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Review Article

Next generation tuberculosis therapy: from drug design to delivery

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ABSTRACT

Background: Tuberculosis (TB) caused by Mycobacterium tuberculosis, continue to remain as one of the paramount infectious diseases especially in developing countries. Issues such as long duration of treatment, side effects to the drugs, and increasing resistance to drugs call for pharmaceutical and pharmacological measures to achieve better therapeutic results.
Objective: This review will encompass recent therapeutic and pharmaceutical advances in the treatment of Tuberculosis and their potential applications to help overcome some limitations faced by current approaches of therapy.
Methodology: The purpose of this review was to analyze relevant articles published over 2015 to 2025 with the assistance of the databases PubMed, ScienceDirect and Google Scholar. Selected articles are all peer reviewed and discuss novel drug delivery systems, pharmacokinetics of anti-TB agents, drug resistance mechanisms, and clinical efficacy of novel pharmacological agents. Both monotherapy and combination therapy, as well as adjunct formulations were analyzed.
Result: New drug delivery technologies have enhanced the bioavailability and patient compliance. These include nanoformulations, liposomal carriers, inhalable drugs for TB and fixed-dose combinations. Appreciable results have been obtained against MDR and XDR TB strains with the advent of bedaquiline, pretomanid and delamanid. Together, these approaches forge a stronger and efficient treatment strategy against TB.
Conclusion: TB control requires a 2 pronged drug pharmacological approach. Advances in drug delivery and pharmacotherapy hold the key to addressing the present treatment challenges and improving patient outcomes.

Introduction

Mycobacterium tuberculosis causes tuberculosis (TB), a severe infectious disease majorly in the developing nation.

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Such a type of TB has nevertheless always been a heavier load to the health care systems all over the world due to the complication of its treatment and dispelling of the health of the population at one time or another in the interests of medical science. These include: the lengthy regimen, significant side effects of medications, development of strains that are resistant to drugs all of which do not contribute much to the fact that the disease is under control. Drug susceptible TB is usually treated using first line drugs such as isoniazid, rifampicin ethambutol and pyrazinamide within a range of six to nine months. This long period of time is often a cause of non-adherence in patients, a great contributor to failure of treatment and drug resistant [1]. The side effects of these drugs, especially hepatotoxicity among isoniazid and rifampicin, worsen non-compliance since it may cause rather strong discomfort to the patient and thus require a close medical supervision. These side effects not just spoil the therapeutic effects but also demoralize the patients to finish their courses which augers them a relapse and continuity of spreading the disease.In the past, treatment would take approximately 6-9 months or so, but then this is the duration treatment of latent TB takes. Its length at times has been discouraging patient compliance with the treatment; which is one of the biggest factors to failure in treatment and drug resistance. The non-compliance is further boosted by the adverse effects of such drugs; mainly isoniazid and rifampicin are hepatotoxic. Such adverse reactions can cause severe discomfort to the patients and there is a need of strict medical observation required [2].

These side effects damage the anticipated treatment success and discourage the patient to finish the regime and turn into relapse getting more time to spread the disease. MDR and XDR TB have also resulted in the establishment of a new order of TB crisis across the globe. MDR-TB is resistant to at least isoniazid and rifampicin and XDR-TB, in addition to them all, is also resistant to the second line drugs including fluoroquinolones and injectable drugs thus making it harder to cure [3]. Such resistant strains take a longer and more complicated duration of about 18 to 24 months of a second line of drugs treatment that is more toxic and less efficient. Moreover, the global burden of TB is highly concentrated on low income countries, which makes the treatment an even greater challenge, with limitations being set to the healthcare system: access to diagnosing, drug supply chains, and patient monitoring. These as well as other biological, pharmacological and socioeconomic conditions are shedding light to the necessity of transfiguring pharmaceutical and pharmacological interventions to remedy the inefficiencies of existing TB treatment protocols. Through reducing length of treatment, adverse effects and resistance, the above gains would stop turning TB treatment outcomes upside down, enhance patient compliance with drug regimens, and guide global TB control efforts in avoiding additional devastation of the disease on susceptible populations [4].

Innovations In Pharmaceutical Formulations

Innovations in pharmaceutical formulations are constantly improving how drugs works in the body, especially for the complex diseases like tuberculosis (TB). One major challenge with TB drugs is that they often have serious side effects and need to be taken for long time. New formulations would aim to solve this by making the drugs more effective at lower doses, reducing side effects, and making it easier for patients to stick to their treatment plan [5]. For example, by packaging drugs in tiny carriers, we can get them exactly where they need to be, like inside the cells where TB bacteria hides. This helps the drugs to work better and reduces the amount of medicine that spreads throughout the rest of the body, which can cause unwanted side effects [6].

