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Advancements in Tuberculosis Treatment: From Epidemiology to Innovative Therapies

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Abstract: ***This review provides a comprehensive overview of current advancements in the treatment of tuberculosis (TB), covering various aspects from epidemiology to novel therapeutic approaches beginning after a brief overview of TB including a global impact and historical context, the review explores the epidemiology of anti-TB medications and the emergence of antibiotic resistance mechanisms in Mycobacterium tuberculosis. It discusses ongoing clinical trials for anti-TB drugs and emphasises the critical need for innovative therapeutic approaches to stop the spread of drug-resistant tuberculosis strains. The review examines recent developments in overcoming M. tuberculosis antibiotic resistance, focusing on innovative treatments designed to circumvent resistance mechanisms. It explores the potential of nano delivery systems for enhancing TB treatment efficacy, discussing the promises and challenges associated with these novel approaches. The review delves into the various approaches and challenges in treating M. tuberculosis, shedding light on the complexities of TB therapy and the importance of multidisciplinary strategies. It specifically investigates dendrimer-based formulations in drug delivery, with a focus on Poly (amidoamine) (PAMAM) dendrimers as potential agents for treating M. tuberculosis. Finally, it explores the antibacterial properties of dendrimers and their potential application in combating TB infections. Given the circumstances, this article offers a thorough summary of the state of TB treatment today, highlighting the need for innovative approaches to address the challenges posed by drug resistance and the complex nature of TB therapy.***

Keywords: *Mycobacterium Tuberculosis*, Novel Treatment, Dendrimer-Based Formulations, Anti -Tb Drug under trials

1. Introduction

Tuberculosis (TB) is a preventable and typically treatable illness. However, despite its potential for cure, in 2022, TB ranked as the second most common cause of death globally due to a single infectious agent, following closely behind coronavirus disease (COVID-19), and caused twice as many deaths as HIV/AIDS. Each year, over ten million individuals remain susceptible to contracting TB. Immediate and concerted measures are imperative to terminate the worldwide TB epidemic by 2030. (1) The World Health Organization classified human tuberculosis (TB), a devastating illness triggered by the gram-positive, acid-fast bacterium *Mycobacterium tuberculosis*, as a worldwide health crisis in 1993. (2) After being infected, the chances of developing TB disease are at their peak during the first two years, at 5%, and then significantly decrease thereafter. (3). Global advancement has deviated from the intended path, and due to challenges faced during the COVID-19 epidemic, a subsequent UN high-level assembly on TB occurred on 22 September 2023. The resultant political statement reiterates prior pledges and objectives while integrating new ones for the duration of 2023 to 2027. (4). In 2022, there were 7.5 million newly diagnosed cases of tuberculosis worldwide. The overall decline in global TB-related fatalities from 2015 to 2022 amounted to 19%, significantly below the WHO's End TB Strategy target of a 75% reduction by 2025. In the year 2022, more than half (55%) of the individuals who contracted TB were males, while approximately one-third (33%) were females, and the remaining 12% comprised children aged between 0 to 14 years. Antimicrobial resistance, a naturally occurring phenomenon prevalent worldwide, stands as one of the foremost global health obstacles of our era, emphasizing the pressing need for the development of advanced therapeutic approaches, The rise in resistance levels contributes to elevated illness and death rates from infectious diseases globally, underscoring the necessity for collaborative initiatives among various research domains to counter this trend. (Figure 1). (5).

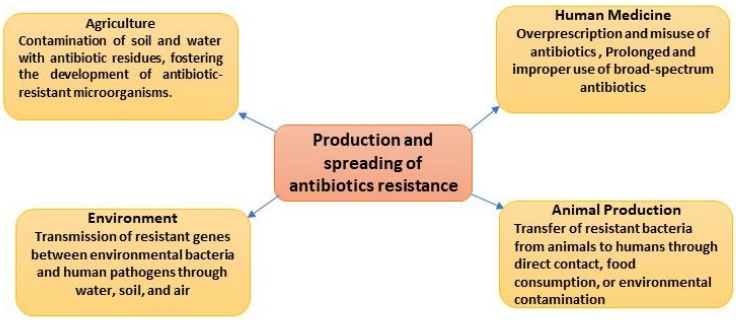

Figure 1: Factors involved in the diffusion of antibiotic resistance: human medicine in the community and in the hospital, animal production, and agriculture and environment.

