Review Article

Overview: The Challenges Involved with Tuberculosis (TB) Treatment Based on Nanotechnology and its Impact on Quality of Life

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ABSTRACT

A third of the world's population is thought to be latently infected with Mycobacterium tuberculosis and in danger of the disease reactivating, making TB a highly contagious chronic disease. TB poses a burden for public health because of its high incidence, morbidity, and death in recent decades, where the sanitary emergency has been since. The prevalence of tuberculosis in India is estimated to be 5.05 per 1,000 persons across all subtypes, with 2.27 per 1,000 cases being smear-positive and an annual average of 84 smear-positive cases per 100,000 people. By exploiting immune-mediated lung damage in individuals with active disease, Mycobacterium TB has developed an incredibly efficient aerosol transmission technique. The size of this reaction is reflected by the estimate that one-third of the world's population has developed one. An antigen-specific T-cell response in exposed contacts can be utilised to determine successful transmission. About one in ten individuals in this infected community get active tuberculosis (TB), often a few years after exposure, although continuing to have a lifetime risk of contracting the illness. To create new approaches and delivery systems for the diagnosis and treatment of diseases as well as to improve the qualities of already created systems, nanotechnology can comprehensively examine and utilise innovative elements and properties of materials. Interestingly, nanotechnology could improve and promote the use of innovative drug/antigen delivery systems by fusing and integrating the most recent knowledge of nanomaterials with the understanding of various biological processes. The alternative TB therapy, challenges, and quality of life are all covered in this review paper.

Keywords: Tuberculosis (TB, Etiology, Pathophysiology, Nanotechnology, Quality of life (QOL), Challenges.

INTRODUCTION

Mycobacterium tuberculosis (Mtb), a tiny aerobic acid-fast bacillus and non-motile intracellular pathogen, causes tuberculosis (TB), one of the deadly chronic infectious diseases. It ranks above HIV/AIDS as one of the top ten global causes of mortality and is the most common infectious agent-related cause of death (WHO, 2019). The disease can strike anybody, anywhere, but the majority of TB cases (approximately 90%) occur in adults, with a male-to-female ratio of 2:1 and case rates ranging from less than 50 to more than 5000 per million people per year at the national level. Infected persons spread the illness by coughing, sneezing, or spitting bacteria into the air. It primarily affects the lungs, causing pulmonary tuberculosis, but it can also damage other body organs, including the kidneys, central nervous system, circulatory system, lymphatic system, bones, and joints (extra-pulmonary TB) [1]. Robert Koch identified the aetiology of tuberculosis (TB), an infectious disease spread through the air by organisms from the Mycobacterium tuberculosis complex, in 1882 [2]. M. tuberculosis can spread illness throughout the body while being largely a lung pathogen. Additionally, Tuberculosis (TB) symptoms can range dynamically from asymptomatic infection to a fatal illness [3,4]. According to estimates, there were more tuberculosis (TB) cases in 2006 than in any previous year in recent memory, despite the World Health Organization's (WHO) and Stop TB partnership's ambitious goal of eradicating TB as a public health issue by 2050 [5,6]. Mycobacterium tuberculosis has developed an extremely effective method of aerosol transmission that takes advantage of immune-mediated lung damage in people with active disease. An antigen-specific T-cell response in exposed contacts can be used to determine successful transmission, and the magnitude of this response is indicated by the estimate that one-third of the world's population has developed one. Although they continue to have a lifetime risk of developing the disease, about one in ten people in this infected population get active tuberculosis (TB), usually within a few years after exposure. Immunosuppressive triggers, such as HIV infection, tumour necrosis factor (TNF) neutralization therapy for other diseases, and diabetes, considerably raise this risk, however, extended isoniazid preventive medication can reduce it [7]. In the first phase, scaling up and broadly implementing current TB control strategies along with ongoing socioeconomic development, particularly in the BRICS (Brazil, Russia, India, China, and South Africa) nations, as well as continuing the rollout of antiretroviral therapy (ART) in sub-Saharan Africa, could result in reductions in TB incidence of 10% yr^{-2}. However, it will need the development of novel technologies and procedures through research and innovation to reduce the global incidence to the levels already found in North America and some parts of Western Europe, which are anticipated to be in the elimination phase by 2035. A renewed focus on understanding and treating the significant reservoir of infected persons with latent infection will be crucial to future development. TB control

has traditionally placed a strong emphasis on the detection and management of active disease, which will continue to be important. Modelling implies that one of the most efficient methods to lower TB incidence would be to treat latent TB in large numbers [8,9]. The End TB Strategy will be put into practice starting in 2016 to end the global TB epidemic. The strategy, which was approved by the World Health Assembly in May 2014 and has goals connected to the recently adopted Sustainable Development Goals, provides nations with a roadmap for reducing the number of TB deaths by 90% by 2030 (relative to 2015 levels). Today's typical short-term treatment for tuberculosis lasts six months and includes the oral administration of many anti-TB medications, including rifampicin (RIF), isoniazid (INH), pyrazinamide (PYR), ethambutol (ETB), and streptomycin (STM). The term "first-line drugs" refers to these [10]. Therefore, as alveolar macrophages (AMs) are a biological repository for latent Mtb forms, the development of actively targeted nanomedicines to AMs remains of major importance for TB infections. In this situation, pulmonary drug administration is still clinically important to reduce systemic adverse effects and increase the absorption of anti-TB medications in the lungs [11].

Epidemiology

According to estimates, the prevalence of tuberculosis across all subtypes in India is 5.05 per 1,000, smear-positive cases are 2.27 per 1,000, and there are 84 smear-positive cases per 100,000 people on average per year [12]. The Indian government recently declared its intention to eradicate tuberculosis (TB) by 2025. For TB to be completely eradicated, there should only be <1 case per 10,000 people. The World Health Organization's (WHO) End TB Strategy, which the World Health Assembly adopted in 2014, seeks to put an end to the global TB epidemic by reducing TB fatalities by 95% and new cases by 90% between 2015 and 2035, as well as by making sure that no family has to bear unaffordable medical costs because of TB [13]. The WHO has set a goal of eradicating TB worldwide by 2035, and the Indian government has stated that it wants to do it by 2025.