A key innovation is the use of lipid-based systems, such as liposomes and solid lipid nanoparticles. Liposomes are like tiny bubbles that are made of fats, similar to our cell membranes. They can be filled with a drug and then delivered to a specific location in the body. For TB, liposomal delivery excists because it can get the drugs directly into the macrophages, which are the immune cells where TB bacteria lives. Studies have shown that the liposomal formulations of drugs like rifampicin and isoniazid can increase the drug concentration inside these cells while reducing the amount of drug in the bloodstream [7]. This means the drug can fight the infection more effectively with a lower risk of side effects. Another example is solid lipid nanoparticles, which are tiny solid particles which are made up of lipids. These can also carries the drugs and offers a stable way to deliver them, which helps to improve the drug's solubility and how well it could absorbed by the body. This is especially useful for the drugs that does not dissolves easily in water [8].

Liposomal Drug Delivery for TB

Liposomal drug delivery is a significant innovation in how we administer the medications, particularly for a complex disease like tuberculosis (TB). Liposomes are tiny, spherical vesicles which are made up of one or more lipid bilayers, which are essentially fatty membranes similar to those which are found in our own cells. They can be filled with a drug and then injected into the body. The main advantage of this system is that it can protect the drug from being broken down too quickly by the body, increase the drug's stability, and

most importantly, delivers it directly to the target site. For TB, this is a game changer because of the bacteria, Mycobacterium tuberculosis, often hides inside the immune cells which are called macrophages which is shown in the fig.1 [9].

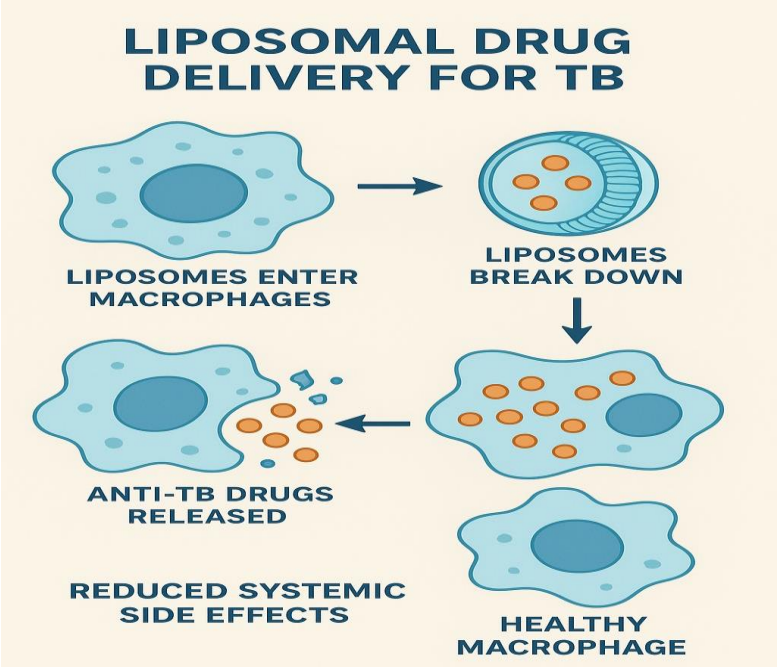

Figure 1: Liposomal Drug Delivery for TB.

Conventional anti-TB drugs, when were taken orally are distributed throughout the entire body, and only a small fraction of drug reaches to the macrophages where the bacteria are located. This is why higher doses are needed, leading to unwanted side effects and a prolonged treatment period. Liposomes, however, can be designed to be preferentially taken up by the macrophages. When a liposomal drug is injected, the liposomes are naturally attracted to these immune cells, which will further then engulf them [10]. Once inside the macrophage, the liposome breaks down and release a high concentration of the anti-TB drug directly to the site of infection. This targeted delivery allows for lower systemic drug concentrations, meaning fewer side effects in the other parts of the body like the liver or kidneys. Scientific studies have shown that liposomal formulations of drugs like rifampicin and isoniazid could effectively clear the infection in animal models of TB demonstrating their potential to improve the treatment outcomes [11].