The global battle against antimicrobial resistance has sparked a growing fascination with peptide-based methodologies. Peptides, known for their multifunctional and modular nature, exhibit a plethora of significant biological functions, thus presenting an opportunity for their utilization in the development of innovative nanotechnologies. (6) Treating active TB disease typically involves the administration of several drugs over a period of 6 to 9 months. The U.S. Food and Drug Administration (FDA) has sanctioned ten drugs for this purpose. The primary medications recommended for initial treatment regimens include isoniazid, rifampicin, ethambutol, and pyrazinamide. (7), As per the findings of the Global Tuberculosis Report 2022, it was observed that globally, in 2021, 7.3% of individuals afflicted with rifampicin-resistant TB (RR-TB) had contracted extensively drug-resistant tuberculosis (XDR-TB). XDR-TB is defined by resistance to at least one of three injectable second-line medications, rifampicin, isoniazid, and any fluoroquinolone. (amikacin, capreomycin, or kanamycin), was detected in this percentage of cases. The report estimated a total of 465,000 instances of rifampicin-resistant TB (RR-TB) in 2021, of which 39% were purported to have undergone testing for XDR-TB (8) Dendrimers are precisely structured synthetic polymers composed of a central core molecule that serves as the base, generating numerous symmetrically arranged, tree-like branches. (9) The antibacterial effectiveness of dendrimers is further improved when they are combined with small molecule inhibitors. The cytotoxicity and biological impacts of a set of poly (ether imine) (PETIM) dendrimers were previously examined in mammalian cell cultures. Those dendrimers that had hydroxyl functionalities at their peripheries demonstrated non-toxic profiles.

2. Epidemiology of Anti-tuberculosis

Approximately two billion individuals globally are currently affected by *Mycobacterium tuberculosis*, constituting roughly 30% of the global population. In 2012, TB afflicted 8.6 million people and claimed the lives of 1.3 million. This disease is particularly widespread in developing nations, where high mortality rates have been documented. (10) Despite governments worldwide allocating billions of dollars annually and demonstrating a steadfast commitment to eliminating TB, the disease persists, continuing to infect millions and claiming the lives of thousands in affected populations.

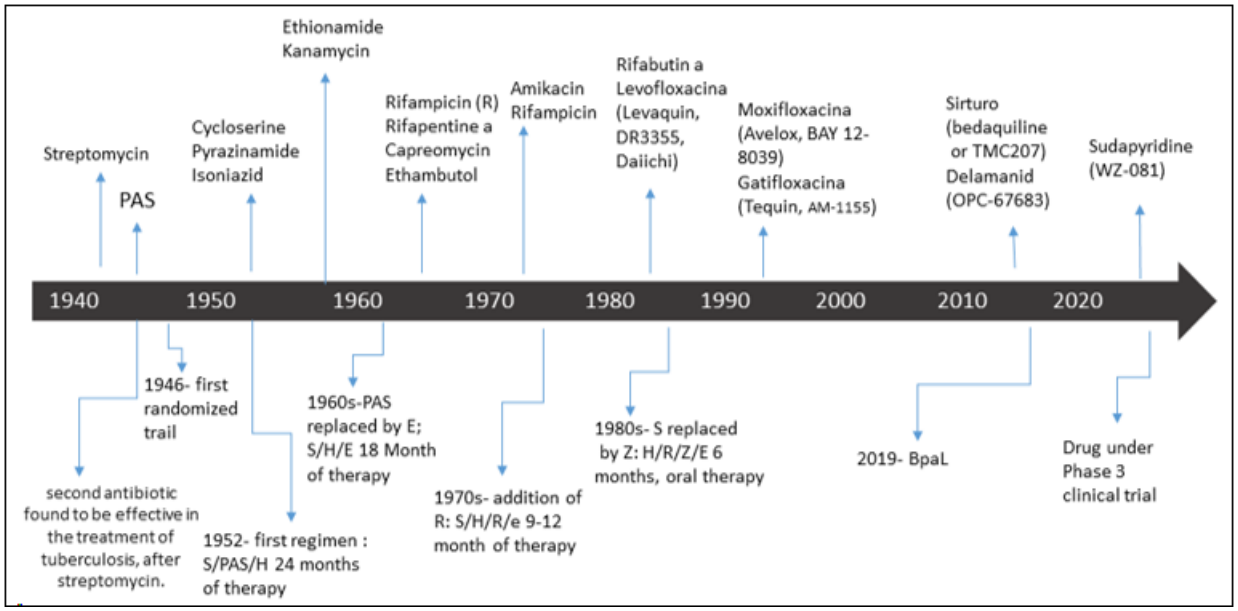

Figure 2: Timeline of Anti-Tb Drug

3. Antibacterial Resistance Mechanisms in *Mycobacterium Tuberculosis*

The identification of *Mycobacterium tuberculosis* as the responsible pathogen, initially determined by Dr. Rober Koch in 1882, marked the beginning of advancements in tuberculosis (TB) treatments. Subsequently, the sanatorium movement gained momentum in Europe and the USA. However, it was only through the later breakthrough in antibiotics that TB became truly treatable in a significant revolution in TB chemotherapy. *Mycobacterium tuberculosis* is currently recognized as one of the most formidable pathogens responsible for infectious diseases, a status it held in the past as well. Presently, this bacillus affects over two billion people worldwide, accounting for about one-third of the total population. (11)