It's a good idea, and the administration has shown good dedication. The incidence of TB has decreased from 289 lakh cases per year in 2000 to 217 lakh cases per year in 2015, and the mortality rate from TB has decreased from 56 lakh cases per year in 2000 to 36 lakh cases per year in 2015. India's national drop rate is trailing behind other countries, with the current global yearly decline rate of TB cases being 1.5% [13]. The overall number of deaths from tuberculosis fell by 15.4% in 2020 compared to 2019, and this decline was seen in 28 of the 36 states in India. Even though the overall death toll rose in 2021 in comparison to 2020, there were declines in 2021 in comparison to 2019. In India, there were 16.0% fewer TB deaths among people who were HIV positive. Tribal populations had a noticeable increase in TB mortality on a national level, while this wasn't true in all states [14].

Etiology

TB is brought on by M. tuberculosis. An alcohol and acid-fast bacillus, M. tuberculosis. It belongs to a collection of organisms known as the M. tuberculosis complex. Mycobacterium africanum, Mycobacterium bovis, and Mycobacterium microtia are additionally included in this category [15]. The majority of other mycobacterial species are categorized as non-tuberculous or atypical mycobacterial species. M. tuberculosis is an intracellular, catalase-negative, facultative, non-spore-forming, non-motile, obligate-aerobic bacteria. The organism had a very poor reaction to the Gram stain, making it neither gram-positive nor gram-negative. Occasionally, Gram stain can show weakly positive cells, a phenomenon known as "ghost cells". The organism differs from other bacteria in several ways, including the existence of various lipids in the cell wall, including Wax-D, cord factor, and mycolic acid. The following characteristics of M. tuberculosis infection are hypothesized to be influenced by the high fatty content of the cell wall. Antibiotic resistance to various drugs. Gramme stain and a few other stains are difficult to stain. Ability to endure harsh environments, such as extremely high or low oxygen levels, excessive acidity or alkalinity, or intracellular survival (inside the macrophage) [16]. Villemin's theory that tuberculosis can spread to animals has been proven numerous times, but it has also been resisted on what appear to be valid grounds, making it impossible to determine for sure until recently whether tuberculosis is an infectious disease or not. Since then, inoculation in the anterior chamber of the eye has been successful for Cohnheim and Salomonsen, and later Baumgarten, while inhalation has been successful for Tappeiner. These studies have unequivocally demonstrated that tuberculosis must be included among the infectious diseases that affect humans [17].

Pathophysiology

The Mycobacterium tuberculosis complex (MTBC) is the infectious agent that causes tuberculosis (TB). MTBC also includes closely related species including M. africanum, M. microti, and M. bovis in addition to M. tuberculosis. Due to the Mycobacterium genus' resistance to acid-alcohol decolourization, it is classified as an acid-fast bacillus (AFB) [18,19]. TB can be classified as pulmonary and extrapulmonary TB (EPTB) depending on the site of infection. M. tuberculosis inhaled in an aerosol causes the infection to start. The droplet nucleus is deposited into the bronchial tree during inhalation, where it attaches to bronchioles or alveoli. An innate immune reaction including inflammatory cells is the hallmark of the initial stage of tuberculosis infection. The antigen presentation in dendritic cells causes T cell activation and expansion into the lungs during the adaptive immune response, which is characterized by bacterial spread in lymph nodes. T, B, macrophage, and leucocyte infiltration results in the creation of granulomas that contain M. tuberculosis [20–22]. Alveolar macrophages primarily digest the bacteria that enter human lungs, however, some of the bacteria also proliferate inside the

macrophages and are subsequently expelled after the macrophages have died. The M. tuberculosis-carrying live macrophages can disseminate the bacterium through the lymphatic or circulation into the tissues and organs, causing EPTB. Meninges, kidneys, the spine, bones, and lymph nodes are among the 15–25% of EPTB sites that are affected. Neoplasia or inflammation frequently triggers EPTB's unusual clinical appearance [23]. When an infected person releases droplets into the air, TB transmission occurs. The primary signs and symptoms of TB in both adults and children include a chronic cough, a low-grade fever, tiredness, weight loss, and night sweats. The spread of TB is influenced by a variety of variables. First, the degree of infectiousness or disease severity is determined by chest radiography and sputum microscopy. The frequency and length of contact between a healthy person and an infected person also affect the likelihood of contracting TB. The longer and more frequent the contact, the greater the risk of contracting TB. The third factor is the exposure space, where transmission is encouraged in cramped, closed-off areas with poor ventilation. Fourth, the infectiousness of the bacterial strain; some M. tuberculosis strains are more contagious than others. For instance, the extrapulmonary strain is more infectious than the pulmonary strain because it may more efficiently destroy macrophages [24,25]. A positive AFB smear or positive radiographic findings are indicators of TB infection in a susceptible person. Hilar lymphadenopathy, lobar or segmental consolidation, pleural effusion, miliary lesions, atelectasis, infiltration calcification, and tuberculoma are some of the radiological findings that are suggestive. Due to their low sensitivity (20–80%) in identifying M. tuberculosis, conventional approaches for diagnosing TB provide significant diagnostic challenges [26–28].

Treatment for Tuberculosis (TB) With Nanotechnology

Generally speaking, nanotechnology can comprehensively examine and utilise innovative elements and qualities of materials to build new approaches and delivery systems for the detection and treatment of diseases as well as to improve the capabilities of systems that have already been created. Interestingly, nanotechnology could improve and promote the use of innovative drug/antigen delivery systems by fusing and integrating the most recent knowledge of nanomaterials with the understanding of various biological processes [29]. To tackle the global endemic of tuberculosis, numerous innovative colloidal drug delivery methods combining anti-tubercular medicines have been created recently. To ensure maximal patient compliance with medication, this method tries to target the medicine to specific areas in a regulated manner while reducing the dose and dosing frequency. The difficulties of treatment failure brought on by patient non-adherence to therapy are effectively addressed by these advances in innovative drug delivery methods [30].

