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Review Article

Nanomedicine Based Approaches for Tuberculosis Treatment

Galaba Yamini Padmasri*, Dr. B. Thangabalan, Subhadeep Pratihar, Shohida Khatun, Sapna Pathak, Pusunuri Pranitha, Chiruvolulanka Dharmik Ram Teja, Varshitha Asukolla

SIMS College of Pharmacy

Mycobacterium tuberculosis is the main organism which responsible for tuberculosis (TB) disease, one of the most enduring infectious diseases throughout the world. Long treatment is still having, low patient compliance, and the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains of tuberculosis remain obstacles to effective for the anti-TB medication treatment. These restrictions have led to the investigation of novel therapeutic approaches for better patients' compliance, one of which is nanotechnology. Novel drug delivery systems made possible by nanotechnology can improve anti-TB agents' stability, bioavailability, and targeted delivery with reducing the systemic toxicity. The ability of various nanocarriers, including dendrimers, lipid-based nanoparticles, polymeric nanoparticles, metallic nanoparticles, and carbon-based nanomaterials, to enhance the pharmacokinetic and pharmacodynamic profiles of anti-TB medications has been studied here. These nonsystems allow for controlled and sustained drug release, help drugs build up at infection sites, and may even help macrophages take in drugs better, which is very important for fighting intracellular M. tuberculosis. Nanotechnology-based diagnostic tools also have promised for the early detection and monitoring of TB. None the less, not withstanding encouraging pre-clinical results, issues including toxicity assessment, extensive production, and regulatory approvals must be resolved essential to clinical application. This review emphasises the latest progress in nanotechnology-driven therapeutic and diagnostic approaches for tuberculosis management system, improving their mechanisms, benefits, constraints, and future prospects in addressing global TB.

Keywords: Tuberculosis, Nanotechnology, Nanoparticles, Macrophages, Mycobacterium.

INTRODUCTION

Despite constant improvements in medicine, diagnostics, and treatments, tuberculosis (TB) continues to be one of the most difficult infectious diseases to affect humanity. TB, which is caused by Mycobacterium tuberculosis, is a systemic threat to global health because it mainly affects the lungs but can infect nearly any organ in the body. [1] According to a recent report by the World Health Organization (WHO), the incidence rate of tuberculosis (TB) is declining at a rate of roughly 2% annually, which must drop at a rate of 4-5% annually by 2020. [2] The severity of national epidemics varies at a larger extent among different countries. There were less than 10 new cases of TB per 100,000 populations in most high-income countries, 150-400 in most of the high TB-burden counties and above 500 in a few countries in 2017. DOTs (directly observed therapy, short duration) strategy and its successor (the stop TB strategy) successfully cured a cumulative total of 5.6 million people between 1995 and 2012. Thus, the strategy saved about 22 million lives. The target of "The Stop TB Strategy" was expected to decline the prevalence of deaths up to 2015 owing to tuberculosis by 50% compared with a baseline of 1990 and by 2050 less than one case per million per year. Now, the 2030 targets set in the end TB Strategy are a 90% reduction in TB deaths and an 80% reduction in TB incidence, compared with levels in 2015. [3] Chemotherapy is currently the only one option for the clinical management of TB patients, with recovery

rates of up to 95% when given correctly to those with drug-susceptible TB. How ever, the majority of anti-TB medicines have below average pharmacokinetic characteristics, which frequently prevent them from performing to their full potential in clinical situations. [4] Poor bioavailability due to variable drug absorption and unnecessary first-pass metabolism, wide profile with high dosing frequencies, and individual and combined drug toxicity as well as severe adverse effects are some of the issues related to the therapeutic limitations of the current anti-TB regimens. These challenges contribute to low patient adherence, therapeutic failure, and the alarming emergence of multidrug-resistant (MDR) strains, all of which explain TB's current lethal state and the pressing need to advance anti-TB treatment. [5,6] There nanotechnology has emerged as a potential game-changer in management of TB. The several advantages of nanotechnology in the pharmaceutical industry include improved therapeutic effectiveness, targeted drug delivery, and reduced toxicity. Nanocarriers are better formulations for patients because of these benefits.[7] This review aims to explore recent advancements in the application of nanotechnology for tuberculosis treatment, emphasizing its potential to overcome existing therapeutic limitations and contribute to global TB eradication efforts.