Table 1: Gives an overview of the first- and second-line anti-tuberculosis drugs currently in use and target of action

Sr. no	Drug	Mechanism of action	Bacterial target/pathway	Reference
1.	Streptomycin	Inhibits protein synthesis	Ribosomal subunit 30S	12
2.	Isoniazid (INH)	Inhibits mycolic acid synthesis	Mycobacterial cell wall	13
3.	Ethambutol	Inhibits arabinosyl transferase	Arabinogalactan synthesis	14
4.	Rifampin (RIF)	Inhibits bacterial RNA synthesis	RNA polymerase subunit beta-	15
5.	Pyrazinamide	Mechanism not fully understood	May disrupt membrane cell potential	

				16
6.	Levofloxacin	Inhibits DNA gyrase and topoisomerase IV	DNA replication	
7.	Amikacin/Kanamycin	Inhibits protein synthesis	Bacterial ribosomal subunits (similar to streptomycin)	17
8.	Bedaquiline	Inhibits mycobacterial ATP synthase	ATP synthesis in mycobacteria	
9.	Delamanid	Inhibits the production of mycolic acid	Mycolic acid synthesis	
10.	Para-amino salicylic acid	Inhibition of folic acid synthesis by targeting dihydrofolate reductase	Thymidylate synthase A	18

Table 2: Anti tuberculosis drug under clinical trial

Compound	Chemical class	Mode of action	Progress	Reference
TBAJ-587	Diarylquinoline	Inhibits mycobacterial ATP synthase and hERG potassium channel	Phase 1	19
TBAJ-876	Diarylquinoline	Inhibits mycobacterial ATP synthase	Phase 2	20
Sanfetrinem (beta-lactam)	Other classes	Inhibits peptidoglycan synthesis	Phase 2	21
Spectinamide-1810 (spectinamide)	Other classes	Selective ribosomal inhibition	Preclinical trial	22
TBI-223	Oxazolidinone	Inhibits the binding of N-formyl methionyl tRNA to ribosome	Phase 1	23
BTZ-043	Benzothiazine	DprE1 inhibitor	Phase 2	24
SPR-720 (ethyl urea benzimidazole)	Other classes	GyrB inhibitor	Phase 1	25
TBI-166 (riminophenazine)	Other classes	Membrane destabilization	Phase 1	26
Levofloxacin	Fluoroquinolone	DNA gyrase inhibitor	Phase 2	27
Rifampicin (high dose)	Rifamycin	RpoB Inhibitor	Phase 2	28
Delpazolid	Oxazolidinone	Inhibition of protein synthesis	Phase 2	29
Sutezolid	Oxazolidinone	Inhibition of protein synthesis	Phase 2	30
Delamanid	Nitroimidazole	Phase 3—approved	Inhibits cell wall synthesis	31
Pretomanid	Nitroimidazole	Phase 3—approved	Inhibits cell wall synthesis	32
Bedaquiline	Diarylqunoline	Phase 3—approved	Inhibits mycobacterial ATP synthase	33

3.2. New Drug Under Trial

- **New Anti -TB Drugs discovery led to be optimization:** Indazole, sulfonamides, Diarylthiazoles, DprE1 Inhibitors, Direct InhA Inhibitors, Mycobacterium tuberculosis energy metabolism, Gyrase inhibitors, Aryl sufonamides, Inhibitors of Mmpl3, Translocase-1, Clpc1, ClpP1P2, PKS13, F-ATP synthase, RNAP, Oxazolidinones, DnaE1/Nargenicin analogs.
- **New Anti -TB Drugs discovery Early to be optimization:** FIM-253, TBD10(MK-3854), CLB-073, SPR720, MPL-447, JSF-3285, CPZEN-45, NTB-3119, MBX-4888A, FNDR-20365.
- **New Anti -TB Drugs under pre-clinical development:** GSK-839, OTB-658.
- **New Anti -TB Drugs under Phase I clinical trial:** TBD09(MK-7762), TBAJ-587, GSK-286, TBI-223, Macozinone (PBTZ-169).
- **New Anti -TB Drugs under Phase II clinical trial:** TBAJ-876, TBA-7371, Telacebec(Q203), Alpibectir (BVL-GSK098), Sanfetrinem, Delpazolid, Sutezolid, Tedizolid, BTZ- 043, Quabodepistat (OPC-167832), Pyrifazimine (TBI-166).
- **New Anti -TB Drugs under Phase III clinical trial:** Sudapyridine (WX-081).
- **New Anti -TB Drugs under Phase IV clinical trial (Regulatory Market Approvals):** Bedaquiline, Delamanid, Pretomanid