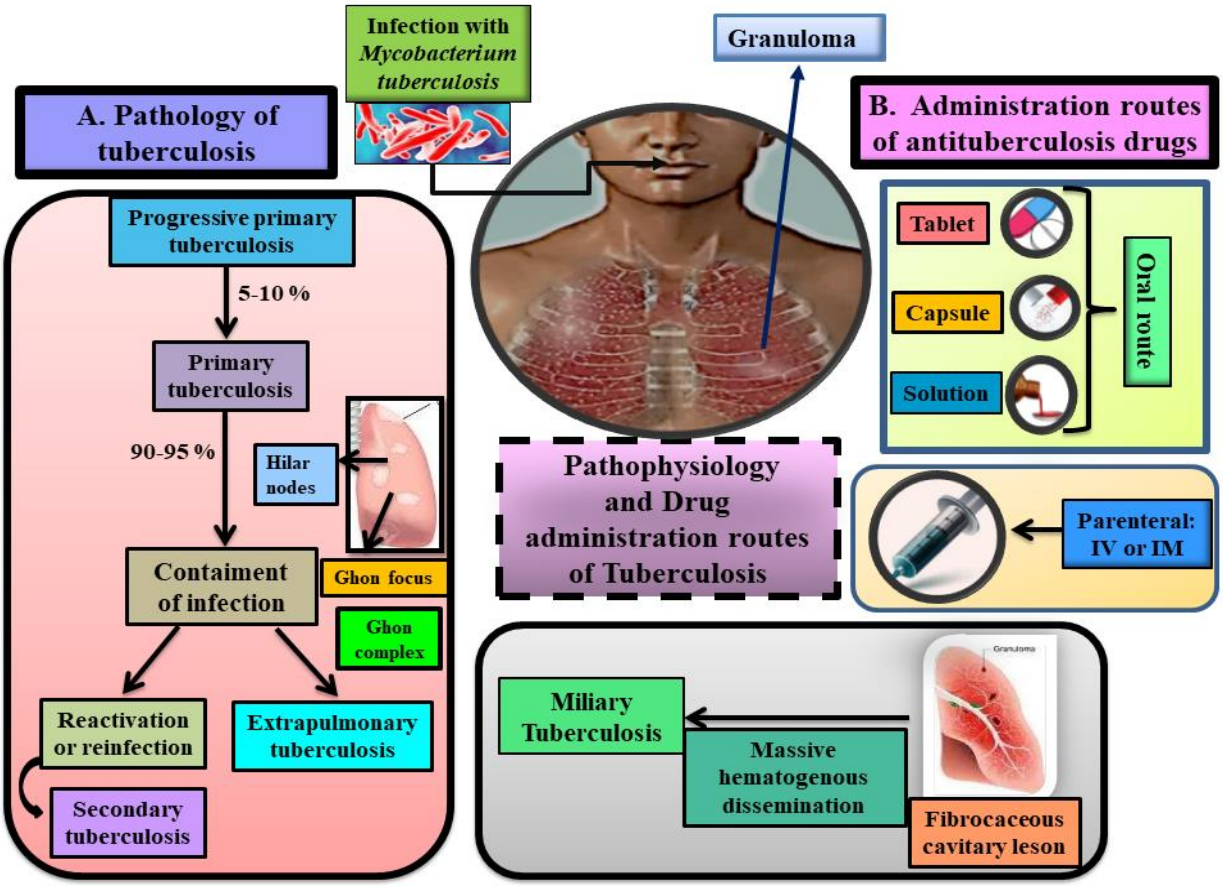

Figure 1: Human tuberculosis infection pathophysiology and anti-TB drug delivery methods[10].

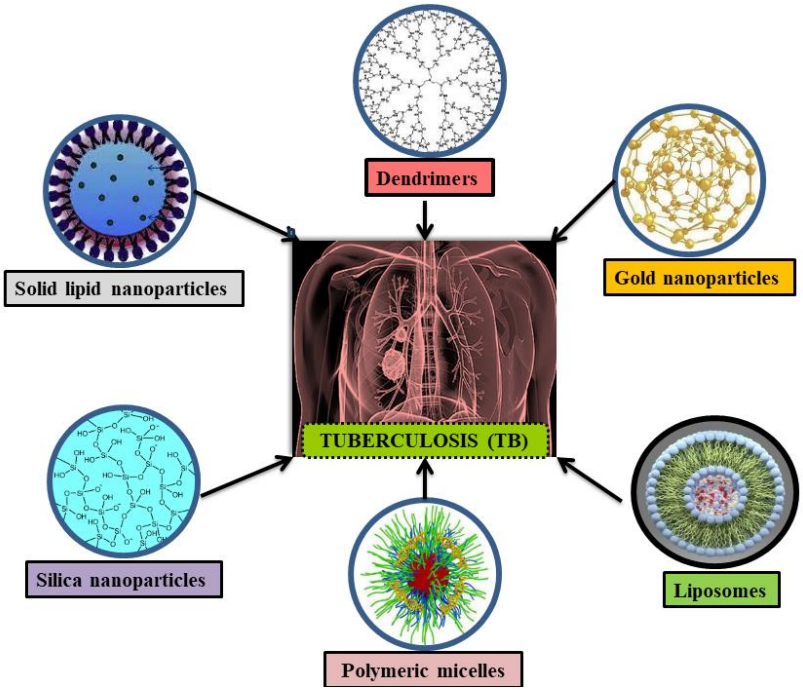

Figure 2: Anti-tuberculosis treatment options using nanocarrier systems[31].

- ***Solid lipid nanocarriers***

Colloidal lipid-based solid lipid nanoparticles (SLN) exist as solid particles at both body and ambient temperatures. An advantage of SLNs over liposomes is that they can be administered orally, which has potential uses in the delivery of medications that aren't easily soluble. Pharmaceutical companies argued that 40% of lipophilic medications have problems with solubility and formulation stability, making them less commercially viable [32]. Solid lipid nanoparticles are a promising method for delivering these medications due to their stability, simplicity in composition, and potential for mass production. These carrier systems also have the benefits of being biocompatible and biodegradable, having a tiny size that prolongs circulation time, not releasing medications in bursts, and being simple to adjust to formulation procedures. Inhalable SLNs that have been produced and tests for MTb. The sustained drug release lasts for 5 days in plasma and 7 days in other organs (liver, spleen, and lung). Only seven weekly dosages were necessary to completely eradicate the bacteria, compared to 46 treatments for traditional therapy. designed targeted SLNs for efficient rifabutin delivery to alveolar macrophages. Mannosylation of the SLNs, which have a preference for alveolar macrophages, was used for targeting [33,34].