Classification Of TB:

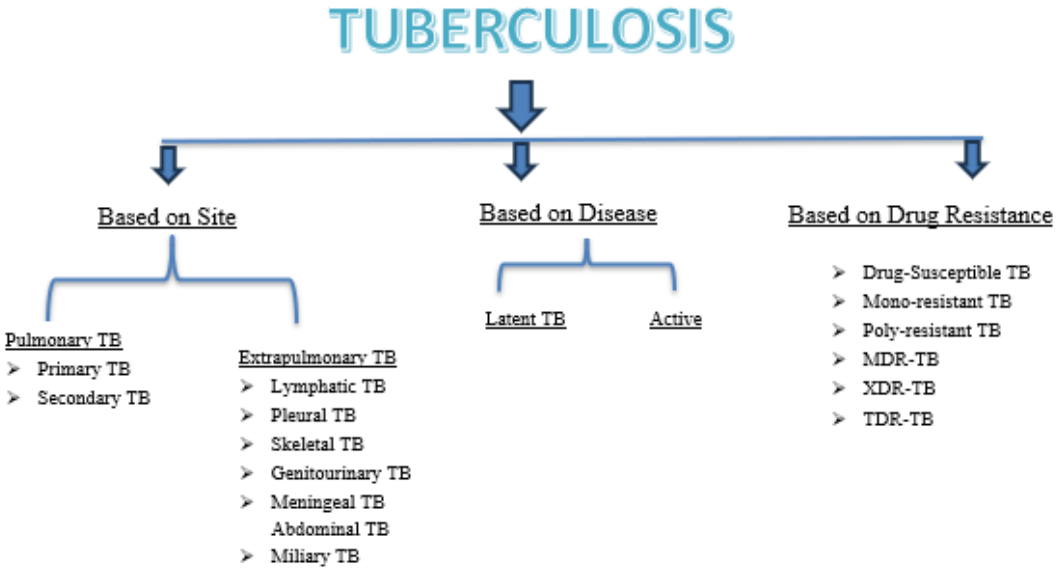


Fig:1 Classification of TB 13,14

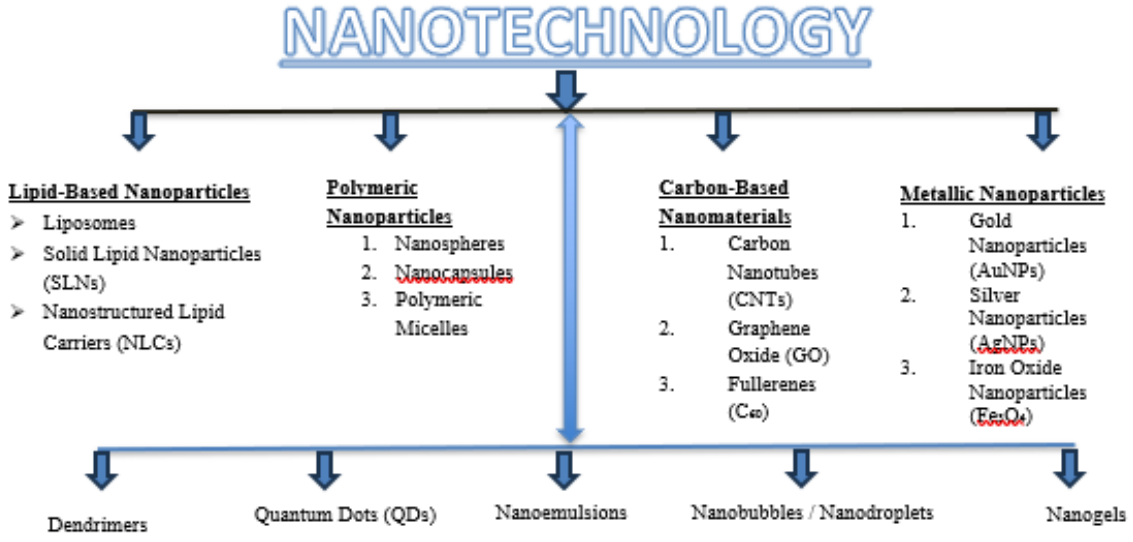
History Of TB:

Tuberculosis (TB) is one of the oldest infectious diseases to human beings. Characteristic skeletal lesions discovered in mummies in Egypt and Peru that date back more than 5,000 years indicate that Mycobacterium tuberculosis has been around for thousands of years, based on archeological and molecular evidence.[8,9] Because of the progressive weakness and pallor that infected people exhibited, TB was known in the past as phthisis, "consumption," or the "white plague". [8] Between the 17th and 19th centuries, tuberculosis (TB) became an epidemic in Europe, especially during the Industrial Revolution when malnutrition, inadequate ventilation, and overcrowding made it simple for the disease to spread. In a number of areas at the time, it was accountable for almost one-fourth of all fatalities. [10] Dr. Robert Koch's discovery of the organism responsible for the disease in 1882 became a turning point in the history of tuberculosis. Mycobacterium tuberculosis. His discovery signified the beginning of modern microbiology and proved that tuberculosis was an infectious disease rather than an inherited one. [8,10] Further advances included the creation of the Bacille Calmette–Guérin (BCG) vaccine in 1921, that is still the only TB vaccine currently in use 21 century. Streptomycin's drug 1943 discovery, which was a subsequently followed by isoniazid, rifampicin, ethambutol, and pyrazinamide, revolutionized the treatment of tuberculosis and brought about the concept of the multidrug therapy. [11] Due to

widespread vaccination, improved hygiene, and efficient chemotherapy, the incidence of tuberculosis (TB) decreased in developed nations by the middle of the 20th century. However, the HIV/AIDS epidemic, rising drug resistance, and economic constraints were among the primary factors of TB's resurgence as a global health emergency in the 1980s. [12] The emergence of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) strains has presented significant challenges to tuberculosis control programs globally. Currently, despite the presence of effective medications, tuberculosis continues to be a major cause of mortality from the infectious diseases through worldwide. investigating its long history of evolution, from the earliest times to current challenges, provides critical insight into the discovery of innovative approaches in TB treatment, such as nanotechnology-based drug delivery systems, aimed at overcoming current therapy challenges and improving the effectiveness of treatments of TB. [10,12]

Classification of Nanotechnology:

Nanotechnology has become a powerful technique in modern medicine, providing new ways to diagnose, deliver drugs to specific areas, and treat diseases. The classification of nanotechnology is predicated on the specific nanocarrier or nanomaterial utilized, each exhibiting distinct structural and functional attributes that render them appropriate for the treatment of particular diseases.



Classification of Nanotechnology Used in Disease Treatment 15,16,17

1. Lipid-Based Nanoparticles (LBNPs):

Lipid-based nanoparticles (LBNPs) are the most promising and biocompatible nanocarrier systems for advanced drug delivery in current time. [18] They are mostly made of the physiological or synthetic lipids that can hold both hydrophilic and lipophilic drugs easily. This makes the drugs more soluble, stable, and available to the body. [19] These nanoparticles help to keep the active pharmaceutical ingredient from breaking down by enzymes and make it possible to safe release the drug in a controlled way to specific tissues, which lowers systemic side effects in body. [18,20] Lipid-based nanocarriers are widely used to treat cancer, tuberculosis, neurological disorders, and other infectious diseases. Traditional treatments often don't work as well as it because the drugs don't dissolve well or don't spread well in the body. [19,20]

Major Types:

- **Liposomes:** These are round vesicles made up of one or more phospholipid bilayers. They can hold hydrophilic drugs in the water core and lipophilic drugs in the bilayer area. Liposomal formulations like Doxil® (liposomal doxorubicin) are approved for use in targeted cancer treatment.[19]
- **Solid Lipid Nanoparticles (SLNs):** These nanoparticles consist of a solid lipid core stabilized by surfactants and are suitable for

controlled and sustained drug release, improving drug stability and patient compliance. [18,20]

- **Nanostructured Lipid Carriers (NLCs):** NLCs are a second-generation lipid system combining solid and liquid lipids, allowing higher drug loading capacity and minimizing drug expulsion during storage. [20]

Key Advantages:

- High biocompatibility and biodegradability, since lipids used are generally recognized as safe (GRAS). [18]
- Improved drug solubility and permeability, especially for poorly water-soluble drugs (19).
- Targeted and controlled release, reducing systemic toxicity and improving therapeutic efficiency. [20]

Example Applications:

Cancer: Liposomal doxorubicin (Doxil®) for tumor-targeted chemotherapy through enhanced permeability and retention effect. [19]

Tuberculosis: Rifampicin-loaded SLNs improve intracellular drug delivery and sustain plasma concentration. [18]

Neurological Disorders: Curcumin-loaded NLCs enhance brain penetration and show neuroprotective activity. [20]

2. Polymeric Nanoparticles (PNPs):

Polymeric nanoparticles (PNPs) are colloidal carrier systems made of natural or synthetic polymers that can hold or adsorb therapeutic agents for controlled and targeted drug delivery. [21] They are used a lot because they are biocompatible, biodegradable, and can release drugs over a long period of time, which makes treatments more effective and lessens side effects. [22] The polymeric matrix acts as a storage space or carrier, keeping drugs safe from being broken down by enzymes and making them more stable and able to move around in biological systems. [21,23] PNPs are especially good at delivering anticancer drugs, antibiotics, vaccines, and gene therapies. They are being studied for use in diseases such as cancer, tuberculosis, and neurodegenerative disorders. [22,23]

Major Types:

Nanospheres: Solid matrix systems where the drug is uniformly dispersed throughout the polymer. [21]

Nano capsules: Vesicular systems in which the drug is confined within a cavity surrounded by a polymeric membrane. [22]

Common Polymers Used:

Natural polymers: Chitosan, alginate, gelatin — known for their biocompatibility and mucoadhesive properties. [21]

Synthetic polymers: Poly (lactic-co-glycolic acid) (PLGA), polylactic acid (PLA), polyethylene glycol (PEG) — used for controlled release and long circulation. [22,23]

Key Advantages:

- Enhanced drug stability and bioavailability. [21]
- Controlled and site-specific release, minimizing systemic toxicity. [22]
- Capability to carry hydrophilic, hydrophobic, and macromolecular drugs. [23]

Example Applications:

Cancer therapy: PLGA nanoparticles delivering paclitaxel for sustained release and targeted tumor accumulation. [22]

Tuberculosis treatment: Rifampicin-loaded PLGA nanoparticles for prolonged pulmonary delivery and improved macrophage uptake. [21]

Gene delivery: Chitosan-based nanoparticles used for DNA and siRNA transport with minimal cytotoxicity. [23]

3. Metallic Nanoparticles (MNPs):

Metallic nanoparticles (MNPs) are very small particles made of pure metals or metal oxides that have special properties of optical, electrical, and catalytic, which make them useful for both diagnosis and treatment of TB. [24] MNPs are the great carriers for targeted drug delivery system, imaging, and photo-thermal therapy because of there high surface-to-volume ratio and can be easily changed on the surface. [25] They can interact with biological molecules at the cellular and molecular levels, which makes them more effective as treatments and more accurate as diagnostic tools. [26] Gold (Au), silver (Ag), iron oxide (Fe_3O_4), zinc oxide (ZnO), and titanium dioxide (TiO_2) are some of the most common metals used. Each has its own unique physicochemical and biomedical benefits. [24] Researchers are looking into MNPs for diseases like cancer, tuberculosis, heart disease, and infections caused by bacteria because they can do many things and may be able to get around drug resistance. [25,26]

Major Types:

Gold Nanoparticles (AuNPs): Known for biocompatibility and ease of functionalization, widely used in drug delivery, photothermal therapy, and biosensing. [24]

Silver Nanoparticles (AgNPs): Exhibit strong antimicrobial and anti-inflammatory properties, making them useful in wound healing and infection control. [25]

Iron Oxide Nanoparticles (Fe_3O_4 NPs): Used as magnetic drug carriers and contrast agents in magnetic resonance imaging (MRI). [26]

Zinc Oxide and Titanium Dioxide Nanoparticles: Employed in antimicrobial, anticancer, and antioxidant therapies. [25]

Key Advantages:

- High surface area and functionalization capacity, enabling conjugation with drugs, antibodies, or ligands. [24]
- Possess dual diagnostic and therapeutic capabilities (theranostic potential) (25).
- Exhibit enhanced cellular uptake and controlled release due to magnetic or photothermal responsiveness. [26]

Example Applications:

Cancer therapy: Gold nanoparticles conjugated with doxorubicin for tumor-targeted photothermal treatment. [24]

Tuberculosis treatment: Silver nanoparticles exhibiting antimicrobial action against Mycobacterium tuberculosis. [25]

Imaging and diagnostics: Iron oxide nanoparticles used as MRI contrast agents for tumor and infection detection. [26]

4. Carbon-Based Nanomaterials (CBNs):

Carbon-based nanomaterials (CBNs) are a group of nanostructures which mostly made up of carbon atoms that are arranged in different allotropic manner, such as fullerenes, carbon nanotubes (CNTs), graphene, and carbon quantum dots. [27] These materials have the great mechanical strength, electrical conductivity, and a large surface area, which makes them good for many biomedical and pharmaceutical uses in various disease treatment. [28] CBNs are good carriers for controlled drug delivery, gene transport, imaging, and bio-sensing because they can cross cell membranes and interact with bio-molecules easily. [27,29] The unique physicochemical and structural features of CBNs enable improved drug loading, controlled release, and targeted delivery to specific tissues, especially in diseases like cancer, tuberculosis, and neurological disorders. [28,29]

Major Types:

Carbon Nanotubes (CNTs): Cylindrical nanostructures with excellent surface area and high drug-loading capacity; used for gene and anticancer drug delivery.[27]

Fullerenes (C_{60}): Hollow spherical carbon cages with potent antioxidant and antiviral properties, used in neuroprotection and photodynamic therapy. [28]

Graphene and Graphene Oxide (GO): Two-dimensional sheets with tunable surface chemistry, ideal for biosensors and targeted cancer therapy. [29]

Carbon Quantum Dots (CQDs): Fluorescent nanoparticles with bioimaging and drug-tracking capabilities, offering high biocompatibility. [28]

Key Advantages:

- High drug loading efficiency due to large surface area. [27]
- Excellent cellular uptake and target specificity through surface functionalization. [28]
- Theranostic potential, enabling combined drug delivery and bioimaging. [29]
- Robust chemical stability and biocompatibility after proper functionalization. [27]

Example Applications:

Cancer therapy: Graphene oxide–doxorubicin conjugates for targeted chemothermal therapy. [28]

Tuberculosis treatment: CNT-based delivery of anti-TB drugs to alveolar macrophages for improved bioavailability. [29]

Bioimaging: Carbon quantum dots used as fluorescent probes for cellular imaging. [27]

Pathophysiology of TB:

Mycobacterium tuberculosis is the main organism of tuberculosis (TB), a chronic infectious disease which spreads mainly by airborne droplets released by a infected person. Following inhalation, the bacilli travel to the lungs' alveoli, where they engage with host immune system cells of the person. The key to the pathogen's persistence have the capacity to survive within macrophages and alter the immune responses in the body. Depending on host immunity, the infection may stay dormant or develop through an active illness. Granuloma growing, tissue necrosis, cavitation, and potential organ dissemination are all effects of active tuberculosis. [30,32]

Flowchart: Pathophysiology of Tuberculosis

Entry and Inhalation of Mycobacterium tuberculosis
⇩
Alveolar Deposition of Bacilli
⇩
Phagocytosis by Alveolar Macrophages
⇩
Intracellular Survival and Multiplication
⇩
Formation of Primary Lesion (Ghon Focus)
⇩
Lymphatic Spread → Ghon Complex
⇩
Latent Tuberculosis (Immune Control)
⇩
Active Tuberculosis (Immune Failure)
⇩
Caseation Necrosis and Cavitation
⇩
Dissemination → Extrapulmonary TB

Description:

Step 1 – Entry and Inhalation of Mycobacterium tuberculosis

Infection begins when airborne droplets containing M. tuberculosis are inhaled and enter the respiratory tract. [30]

Step 2 – Alveolar Deposition of Bacilli

The bacilli bypass upper airway defenses and lodge in the alveoli, initiating local infection. [30]