4. Need for novel system for treating tuberculosis

Tuberculosis (Tb) is the deathliest disease worldwide. For relief disease can be take multiple first line drug for 6 months regularly. Nanotechnology has greatly benefited modern pharmacology and the enhancement of drug efficacy in biopharmaceuticals. With its potential, there is the ability to engineer drug delivery systems specifically targeting phagocytic cells, which are often infected by intracellular pathogens like mycobacteria. Leveraging nanotechnology in delivery systems opens extensive possibilities for enhancing therapies across various diseases, including tuberculosis (34) Achieving the utmost therapeutic efficacy requires meticulous formulation of a drug, which underpins the core principle of a drug delivery system. A drug delivery system is categorized by four key elements known as the "Four D's": drug, destination, disease, and delivery. Among these, the delivery aspect stands out as the sole variable factor. (35) Multiple drugs, frequent dosage, side effects, poor patient compliance, and drug resistance are all part of the traditional treatment for tuberculosis. tuberculosis drug formulation involved incorporating isoniazid (INH) into three distinct polymers: poly (methyl methacrylate), poly (vinyl chloride), and carbomer. (36) Spherical microcapsules were created utilizing different polymers, with a focus on recognizing the exceptional biocompatibility, biodegradability, and mechanical resilience of aliphatic polyesters like PLA, PGA, and PLG. (37)

4.1. New treatment to overcomes antibiotics resistance against *mycobacterium tuberculosis*

Furthermore, dysbiosis induced by antibiotics could impact the interaction between the microbiota and the immune system, potentially exacerbating the progression of TB and heightening the likelihood of reinfection. (38) Recently, research has shown that probiotics possess bactericidal properties capable of suppressing certain antibiotic-resistant superbugs. Consequently, efforts have been initiated to explore their application in combating tuberculosis. (39)

Polyphenols, found abundantly in fruits, vegetables, cereals, red wine, and extra virgin olive oil, are natural compounds. Due to their antioxidant, anti-inflammatory, and antimicrobial properties, polyphenols are employed in the prevention and treatment of chronic diseases. Specifically, they exhibit anti-inflammatory effects by either inhibiting the NF-κB pathway, leading to reduced expression of pro-inflammatory cytokines, or by activating TREG cells, resulting in increased expression of the anti-inflammatory cytokine IL-10(40) as far as we know, little study has been done on using polyphenols to treat tuberculosis. However, a treatment involving a mixture of flavonoids was evaluated on TPH-1 infected macrophages and human granulomas. This treatment showed reduced intracellular survival of Mtb and increased granuloma formation. Additionally, it led to higher levels of IL-12 and IFN-gamma, and lower levels of IL-10. (41)

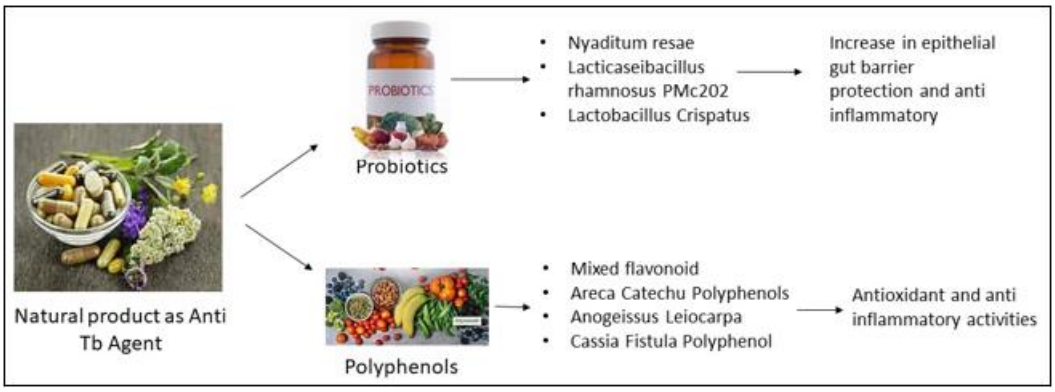

Figure 1: Potential use of natural products as anti-TB agents. Both probiotics and polyphenols been experimented with as anti -Tb Pharmaceuticals

IFN-gamma, a crucial cytokine in protecting produced soon after infection by Th1 and T cytotoxic cells, which prevent the spread of tuberculosis. For an anti-TB response to be effective, multiple genes encoding IFN-gamma and its receptors must be expressed. IFN-gamma stimulates the generation of reactive oxygen species and nitric oxide, which increases macrophages' capacity for microbicidal action. as well as enhancing antigen presentation. (42)

4.2. Nano Delivery Systems for Treating Tuberculosis

The rise of nanotechnology offers promising potential for improved treatment of severe illnesses like tuberculosis and AIDS. Addressing challenges such as frequent treatment failures, the rise of strains that are resistant to drugs, and the necessity to shorten treatment duration while minimizing drug interactions underscores the importance of developing nanocarrier systems for delivering drugs against these diseases. Contemporary pharmaceutical technologists are focused on enhancing the effectiveness and diminishing the toxicity of antimicrobial therapeutic drugs (ATDs) by specifically targeting infection sites. Nanotechnology holds promise for achieving greater efficacy and adherence to therapy using current drug molecules. (43)