- ***Dendrimers***

Due to their distinctive qualities, dendrimers have garnered a lot of attention in recent years. In the developing field of nanomedicine, dendrimers, a family of well-defined three-dimensional hyperbranched polymeric macromolecules, have played a significant role due to their high biocompatibility, superb structural homogeneity, multivalency, and adjustable surface functionality. Nevertheless, despite this significant benefit, it has numerous disadvantages that limit its usage in clinical settings, including quick clearance for systemic circulation, inadequate drug loading, and low targeting capacity [35]. To deliver rifampicin effectively, 4th generation poly(amidoamine) (G4-PAMAM) dendrimers were created. The complex was discovered to be substantially more stable in a neutral pH than in an acidic pH, where the complex dissolves and RIF escapes into the environment. Given that macrophages, where tubercle bacilli are found, have an acidic pH, this pH-dependent stimulus-response functions as a reliable switch for targeted medication release. Finally, they concluded that pH-dependent dendrimers would work well as RIF and derivative drug delivery vehicles [36].

- ***Gold nanoparticles***

Unaltered gold nanoparticles (AuNPs) and microfluidic paper-based analytical devices (PAD) are used in a colourimetric sensing technique to diagnose tuberculosis (TB). Unmodified single-stranded deoxyribonucleic acid (ssDNA) detection sequences were directly hybridized with extracted double-stranded DNA (dsDNA) from TB patients or healthy individuals without complex AuNP probe preparation processes after mixing with the AuNPs colloid and triggered with sodium chloride solution [37]. The Mycobacterium tuberculosis complex (MTBC) IS6110 dsDNA sequence was selected as the diagnostic target for identification. The detection ssDNA sequences were absorbed on the AuNP surfaces and prevented unmodified AuNPs from aggregating in the high salt solution when the target DNA sequences were missing. When the target DNA sequences were present, the detection ssDNA sequences hybridized with them, changing the colour of the unprotected AuNPs colloid from red to blue [38–40].

- ***Liposomes***

The vesicular system known as a liposome consists of aqueous compartments encased in lipid layers. These systems' superior biodegradability, biocompatibility, and ability to contain both hydrophilic and hydrophobic drug moiety are all due to their lipoidal structure. Macrophages, the primary host in tuberculosis, are a natural target for liposomes, and their surfaces can also be surface-decorated with different ligands to impart diverse capabilities such as stimulus responsiveness, targeting ligands, and diagnostic agents to target specific areas. It is possible to surface-modify liposomes with hydrophilic polymers, such as polyethene glycol, to prevent the reticuloendothelial system from recognizing them and lengthen the period that blood circulates. By functionalizing the surface of stealth liposomes with O-stearyl amylopectin (O-SAP), which improves the liposomes' affinity towards mouse lung tissue, lung-specific stealth liposomes were created [41–43]. created a unique PEGylated liposomal formulation to combine the main anti-tubercular medications with small interfering RNA (siRNA) to block transforming growth factor-β1. Compared to free medicine, this system proved successful in eradicating the sickness by focusing on the macrophage infection. guinea pigs were administered rifampicin, isoniazid, and pyrazinamide in capsule form, and researchers discovered that rifampicin and isoniazid remained in the blood for 24-48 hours but lasted for five days in macrophages after being inhaled [44,45].

- ***Polymeric micelles***

Amphiphilic copolymers self-assemble into polymeric micelles in an aqueous environment when the critical micelle concentration (CMC) is exceeded. Due to their high drug loading capacity, high drug loading capacity, low CMC, and ease of formulation, these drug carriers have received the greatest research attention. Micelles are formed out of a hydrophilic shell, which is often made of polyethene glycol (PEG), and a hydrophobic core, which is made of hydrophobic copolymers and is used to incorporate poorly water-soluble pharmaceuticals. Micelles are attractive options for the encapsulation and distribution of antitubercular medicines because of their distinct quality and structural characteristics [46]. Rifampicin was made into polymeric micelles by Moretton et al. to improve its stability and solubility in water. Rifampicin's oral bioavailability was increased when it was micellarly encapsulated as opposed to when it was free, in the presence of isoniazid [47].

- ***Silica nanoparticle***

Due to their huge surface area and pore volume, silica nanoparticles are desirable candidates for the administration of anti-tubercular medicines because they operate as a natural reservoir for high doses of these agents. Additionally, it has good chemical and mechanical stability, biocompatibility, and biodegradability [48]. The silica nanoparticles are frequently coated with hydrophilic polymers to create stealth nanoparticles, which prevent opsonization and uptake by the reticuloendothelial system (RES) and thereby lengthen blood circulation time. For the targeted delivery of rifampicin and isoniazid, functionalized mesoporous silica nanoparticles have been produced. To control the release of isoniazid at the acidic pH of infected macrophages, they created a dual drug release smart stimuli sensitive system coated with a poly-ethyleneimine to release rifampin. The uptake of these functionalized drug-loaded nanoparticles is increased, and the positive charge coating aids in the particles' escape from endosomes and entry into the cytoplasm, increasing the drug's effective concentration at the site of action for a longer period. They concluded that mesoporous silica nanoparticles can intelligently manage intracellular drug release with high drug loading capacity and can be surface-changed to impart unique capabilities as needed [49].

- ***Microparticles***

Patient noncompliance caused by repeated high doses of strong antibiotics, significant side effects, and prolonged therapy is the main issue with antitubercular medications. A promising solution to this issue is the use of microparticulate drug delivery systems, which produce gradual sustained drug release over a longer period. It offers many benefits, including preventing the medication from degrading, ease of administration by any route, acting as a drug depot for an extended period, and an affordable and simple manufacturing procedure for large-scale manufacture. microparticles made of chitosan that transport isoniazid to the lungs. The spray drying process was used to create the mucoadhesive chitosan nanoparticles, which ranged in particle size from 3.2 nm to 3.9 nm and had a drug entrapment effectiveness of greater than 89%. By adjusting the cross-linking of the chitosan polymer, the drug's prolonged release behaviour was managed. It was discovered that the microparticles boost the drug's targeting and efficacy while producing very little harm. To deliver different antitubercular medications to the intended place, low molecular weight chitosan microparticles function as a non-cytotoxic carrier [50–52].

