-changing medical technique. It has given rise to several significant discoveries that have helped treat difficult-to-treat illnesses. Additionally, it has eliminated the requirement for patient invasion and sensitization. The intrinsic characteristics of this technology have allowed for the crossing of blood-brain barriers [60]. A revolution in the treatment of tuberculosis (TB) has been made possible by the employment of systems like NanoElectroMechanical Systems (NEMS) and BiomicroElectroMechanical Systems (MEMS) that allow for highly fine efficient and control conduct of these nano-drug carriers based delivery [61]. In conclusion, prolonged and regulated drug release, increased drug bioavailability, decreased toxicity, abolition of invasive operations and painful sensitization, simpler scaling of the biobarriers, and target-specific-target delivery are the key benefits of nanotechnology-mediated drug delivery [62].

6. Future Directions and Challenges

The biological consequences of nanosystems are now well understood thanks to developments in nanomedicine, which will result in significant, clinically useful advancements in drug delivery [63-66]. Nanosystems must supply the ingredient that is active at sufficient absorption during the whole treatment time and guide it to the intended site of action to meet the requirements that traditional forms of therapy cannot fully meet. Clinical trials will be the most reliable method of verifying the efficacy of these novel medications' efficacy. The feasibility of scaling up processes to quickly introduce novel therapeutic techniques to the market and the potential for obtaining multifunctional systems that will be able to satisfy several biological and therapeutic requirements, including the use in MDR and XDR patients, new task in advance of nanotechnology-based drug delivery systems for the treatment of tuberculosis. Research on the effectiveness of nanosystems for targeting and global norms for their toxicity and biocompatibility are additional hurdles.

7. Conclusions

Nanotechnology-based medication delivery has been shown to be a significant help in identifying and curing TB. It has addressed several exceedingly delicate concerns, ranging from bioavailability to formulation stability. However, two issues remain relevant in this situation. First, the damaged organs should only get the prescribed medication, leaving the healthy tissues alone. Second, attention must be paid to what happens to the medications once they have been transported to the contaminated location. Practical considerations suggested that the preferred method of anti-TB medication administration could be via the oral route using PLG nanoparticles. Future research should focus on developing antituberculosis medication PLG-nanoparticles on a large scale, particularly in conjunction with nanoparticles based on alginate. Future developments in nanodiagnostics will enable non-specialized medical staff to employ them for diagnostics using a specimen-in, answer-out methodology by downsizing biochip technology to a nanoscale advancement range. All newly developed anti-TB medications are still in the pipeline, waiting for funds and more preclinical research before proceeding to the next phase and administering them to TB patients. Another significant factor to be taken into account is the approval status of the biomaterials used as nano vehicles. Clinical investigations are less likely to use items without regulatory agency approval. In this situation, the necessary toxicity studies would boost a unique nanoformulation’s overall value. Nanomedicine stands out as a desirable weapon with several benefits to combat this mycobacterial illness. Further preclinical and clinical data are still needed to understand better the potential of nanoparticle-based treatment to become commercially accessible nanotechnological formulations.

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Conflicts of Interest

The authors declare no conflict of interest.

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