Dendrimers are large molecules characterized by precisely defined, highly branched three-dimensional structures, featuring relatively low molecular weight and polydispersity, along with versatile and adjustable functionality. Originating from the synthesis of polyamidoamines (PAMAM) in the early 1980s, dendrimers represent a pioneering concept in macromolecular design. (44) Because of their distinct architecture, dendrimers appear as promising contenders for encapsulating and delivering anti-TB agents via various routes of administration. Nevertheless, only a limited number of researchers have delved into their potential for this specific application. (45)

Polymeric nanoparticles serve as extensively utilized delivery vehicles for enhancing drug solubility, stability, and targeted delivery. Their remarkable stability and simplicity of use through different routes, and capacity to encapsulate both hydrophilic and hydrophobic drugs have established them as highly regarded methods for drug encapsulation. (46.)

Amphiphilic polymers undergo self-assembly in water, resulting in the formation of polymeric micelles. The micellar shell forms through the interaction of hydrophilic blocks with the aqueous environment, enabling the solubilization of the amphiphile in water and stabilizing the aggregate. Conversely, hydrophobic blocks constitute the inner micellar core, which facilitates the solubilization of poorly water-soluble drugs, shielding them from degradation. These micelles can be modified to become more lipophilic, thereby enhancing the penetration of the incorporated drug into pathogens and improving its antibacterial activity against Mycobacterium. (47) Nano emulsions are widely favoured as a drug delivery method due to their thermodynamic stability and the ability to undergo sterilization through filtration. These oil-in-water dispersions, spontaneously formed and typically ranging in size from 10 to 100 nm, have been utilized extensively for delivering drugs and enhancing their uptake by the phagocytic cells (48) Liposomes are nano- to micro-sized vesicles consisting of a phospholipid bilayer encapsulating a desired drug within an aqueous core. Extend their sustainability and circulation time, liposomes are

occasionally PEGylated. Studies have shown that intravenous administration of gentamicin encapsulated in liposomes led to a notable decrease in mycobacterial count in the liver and spleen of a mouse model with disseminated M. avium complex infection. (49) Solid lipid nanoparticles (SLNs) are suspensions of nanocrystals in water, composed of lipids that are solid at ambient temperature. Representing a novel form of nanoparticulate carriers, SLNs are an adjunct to more conventional methods such as polymeric nanoparticles (PNPs), lipid emulsions, and liposomes.

In delivery system Nanoparticles (PLGA) in which drug used RIF and which show strong therapeutic efficacy, high encapsulation efficiency.(50) Enhanced in vitro and in vivo therapeutics efficacy with moxifloxacin in nanoparticles(poly(butyl-2-cyanoacrylate)).(51) Sustained drug release and 6- fold increase in anti – Tb activity with INH,PZA,RIF drug in micelles (poly(ethylene glycol) – poly(aspartic acid) conjugate)(52) Improved selective uptake of drug-loaded nanocarriers by macrophages, increased drug entrapment with RIF in dendrimer nanocarriers.(53) Reduction in bacterial load in lung with clofazimine drug in nanosuspension (nanocrystals)(K. (54) Complete TB bacilli clearance following five oral doses of the drugs RIF, INH, and PYR in PLGA nanoparticles (55). Polypropylimine dendrimers containing RIF medication showed improved solubility, an in vitro sustained release action lasting up to 129 hours and enhanced intracellular concentrations.