- ***Nanosuspensions***

Nanosuspension is a colloidal dispersion of the drug moiety that is stabilized at high surfactant concentrations. The main goal of nanosuspension formulation is to improve the solubility and bioavailability of insoluble medications. Most novel chemical entities developed for medication development have been abandoned due to their major water solubility issue [53]. Inhalation therapy is the preferred method for treating pulmonary tuberculosis. With direct medication targeting the site of action, less systemic toxicity, and increased patient compliance with a high rate of cure, this is preferable to alternative routes of administration. Using nanosuspensions to administer antitubercular medication through inhalation, nebulization, or aerosolized devices is an alluring and promising method. a booster molecule and the major second-line medication Ethambutol were combined to create a nanosuspension for pulmonary delivery that significantly increased the treatment's effectiveness. Only after six doses, relative to

the animals without receiving treatment, was the lung bacterial load reduced by 3 log-in nanoparticulate suspensions of medication plus booster molecule. gives Ethambutol the potential of nanosuspension and the booster molecule to lessen its hazardous side effects [54].

- ***Nanoemulsion***

Due to the medications' poor oral bioavailability, conventional pharmacological therapy used to treat tuberculosis is not very effective. One of the most viable options for boosting the oral bioavailability of anti-TB medications and enhancing their therapeutic potency is nanoemulsion. The systemic circulation, which is the objective for reducing the burden of MTb, can be reached by the nanoemulsion loaded with anti-TB medications with ease. Additionally, the lipid structure of these systems makes it easier to focus the medications on the lymph nodes, which enhances the drug. Bioavailability and a decrease in the frequency of dose [55]. The potential of nanoemulsion in the treatment of tuberculosis will be investigated. Anti-tubercular medicine was created as a nanoemulsion, and it was discovered that all pharmaceuticals have enhanced bioavailability. Reddy et al. created a nanoemulsion of the antibiotic capreomycin in a different research to treat MTb. When compared to free medication, the formulation made with the emulsifier tocopheryl polyethene glycol succinate (TPGS) has much more activity against M-TB [56].

- ***Niosomes***

Niosomes are nanocarrier systems that mostly include cholesterol and non-ionic surfactants with or without phospholipids and have a liposome-like shape. The hydrophobic tails of the self-assembled niosomes create the bilayer facing each other, while the hydrophilic heads make up the vesicle's core and outside. This system demonstrated good biocompatibility, biodegradability, non-immunogenicity, low toxicity, and the ability to control the drug release over an extended length of time. It is also thermodynamically stable. Niosomes are also simple to prepare, have low production costs, are simple to handle, and don't need any special storage conditions. Levofloxacin will be delivered to the lungs using prepared extended-release niosomes with the use of a surfactant (Span 60) and cholesterol in various ratios, Niosomes were created using the thin film hydration and sonication process. A 98% drug entrapment efficiency in niosomes was discovered. While it utilised non-fiction diffusion and zero-order drug release kinetics [57–59]. To treat drug-resistant tuberculosis, rifampicin and ofloxacin were synthesized in a niosomal formulation. Utilising a nonfickian diffusion mechanism, the controlled release niosomes were able to delay the drug's release for up to 15 days. The niosomes' size was determined to be in the range between 100 and 300 nm, with an excellent entrapment effectiveness of 81.76%. Finally, scientists concluded that the most promising method for treating tuberculosis is controlled release niosomes containing anti-tubercular medicines. increases the safety and effectiveness of ethambutol for the treatment of tuberculosis by niosomal formulation. It was discovered that niosomes target the tuberculosis-infected lungs and release ethambutol in a regulated manner for a long period, with less non-specific toxicity and better treatment effectiveness compared to the free drug [60,61].

- ***Liquid crystals***

Loosely oriented liquids are known as liquid crystals (LC). As a transitional condition between the liquid and solid phases, it is also referred to as a mesomorphic phase. Due to their distinctive structure, LCs maintain the fluidity and crystallinity of both the solid and liquid phases. The unique physiochemical properties of LCs, a new drug delivery system, have drawn researchers' attention because they significantly increase solubility and bioavailability compared to other drug delivery systems, have a high drug loading capacity, and successfully protect and stabilize drugs from the harsh environment of the body [62–64]. Rifampicin liquid crystals for inhalation systems made from cholesterol. In different carrier systems, including cholesterol, cholesteryl cetyl carbonate (CCC), cholesteryl carbonate (DCC), sodium cholesteryl carbonate (SCC), and PEG 4000, the solubilization of rifampicin was assessed. They discovered that the cholesteryl cetyl carbonate (CCC) and PEG 4000 system, when combined in a 1:1 mol ratio, produced a homogenous mixture with a comparatively high rifampicin content. For the effective distribution of pyrazinamide and metronidazole, a smart stimuli-sensitive liquid crystal device is used. Thermal fluctuations control the drug's release through the system. Two low molecular weight liquid crystals, n-pentyl-cyanobiphenyl and n-heptyl-cyanobiphenyl, were combined for these thermoresponsive systems using the vacuum filtration process. Reversible and using zero-order kinetics, the temperature-responsive drug release [65,66].

Different Approaches to Treating Tuberculosis (TB)

- ***Important medication in the treatment of tuberculosis***

- The prodrug protomanid needs to be activated intracellularly through a glucose-6-phosphate-dehydrogenase pathway that is dependent on F420. Reactive nitrogen species are created by the activation of des-nitro metabolite, which lowers intracellular ATP and causes anaerobic death [67,68].
- The diarylquinoline bedaquiline reduces intracellular ATP by inhibiting mycobacterial adenosine triphosphate (ATP) synthesis. It functions on mycobacteria that are actively reproducing as well as those that are dormant and keeps the ATP synthase active [69,70].
- Sutezolid, a linezolid analogue, exhibits less toxicity and better in vivo action than linezolid [71].
- The drug demand is a derivative of the antibiotic metronidazole and the compound nitroimidazopyran, also known as 6-nitro-2,3-dihydroimidazo(2,1-b) oxazole. It works by blocking the manufacture of mycolic acid, is a pro-drug, and needs activation [72,73].