Step 3 – Phagocytosis by Alveolar Macrophages

Macrophages engulf the bacilli as part of innate immunity; however, not all bacteria are destroyed. [30,31]

Step 4 – Intracellular Survival and Multiplication

M. tuberculosis survives by inhibiting phagosome-lysosome fusion, allowing replication within macrophages. [31]

Step 5 – Formation of Primary Lesion (Ghon Focus)

Accumulation of infected macrophages, lymphocytes, and fibroblasts forms a granulomatous lesion—the Ghon focus. [30,32]

Step 6 – Lymphatic Spread (Ghon Complex)

Infected macrophages migrate to regional lymph nodes, forming the Ghon complex characteristic of primary TB. [31]

Step 7 – Latent Tuberculosis (Immune Control)

If cellular immunity is effective, granulomas contain the bacilli in a dormant state without active disease. [30,31]

Step 8 – Active Tuberculosis (Immune Failure)

Weakened immunity permits reactivation and bacterial proliferation, producing tissue damage and symptoms. [32]

Step 9 – Caseation Necrosis and Cavitation

Granulomas undergo caseous necrosis; liquefaction may form cavities that promote bacterial spread. [30]

Step 10 – Dissemination and Extrapulmonary Tuberculosis

Bacilli disseminate via blood or lymph to other organs (e.g., meninges, bones, kidneys), causing extrapulmonary TB. [31,32]

Drug Regimens:

First-Line Drugs

Tuberculosis treatment primarily based on the first-line anti-tubercular drugs, which are the most effective and minimal toxic agents. The standard protocol consists of a combination of isoniazid, rifampicin, pyrazinamide, and ethambutol, administered orally for several months. These drugs exhibit strong bactericidal and sterilizing activities against Mycobacterium tuberculosis (Mtb), ensuring complete eradication of both actively replicating and dormant bacilli when used together for the treatment of TB. [33] The usual course includes an intensive phase of two months with all four drugs, followed by a continuation phase of isoniazid and rifampicin for four additional months. This multi-drug approach minimizes relapse and prevents the emergence of resistant strains against the mycobacterium. [34]

Second-Line Drugs

When Mycobacterium tuberculosis develops resistance to isoniazid and rifampicin, the disease progresses to multidrug-resistant tuberculosis (MDR-TB). In such cases, second-line drugs are came in used, which include aminoglycosides (amikacin, kanamycin), polypeptides (capreomycin, viomycin, enviomycin), fluoroquinolones (levofloxacin, moxifloxacin, ciprofloxacin), and thioamides (ethionamide, prothionamide, cycloserine). While these drugs are effective against resistant strains of M. tuberculosis, they are consist of greater toxicity, higher costs, and longer treatment durations compared to first-line agents. [35] Patient compliance becomes a major concern, as prolonged therapy and adverse effects can contribute to further resistance and treatment failure if not carefully monitored.

Third-Line Drugs

In cases resistant to both first- and second-line drugs, third-line or reserve drugs are considered for the treatment of the M. tuberculosis. These include rifabutin, linezolid, thioridazine, arginine, vitamin D, macrolides (clarithromycin), and thioacetazone. However, these agents have limited efficacy or unproven effectiveness and are not officially listed by the World Health Organization (WHO) as standard

TB drugs. [36] They are reserved for use in extensively drug-resistant TB (XDR-TB) treatment when no other effective options remain. Recent research focuses on developing of carrier-based drug delivery systems—including biodegradable polymers, liposomes, and microspheres—to enhance the therapeutic index of anti-TB drugs. These systems allow for controlled release, improved bioavailability, and reduced toxicity, thus decreasing the overall dose and treatment duration which is an important factor in TB. [37]

Nanotechnology and Future Strategies

Although conventional anti-TB drugs remain the key factor of therapy, challenges such as drug resistance, patient non-adherence, and systemic toxicity demand innovative delivery systems. Nanotechnology-based drug delivery platforms are emerging as powerful tools to address these limitations and complacence. Nanocarriers improve drug solubility, stability, and targeted delivery, particularly to alveolar macrophages, where M. tuberculosis resides. Nanosized particles (50–200 nm) enable deep pulmonary penetration, sustained release, and reduced mucociliary clearance. [38] Furthermore, by bypassing first-pass metabolism and achieving site-specific delivery, nanocarrier systems reduce systemic side effects and enhance patient tolerance. These formulations can potentially shorten treatment duration, improve adherence, and optimize therapeutic outcomes. Thus, nanotechnology represents a transformative approach toward next-generation anti-TB therapy and vaccine delivery systems. [39]