5. Approaches and challenges in treating *mycobacterium tuberculosis*

The prevalence of tuberculosis is associated with malnutrition in patients, which can compromise the hosts. Immune responses to Mycobacterium tuberculosis (MTB) infection. Protein deficiency contributes to increased bacterial growth and dissemination by causing thymic atrophy and affecting the generation and maturation of T-lymphocytes. This deficiency also hinders the protective interaction between macrophages and T-lymphocytes. Moreover, it leads to elevated production of transforming growth factor-β, a mediator of immunosuppression and immunopathogenesis in tuberculosis, reduces the production of Th1 cytokines, and diminishes the resistance to tuberculosis following BCG vaccination. (56) Mycobacterium tuberculosis (MTB) is extensively researched because of its pathogenic nature. The complete genome sequencing of MTB H37Rv has been available for an extended period, providing valuable insights into the bacterium's life cycle and facilitating the identification of potential drug targets through comprehensive annotation. (57) The fluoroquinolone class stands out prominentlyin the second-line drug regimen for tuberculosis. This category encompasses broad-spectrum antibiotics known for their capability to hinder both DNA gyrase (topoisomerase II) and DNA topoisomerase IV vital type IIA bacterial enzymes that require ATP. (58) In Mycobacterium tuberculosis (MTB), DNA gyrase functions by facilitating the cleavage of DNA at the gate segment, allowing for the ATP-dependent transfer of another DNA segment. Meanwhile, topoisomerase plays a crucial role in regulating the topological structure of DNA. (59) Given that mycobacteria have only one type IIA enzyme, the MTB DNA gyrase takes on an additional role of separating the chromosome, a function typically attributed to topoisomerase IV (60) Rifamycin is a class of antimicrobial agents that can be naturally produced by Amicolatopsis rifamycinica; however, the majority of medications containing rifamycin are synthetically manufactured. This class encompasses well-known rifamycin drugs, including rifampicin, rifabutin, rifapentine, rifalazil, and rifaximin. (61) Oxazolidinone, a category of antibiotics with efficacy against Gram-positive bacteria, was initially employed in treating Staphylococcus aureus infection. The inaugural oxazolidinone drug was formulated to address various plant diseases. Although oxazolidinone-based antibiotics for human application were synthesized, their usage was discontinued due to identified toxicity properties. (62). Delamanid and pretomanid, both recently sanctioned for the treatment of MDR-TB are members of the nitroimidazole class. Nitroimidazole, recognized for its antibacterial properties since the introduction of the first agent, metronidazole, in the mid-1950s, has been extensively utilized in antibacterial treatments and is a commonly employed therapy for infectious diseases. (63) The strategy of drug repurposing is employed to identify new antituberculosis agents, providing an efficient and cost-effective approach. This method also reduces the likelihood of cross-resistance, as the targets of these repurposed drugs are likely novel in Mycobacterium tuberculosis (MTB). Nitazoxanide and sanfetrinem represent two antituberculosis drug candidates that were unearthed through the drug repurposing approach. (64) Nitazoxanide, recognized initially as a broad-spectrum antiprotozoal agent, is a derivative of nitrothiazolyl- salicylamide (2-acetyloxy-N-(5-nitro-2-thiazoyl)-benzamide). This compound functions as an inhibitor of the pyruvate ferredoxin oxidoreductase enzyme. Subsequently, it was established that nitazoxanide also demonstrates activity against various anaerobic bacteria sharing the same cellular target (65) Despite the identification of numerous chemotherapy agents, human tuberculosis remains a significant global threat with high mortality rates. Existing tuberculosis therapy faces various challenges, including prolonged treatment duration, complex regimens, and drug-related toxicity. The emergence of drug-resistant tuberculosis (DR-TB) underscores the pressing need for alternative approaches to effectively contain and address this disease (66) Host-directed therapy (HDT) stands as an innovative approach that can serve as an additional strategy in the treatment of tuberculosis (TB). The fundamental principles of HDT involve disrupting crucial host–pathogen interactions associated with pathogen replication and boosting the host immune response by stimulating host factors or other immunogenic components. The implementation of HDT can be accomplished through the use of small molecules or biologics (67)

6. Challenges In Treating Mycobacterium Tuberculosis

The 2018 WHO Global Tuberculosis Report indicated that the effectiveness of drug-resistant tuberculosis (DR-TB) treatment in 30 countries facing a high burden of tuberculosis ranged from 48% to 86%, averaging 56%. Notably, India, Indonesia, Mozambique, and Ukraine exhibited the lowest success rates in DR-TB treatment. (68) A new study that predicts the rise of drug-resistant tuberculosis (DR-TB)

suggested a substantial rise in multidrug-resistant tuberculosis (MDR-TB) cases from 2015 to 2025. Additionally, the study highlighted that implementing widespread resistance testing for all tuberculosis patients by 2017 could potentially reduce MDR- TB incidence by 29% by the year 2025. multidrug-resistant tuberculosis (MDR-TB) cases from 2015 to 2025. Additionally, the study highlighted that implementing widespread resistance testing for all tuberculosis patients by 2017 could potentially reduce MDR- TB incidence by 29% by the year 2025. (69)

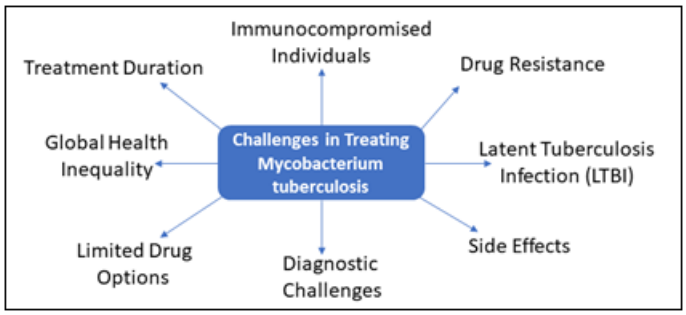

Figure 2: Challenges in treating Mycobacterium tuberculosis.