- The oxazolidinone AZD5847 has more in vitro bactericidal action than linezolid because it inhibits mycobacterial protein production by attaching to the 50S ribosomal subunit [74].
- As prospective TB medications, the nitroimidazoles OPC-67683 (Delamanid) and PA-824 are currently being developed [75].
- SQ109 is a 1,2-ethylenediamine that shares structural similarities with ethambutol but has a different mode of action. SQ109 prevents the formation of the cell wall by focusing on the transmembrane transporter that the mmpL3 gene encodes [76].
- Moxifloxacin and gatifloxacin, two fluoroquinolones, are being created to treat drug-sensitive TB [77].
- Combinations of anti-TB medications: The most effective early bactericidal action was seen with the use of moxifloxacin and pyrazinamide. This medication combination has the benefit of not including either rifampicin or isoniazid. As a result, it is appropriate for use with patients who have developed medication resistance. A regimen without rifampicin would make administering TB treatment alongside HIV antiretroviral therapy significantly simpler [78].

- ***A combined treatment for tuberculosis***

- The main factor causing the emergence of microorganisms with medication resistance is the prolonged length of TB treatment. As a result, an experiment is being conducted to provide shorter, more cost-effective oral dosages of the medication that do not require it in injectable form. It contains pretomanid, bedaquiline, and linezolid in combination[80,81].
- Isoniazid- and rifampicin-resistant M. tuberculosis strains can be treated with Cornerstone drugs for multidrug-resistant TB [82].
- XDR-TB (extensively drug-resistant TB): resistance to fluoroquinolones, capreomycin, kanamycin, and amikacin Multidrug resistance therapy combined with XDR-TB can be used to treat M. tuberculosis [83].

- **Ayurvedic medications used in TB**

The Ayurvedic names for TB are Rajyakshma or Kshayaroga. Snehana, which is Ayurveda's word for "oleation," is one of the prescribed TB therapy methods [84]. To treat irritated doshas and assist in liquefying and expelling toxins from the body's smallest channels, it mostly entails massaging the affected areas with heated medicinal oils infused with the characteristics of herbs. Swedana, also known as sweat therapy (there are three forms), To warm the body, tapa, or fomentation, uses a metal item, a heated cloth, or warm hands. Ushma refers to the use of warm steam created by boiling the appropriate herbs depending on the dosha that needs to be balanced, and Dhara involves pouring warm medicated liquid over the body. Other traditional treatments include Vamana, which means medical emesis, and Virechana [85]. However, only those with severe doshas and those who are strong enough to tolerate these therapies can benefit from these operations. Purification therapies, also known as shodhana karma, should not be administered to those who are already weak, and they should be used sparingly even on healthy individuals who have TB. This is because TB has kshaya, which is the depletion of all seven dhatus. To strengthen the body, the treatment should be nourishing. Care should be taken to ensure that dhatu agni is unaffected, though [86–88].

Challenges in the treatment of TB

The development of anti-TB medications, which were mostly discovered in the 1950s to 1970s, involved several clinical trials that continued until the 1980s. The succeeding 30 years, up until around 2000, were a fallow time for TB drug research and development. This gap considerably contributed to the significant difficulties currently encountered by the community of drug developers working to improve active MDR-TB and XDR-TB treatments. Currently, only four of these medications were created specifically for the treatment of TB, and MDR-TB is treated with a mixture of several drugs throughout 18 to 24 months [89,90]. Nearly 30% of MDR-TB patients who get subpar therapy experience treatment failure. Due to the XDR-TB bacilli's resistance to fluoroquinolones, including injectable medications like aminoglycosides, in addition to INH and RIF, there are very few therapeutic alternatives available. Additionally, there are significant adverse effects associated with the majority of MDR-TB and XDR-TB medications, such as nephrotoxicity and ototoxicity when aminoglycosides are used, hepatotoxicity when ethionamide is used, and dysglycemia when gatifloxacin is used [91,92]. The great majority of TB cases and fatalities take place in developing nations, and around one in four of the deaths include HIV-positive individuals. According to reports, 11-2 percent of the 9,4 million people diagnosed with TB in 2009 also tested positive for HIV, with 80% of these morbidities occurring only in Africa. Due to a lack of access to healthcare and decreased compliance with therapeutic regimens brought on by an increase in pill burden, drug-drug interactions, and overlapping severe side effects, this is the case. RIF-induced upregulation of the hepatic cytochrome (CYP P450) oxidase system is the main way that HIV and anti-TB medications interact with one another. According to studies, CYP accelerated the pharmacokinetic rate and reduced the effectiveness of several co-administered drugs, including HIV protease inhibitors. It is highlighted that typical trench levels of several kinds of protease inhibitors cannot be attained when CYP450 inhibitors, such as ritonavir, are used. They have thus been demonstrated to engage in intracellular phosphorylation competition with rifampicin. As a result, these medications shouldn't be taken together. However, the inclusion of ritonavir in a protease cocktail raises the serum levels of rifabutin, raising the toxicity that goes along with it [93–96]. Studies conducted in 2000 found that diabetes was present in about 20% of smear-positive TB cases in India. In the interim, 42% of smear-positive TB cases in

India by 2030 will be attributed to diabetes if the expected increase from 25 million diabetes patients in 2000 to 80 million in 2030 materialises and the risk ratio stays the same. Each diabetes-related TB case could also result in the infection of more people, increasing the overall TB burden in the neighborhood. It is unclear what biological factors contribute to diabetics' poor anti-TB drug response and higher risk of MDR-TB development. However, it is thought that diabetes suppresses cell-mediated immunity, which leads to greater rates of tuberculosis infection [97,98].