DISCUSSION:

Nanotechnology has emerged as a powerful and innovative approach for improving tuberculosis (TB) therapy, especially because it addresses several long-standing limitations of conventional anti-TB drugs. Many earlier studies have shown that standard medications often suffer from low solubility, poor tissue penetration, and the need for prolonged treatment, which commonly results in non-adherence and drug resistance. [40] Nanocarrier-based systems were developed to overcome these challenges, and the available literature consistently reports encouraging progress across different nanoparticle platforms. Research on lipid-based nanoparticles, including liposomes and solid lipid nanoparticles, has demonstrated their ability to efficiently encapsulate drugs like rifampicin and isoniazid. These formulations mainly target alveolar macrophages—where Mycobacterium tuberculosis primarily resides—and provide sustained drug release while reducing systemic toxicity. [41] In same way, polymeric nanoparticles, particularly PLGA and chitosan-based systems, have shown enhanced uptake by macrophages, improved bioavailability, and better pulmonary retention, making them attractive candidates for shorter treatment regimens. [42] Silver, gold, and zinc oxide are examples of metallic nanoparticles that are the focus of less amount of published research. By breaking bacterial cell membranes and producing reactive oxygen species, these nanoparticles show inherent antimycobacterial activity. Also, they have been shown to improving the therapeutic effect of first-line TB medications by working in concert with them. [43] Large surface area and adjustable texture of carbon-based nanomaterials, particularly carbon nanotubes and graphene derivatives, enable them to carry several medications or targeting ligands at once, improving delivery efficiency. [44] Comparably, dendrimers—which are well known by their highly branched structure—have observed enhanced solubility and deeper penetration into granulomatous tissue, allowing for more efficient drug release at infection sites. [45] Overall, the literature highly suggests that nanotechnology holds the potential to transform TB therapy by increasing drug targeting, reducing toxicity, and overcoming emerging the drug resistance. However, farther work must prioritize safety evaluation, cost-effective production, standardization of nano-formulations, and large-scale clinical studies. With sustained research efforts and global health collaboration, nanotechnology could pave the way for shorter, safer, and more effective TB treatment strategies in the near future.

CONCLUSION:

Tuberculosis remains one of the most challenging infectious diseases worldwide, continuing to pose a serious threat to global health, particularly in developing countries where infection rates and multidrug-resistant infections are continuously

growing. Although conventional anti-tubercular drug profile involving first-line and second-line drugs have been effective for decades, they are often limited by long time treatment duration, severe side effects, patient non-adherence, and the emergence of drug resistance. These challenges highlight the urgent need for improved therapeutic approaches that can improve treatment efficacy while decreasing toxicity and duration. In recent years, nanotechnology has emerged as a promising solution to overcome the limitations of traditional therapies. Through the development of advanced nanocarrier systems such as lipid-based nanoparticles, polymeric nanoparticles, metallic nanoparticles, carbon-based nanomaterials, and dendrimers, researchers have achieved a great progress in improving drug solubility, stability, bioavailability, and targeted delivery to infected macrophages, the primary carrier of Mycobacterium tuberculosis. These nonsystems help in controlled and sustained drug release, reduce systemic exposure, and lower dosing frequency, as a result enhancing patient compliance and therapeutic success. Hence drug delivery, nanotechnology also offers opportunities for early diagnosis, vaccine development, and the creation of theragnostic platforms that combine therapeutic and diagnostic functions within a single system. However, despite these advancements, challenges related to large-scale manufacturing of dosses, biocompatibility, cost, and regulatory approval must be addressed before nanotechnology-based approaches can be fully implemented in clinical settings. Overall, nanotechnology represents a transformative approach in tuberculosis treatment, which offering the potential to shorten therapy duration, improve patient outcomes, and ultimately contribute to the long-term goal of global tuberculosis eradication through safer, smarter, and more efficient therapeutic strategies.

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