7. Dendrimer-based formulations in drug delivery

Dendrimers represent a crucial category of nanostructured vehicles in the advancement of nanomedicine for diverse disease treatments. Their structural versatility and adaptability make them valuable in various approaches for delivering drugs and genes. (70) As an example, dendrimers featuring a hydrophobic core and a hydrophilic outer layer can exhibit characteristics akin to individual micelles. These dendrimers have been employed to enhance the solubility of hydrophobic drugs by encapsulating them within their intramolecular cavities. Conjugating drugs with dendrimers have the potential to decrease systemic side effects and enhance effectiveness at specific target sites, surpassing the performance of free drugs. Studies indicate that drug half-lives can be prolonged through dendrimer conjugation. For example, the half-life of methotrexate extends from 24 minutes to 24 hours when coupled with PAMAM dendrimers. (71) As per the guidelines of the United States Food and Drug Administration (FDA), dendrimer-drug conjugates can be categorized either as novel drugs or combination devices. (72)

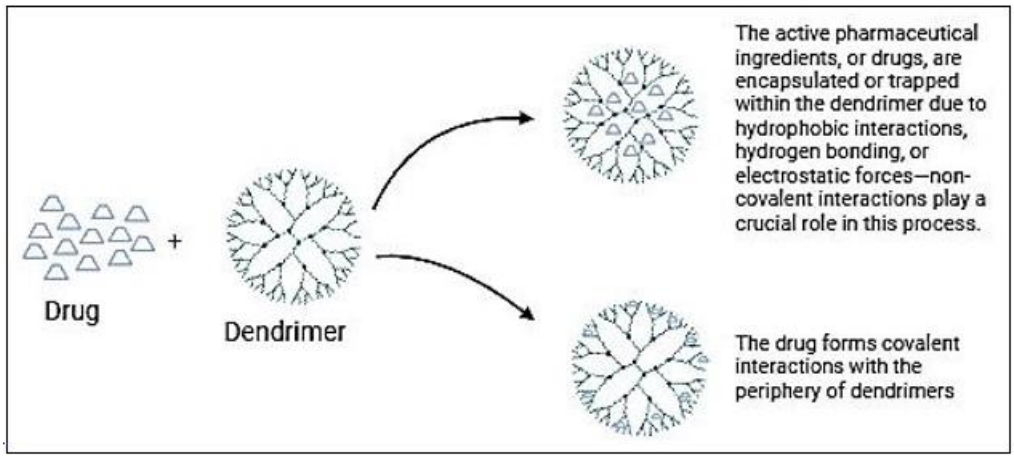

Figure 3: Dendrimers interaction with drug

Dendrimers serve as a versatile platform for drug attachment, enabling the binding and controlled release of pharmaceuticals through diverse mechanisms. Their compact and spherical structure, coupled with numerous surface functional groups, allows for the encapsulation of drug molecules within and attachment to the surface groups. Utilizing dendrimers has proven effective in delivering drugs directly to specific sites, emulating sustained release formulations, and ensuring heightened efficacy, particularly in the case of anti-TB medications. Given the inherent challenges correlated with poor permeability, low solubility, and adverse side effects related to biodistribution that are connected to a number of the anti-TB medications currently in use, there is a growing consensus among researchers to explore dendrimers as a promising avenue to enhance the effectiveness of these drugs and mitigate their limitations.

7.1. Pamam dendrimers for treating *mycobacterium tuberculosis*

Polyamidoamine (PAMAM, presently accessible commercially under the name StarburstTM) has undergone thorough exploration since 1997 due to its remarkable ability to enhance solubility, exhibit biocompatibility, and demonstrate relatively low levels of toxicity. (73) PAMAM dendrimers represent a group of extensively branched and uniformly sized synthetic macromolecules possessing precisely defined structures and compositions. The synthesis of these nanocarriers typically follows the divergent

approach, wherein ethylenediamine serves as the core, and successive additions of methyl acrylate and ethylenediamine (EDTA) occur based on the intended number of generations, such as G0, G1, G2, G3, G4, and so forth. The dimensions and configurations of G3, G4, and G5 PAMAM dendrimers closely resemble those of insulin, cytochrome C, and hemoglobin, respectively, underscoring their characterization as "artificial proteins." These dendrimers possess internal voids and external functional groups, offering opportunities for customization to encapsulate drugs or other payloads. (74) Rifampicin, a primary antituberculosis medication, faces challenges related to its solubility in aqueous environments, leading to its classification as a BCS (Biopharmaceutics Classification System) class II drug. (75)

Pharmacokinetic characteristics of PAMAM dendrimers in generations G1, G2, and G3 were assessed and compared at pH 5.4, representative of alveolar fluid, and at pH 7.4, corresponding to cytoplasmic pH. The examination revealed that the complex formed between the drug and G3 PAMAM dendrimer exhibited an extended and sustained release, surpassing the performance of the other two generations. (76)