Quality of Life (QoL) with Tuberculosis

The concept of quality of life (QOL) is vast and multifaceted, encompassing the physical, social, psychological, economic, and other realms. Consequently, it is challenging to define and quantify but may be essentially characterized as people's beliefs of their place in life about the culture and value systems they live in as well as their objectives, expectations, standards, and concerns [99]. Evaluation of a patient's quality of life (QOL) aims to measure the functional impact of a disease and the treatment that follows on a patient, as experienced by that patient. Self-rated QOL in patients with active TB has been assessed using a wide range of questionnaires and measures. While some of these assess QOL holistically, others concentrate on certain areas, such as physical health or psychological morbidity. The most straightforward method of measuring quality of life is to use one single summary item as a broad measure of QOL. A single question, a visual analogue scale (VAS), or a conventional gambling approach can be used to measure this [100]. This is likely to overlook crucial data on several QOL aspects that may be significant to TB patients. To get a more complete picture of the pertinent features and domains, investigators increasingly rely on standardized multidimensional measures. As a result of the fact that many of these instruments are generic, they can be utilised with a variety of illnesses (and even healthy people). Short Form 36 (SF-36) is a regularly used scale in TB research [101]. Scaled scores for each of the eight domains—Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional, and Mental Health—as well as two summary scores—Physical Component Score and Mental Component Score—are presented. The European QOL Group created the EQ-5D, which is another instrument that is frequently utilised[102–107]. It consists of 76 items, the results of which can be combined to get an overall score, as well as three domain scores for Symptoms, Activity, and Impact. Using tools designed for a particular ailment is another strategy. Unfortunately, there hasn't been much use of TB-specific QOL tools. A disease-specific QOL instrument (DR-12) was proposed by Dhingra and Rajpal based on information on TB patients in India receiving programmatic care. Twelve items make up this measure, which comprises two domains: symptoms and sociopsychological/exercise adaptation. The scale's creation, however, lacked scientific rigour, and the way the items are worded makes it seem more like a measure of health status than of quality of life. It hasn't been used very much [108–110].

Table 1: Current status of clinical trials on Tuberculosis diseases (TB).

Drug	Mode of administration	Enrollment	Allocation/ Intervention model/ Masking	Official Title of the study	Status	Clinical trial	Year
NA	Observational	205	NA	Interferon Gamma Release Assays Versus Tuberculin Skin Testing for the Detection of Latent Tuberculosis Infection in Renal Transplant Recipients	NA	NCT01608685	2012
CTBdatabase	Observational	4600	NA	Prospective Database of All Patients With Microbiologically Proven Mycobacteria Tuberculosis Infection Treated at Singapore General Hospital	NA	NCT01601275	2019
Radiological assessment	Observational	55	NA	Conception and Validation of a Clinico-radiological Classification of Peritoneal Tuberculosis	NA	NCT03927664	2020
Enhanced TB IC Package	Observational	22	NA	Evaluation of an Enhanced Tuberculosis Infection Control Intervention in Healthcare Facilities in Vietnam and Thailand	NA	NCT02073240	2021
Latent Tuberculosis Infection program evaluation & diagnosis	Interventional	24	Randomized/Parallel Assignment/ None (Open Label)	Enhancing the Public Health Impact of Latent Tuberculosis (TB) Infection Diagnosis and Treatment: A Pragmatic Cluster Randomized Trial	NA	NCT02810678	2020
NA	Observational	409	NA	A Prospective Observational Study of Usefulness of a T Cell-based Assay for Latent Tuberculosis Infection in Hematopoietic Stem Cell Transplant Recipients	NA	NCT01021124	2013
Nyaditum resae 10e5 of heat-killed Mycobacterium manresensis/ Placebo	Interventional	24	Randomized/ Parallel Assignment/ Triple (Participant	Pilot Phase I Clinical Trial, Double-blind, Randomized, Placebo-Controlled and Masked to Evaluate the Tolerability and Immunogenicity of Nyaditum Resae® Probiotic Administered to	NA	NCT02581579	2019

			Care Provider Investigator)	Pediatric Population in Contact with Tuberculosis With or Without Latent Tuberculosis Infection			
RUTI/ RUTI/ RUTI/ RU TI Matching Placebo	Interventional	95	Randomized/ Parallel Assignment/ Quadruple (Participan t Care Provider Investigator Outcomes Assessor)	Double-Blind, Randomized, Placebo-Controlled Phase II Clinical Trial to Investigate the Safety, Tolerability, and Immunogenicity of the Novel Antituberculous Vaccine RUTI® Following One Month of Isoniazid Treatment in Subjects With Latent Tuberculosis Infection	Phase-2	NCT01136161	2013
Isoniazid/ isoniazid	Interventional	200	Randomized/ Parallel Assignment/ None (Open Label)	Drugs for Treatment of Latent Tuberculosis Infection Objective 4: Identify Biomarkers for Clinical Trials of Drugs Active Against Latent TB	Phase-4	NCT00293228	2010
MTBVAC/ BCG	Interventional	144	Randomized/ Parallel Assignment/ Quadruple (Participan t Care Provider Investigator Outcomes Assessor)	MTBVAC Phase 1b/2a Randomized, Double-blind, Active-controlled, Safety, Immunogenicity, and Dose-escalation Study in Adults With and Without Latent Tuberculosis Infection in South Africa	Phase-1 & 2	NCT02933281	2023
NA	Observational	201	Cohort	Assessing the Ability of the T-SPOT®.TB Test to Identify Those at Risk of Active Mycobacterium Tuberculosis Infection Us ing the Normalized Tuberculosis (TB) Specific Lymphocyte Response.	NA	NCT03973970	2021
Isoniazid/ Rifampin	Interventional	6031	Randomized/ Parallel Assignment/ None (Open Label)	A Randomized Clinical Trial of 4 Months of Rifampin vs. 9 Months of Isoniazid for Latent Tuberculosis Infection. Part 3 - Effectiveness	Phase-3	NCT00931736	2017
NA	Observational	200	NA	The Clinical Utility of Quanti FERON in the Diagnosis of Active Tuberculosis Among Young Adults	NA	NCT00982969	2010
CST001	Observational	66	NA	Evaluation of the 4th Generation QuantiFERON-TB Test (QFT-Plus) for the Detection of Tuberculosis Infection	NA	NCT02687529	2019
blood test, not yet marketed, no trade name	Interventional	675	N/A/ Single Group Assignment/ None (Open Label)	Predictive Values of Next-Generation Interferon Gamma Release Assays for Latent Tuberculosis Infection	NA	NCT02512939	2023
Isoniazid	Interventional	300	Randomized/ Parallel Assignment/ None (Open Label)	Preventing Mycobacterium Tuberculosis Infectio n in HIV-Exposed Infants	Phase-2	NCT02613169	2023
Immunohistochemical staining	Observational [Patien t Registry]	45	NA	Immunology Dysregulation in Lymphadenitis Tuberculosis: An Observational Study Using Patient' Block Paraffins 2019 Until 2021	NA	NCT05202548	2022
Preventive treatment with Isoniazid./ Preventive treatment with Isoniazid	Interventional	871	Randomized/ Parallel Assignment/ None (Open Label)	Comparison of Two Strategies for Therapeutic Decision-making in Tuberculosis Contact Tracing: a Standard Strategy Based on Tuberculin Skin Test (TST) Alone vs TST Combined With QuantiFERON®-TB Gold In-Tube (QFT-IT)	Phase-4	NCT01223534	2016
Self-administered therapy (SAT)/ SMS reminders/ isoniazid and rifapentine	Interventional	1002	Randomized/ Parallel Assignment/ None (Open Label)	TBTC Study 33. An Evaluation of Adherence to Latent Tuberculosis Infection (LTBI) Treatment With 12 Doses of Once Weekly Rifapentine (RPT) and Isoniazid (INH) Given as Self-administered (SAT) Versus Directly-observed Therapy (DOT): there.	Phase-3	NCT01582711	2015
1-step tuberculin skin test (TST) and blood sampling	Interventional	322	N/A/ Single Group Assignment/ None (Open Label)	Diagnosis of Tuberculosis Infection in Health Care Workers Using Ex-vivo Interferon-gamma Assay	NA	NCT01007396	2012
Nanodisk-MS assay	Observational	100	NA	Detection of Circulating Mycobacterium Tuberculosis Antigen Peptides for the Diagnosis of Active Pulmonary and Extrapulmonary Tuberculosis in Hospitalized Patients	NA	NCT03271567	2020
BST/ TST/ FT/ T-spot	Interventional	2017	N/A/ Single Group Assignment/ Double (Participant Outcomes Assessor)	Screening for Latent Tuberculosis Infection (LTBI) in US Army Recruits	NA	NCT00804713	2023
Prednisolone	Interventional	1500	Randomized/ Parallel Assignment/ Double	A Multicentre, Placebo-Controlled, Double-Blind, Randomized Clinical Trial to Evaluate the Efficacy	NA	NCT00338793	2008