7.2. PPI Dendrimers for Tuberculosis Treatment

The initial synthesis of polypropylene imine dendrimers, credited to Voegtle et al., took place in 1978, marking the inception of these dendritic structures (77) The process of PEGylation applied to the 5th generation polypropylene imine (PPI) dendrimer, akin to PAMAM dendrimer, not only amplifies the biodistribution of the antituberculosis drug but also significantly improves the dendrimer's capability to encapsulate the drug. Additionally, this modification mitigates the toxicity concerns associated with PPI dendrimers. (78) Vijayaraj Kumar and colleagues synthesized 5th generation EDA-PPI dendrimers, with ethylenediamine as the central core, and subsequently mannose-functionalized them to enable targeted drug delivery specifically to macrophages in the alveolus. Rifampicin, a primary antituberculosis medication, was chosen and incorporated into the described complex. (79)

7.3. Dendrimers as Antibacterial agents

Antimicrobial dendrimers are characterized by cationic surfaces, often altered with amino groups or tetraalkyl ammonium groups. Typically, these compounds bind to the anionic cell wall of bacteria, resulting in damage and subsequent breakdown of the entire bacterium. An illustration of such an antibacterial dendrimer is the polypropylene imine (PPI)-based dendrimer, modified with tertiary alkyl ammonium groups, demonstrating strong antibacterial efficacy against both Gram-positive and Gram-negative bacteria. (80) Shaunak's research team examined the dendrimer-glucosamine conjugate (PETIM-DG) across a wide range of infectious diarrheal diseases induced by E. coli, Shigella, and Salmonella. The findings indicated that the PETIM-DG conjugate served as an inhibitor specifically against the Shigella genus, preventing harm to the intestinal epithelial wall in rabbits. (81) Dendrimers have potential applications as prophylactic agents against Vibrio cholera, a Gram-negative bacterium responsible for causing cholera. To thwart infection, a method employed involved the use of dendrimers featuring a core composed of 3,5-bis(2-aminoethoxy) benzoic acid and a GM1-mimic ligand. (82) Staphylococcus aureus stands out as a highly resilient and infectious Gram-positive bacterium, particularly challenging to combat. This opportunistic pathogen poses a significant threat to individuals with chronic ailments, weakened immune systems, those who have undergone surgery, and individuals relying on catheters, such as dialysis patients. (83) G1 polyphenolic carbosilane dendrimers, modified with caffeic and gallic acids, have demonstrated the ability to impede the growth of S. aureus. The mode of action for these dendrimers relies on their antioxidant properties, which correlate with the quantity of hydroxyl groups present in the polyphenol structure. (84)

8. Remaining challenges in dendrimer-based mycobacterium treatment

The discussion should encompass challenges such as limited drug-loading capacity, potential toxicity concerns, and the need for further optimization of dendrimer formulations for enhanced efficacy. For example, studies by Sareen et al. (85) highlight challenges in achieving optimal drug release profiles and potential cytotoxic effects that need careful consideration.

8.1. Potential Strategies to Overcome Current Limitations: This part should explore proposed solutions and strategies to address the identified challenges. References to studies demonstrating successful modifications or innovations in dendrimer design to enhance drug-loading capabilities or reduce toxicity would be valuable. For instance, the work of Smith et al. on surface modifications improving dendrimer biocompatibility can be cited as a potential strategy. (86)

8.2. Emerging Trends in Dendrimer Research for Antibacterial Therapy: Highlighting recent developments and cutting-edge research in dendrimer-based antibacterial therapy is crucial. Citations from reputable sources, such as the review by Jones et al. discussing the latest trends in dendrimer research for antibacterial applications, can be included. This section should provide insights into novel dendrimer formulations, delivery strategies, or antimicrobial mechanisms being explored by researchers. (87)

9. Conclusion

In conclusion, this comprehensive review has highlighted the multifaceted landscape of tuberculosis (TB) treatment, spanning from understanding the disease's epidemiology to exploring innovative therapeutic avenues. We have examined the challenges posed by antibacterial resistance mechanisms in Mycobacterium tuberculosis and discussed the ongoing efforts in clinical trials for new anti-TB drugs. Moreover, we have underscored the critical need for novel treatment systems to combat TB effectively, particularly in the face of escalating drug resistance. Our exploration of new treatments to overcome antibiotic resistance against M. tuberculosis has revealed promising strategies that hold potential for improving patient outcomes. Furthermore, the review has

delved into the emerging field of nano delivery systems for TB treatment, offering insights into their advantages and challenges. We have also discussed the various approaches and complexities in treating M. tuberculosis, emphasizing the importance of multidisciplinary strategies and collaborative efforts. Finally, our examination of dendrimer-based formulations and their potential as antibacterial agents against M. tuberculosis sheds light on innovative approaches to TB therapy. In summary, this review highlights the significance of ongoing research and innovation in the field of tuberculosis therapy to answer the changing needs and enhance patient care on a global scale.

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