				and Safety of Corticosteroids for Treatment of Patients With Tuberculous Pleurisy			
NA	Observational	10000	NA	Prognostic Value of Interferon Gamma Release Assays in Predicting Active Tuberculosis Among Individuals With, or at Risk of, Latent Tuberculosis Infection	NA	NCT01162265	2020
Pigtail drainage	Interventional	64	Randomized/ Parallel Assignment/ Triple (Participant Investigator Outcomes Assessor)	Drainage of Tuberculous Pleural Effusions	NA	NCT00524147	2010
81mg aspirin/ 1000mg aspirin/ Placebo	Interventional	120	Randomized/ Parallel Assignment/ Quadruple (Participant Care Provider Investigator Outcomes Assessor)	A Pilot Phase II Randomized Controlled Double Blind Trial of 81mg Aspirin Daily vs. 1000 mg Aspirin Daily vs. Placebo as Adjunctive Therapy in HIV Negative Adults With Tuberculous Meningitis	Phase-2	NCT02237365	2017
NA	Observational	596	NA	Contact Tracing by Social Network Analysis to Enhance Multi-Drug Resistant Tuberculosis Case Finding in Hanoi, Vietnam	NA	NCT02175849	2016
Rifampicin intravenous/ Oral rifampicin	Interventional	30	Randomized/ Parallel Assignment/ None (Open Label)	Explorative PK Study Comparing 600 mg Rifampicin i.v. With 750 mg and 900 mg Rifampicin Oral in Tuberculous Meningitis Patients	Phase-2	NCT01802502	2014
NA	Observational	560	NA	Evaluating Diagnostics for Paediatric Tuberculosis by Blood Culture	NA	NCT01434758	2016
NA	Observational	316	NA	Diagnosis of Tuberculous Meningitis by a Secretory Antigenic Target 6 (ESAT-6) in CSF	NA	NCT01371916	2014
Prednisolone/ Mycobacterium w immunotherapy	Interventional	1400	Randomized/ Factorial Assignment/ Quadruple (Participant Care Provider Investigator Outcomes Assessor)	A Trial of Adjunctive Prednisolone and Mycobacterium w Immunotherapy in Tuberculous Pericarditis	Phase-3	NCT00810849	2014
Xpert MTB/RIF	Interventional	62	N/A/ Single Group Assignment/ None (Open Label)	Xpert MTB/RIF Assay for Diagnosis of Tuberculous Meningitis (TBM) in Maharaj Nakorn Chiang Mai Hospital	NA	NCT05781646	2023
NA	Observational	200	NA	Osteoarticular Infections on Material in Children Under 16 Years Old at the CHU of Montpellier From 2014 to 2021	NA	NCT04887740	2021
Gene Xpert chest X-ray and MSCT chest	Observational [Patient Registry]	50	NA	Prevalence and Burden of Bronchiectasis in Tuberculous Patients	NA	NCT04085133	2023
No intervention	Observational	705	NA	Time-to-Detection in Culture of Mycobacterium Tuberculosis: Performance for Assessing Index Cases Infectivity	NA	NCT05568368	2022
NA	Observational	270	NA	Characterization and Evaluation of Diagnostic Biomarkers for Tuberculosis	NA	NCT01269268	2019
NA	Observational [Patient Registry]	38	NA	The Role of Therapeutic Drug Monitoring in Tuberculosis - a Pilot Study	NA	NCT02042261	2016

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CONCLUSION AND FUTURE DIRECTION

Introductions on epidemiology, aetiology, pathophysiology, advanced nanotechnology, alternative treatments, difficulties, and quality of life (QoL) are included in the opening sections of our review articles. Our investigation shows that while non-pharmacological and natural supplements offer a respectable outcome but take some time to work and have no unfavourable side effects, medicine does treat but not completely. More randomized controlled studies are required to better understand how to treat TB. We plan to carry out preliminary research on tuberculosis in the future. Future counseling-based research will be conducted in our nation or state with the assistance of our colleagues to evaluate patients' physical and mental health and provide more precise data on tuberculosis and its treatment.

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