Solid Lipid Nanoparticles and Nanoemulsions

Beyond liposomes, other innovative lipid based systems like solid lipid nanoparticles (SLNs) and nanoemulsions are also being explored to revolutionize the TB treatment. Solid lipid nanoparticles are tiny particles, which are just a few nanometers in size, made from solid lipids at room temperature. They can encapsulate a drug within their solid core. This offers several benefits, including a high drug payload and a very stable formulation. Unlike some other systems, SLNs are easy to produce and could be made from a variety of biocompatible and biodegradable lipids, and makes them a safe and effective option. For drugs that don't dissolve well in water SLNs could significantly improve their solubility and absorption into the body. This is a critical factor for many anti-TB drugs, which are often poorly soluble [12].

Similarly, nanoemulsions are mixtures of oil, water and surfactants that form a very stable and transparent liquid. The drug is dissolved in the oil phase, which is then dispersed as tiny droplets within the water. This structure provides a large surface area, which enhances the drug's absorption and bioavailability [13]. For example, a drug that is difficult for the body to absorb on its own could be dissolved in a nanoemulsion, and the small droplet size allows it to be more readily taken up [14]. For TB the nanoemulsions can be formulated to deliver drugs through different routes, including oral, pulmonary, or even topical applications. Both SLNs and nanoemulsions offer a way to protect the drugs, improve their solubility, and enhance their delivery, ultimately making them more potent against the TB bacteria while potentially reducing the overall dose needed and minimizing side effects [15].

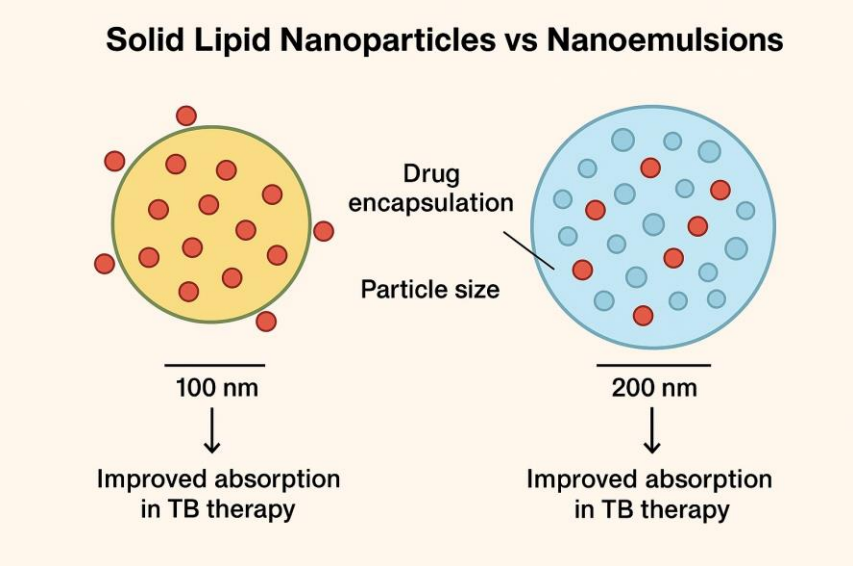

Figure 2: Solid Lipid Nanoparticles and Nanoemulsions.

Drug Delivery Systems in Tuberculosis

Treating tuberculosis effectively requires a long and a very complex regimen of multiple drugs. The traditional method of taking pills every day for six months or more often leads to patients not finishing their treatment, a major cause of drug resistance. To combat this, new drug delivery systems are being developed to make the treatment more efficient, tolerable, and easier for patients to follow [16]. These innovations aims to reducing the total number of pills a patient has to take, they minimize side effects by targeting the drug to the site of infection and ensure a consistent level of the drug in the body over time. The ultimate goal is to improve the treatment adherence, which is critical for curing the disease and preventing the spread of resistant strains [17].

One major challenge with TB drugs is that they need to be taken for an extended period, the bacteria could go dormant, making them hard to kill. This is why a steady and constant supply of medication is essential. New delivery systems, such as sustained release formulations, can maintain a therapeutic drug level for a much longer time. This means a patient might only need to take a dose once a week or even less frequently, rather than daily. This type of system could completely transform the treatment experience, making it much more manageable for patients. Furthermore, by improving how the body absorbs and uses the drugs, these systems can lower the required dose, which directly translates to fewer side effects and a better quality of life for the patient throughout the long treatment course [18].

Inhalable Anti-TB Formulations

Inhalable anti-TB formulations represent a paradigm shift in how we approach tuberculosis treatment. Since TB is primarily a pulmonary disease which is a major limitation of oral drugs is that they have to travel through the entire body to reach the lungs where the infection is located. This process dilutes the drug, so a large number of dose is required to achieve a therapeutic concentration in the lungs. Inhaling the medication, however it delivers a high concentration of the drug directly to the site of infection in the alveoli deep inside the lungs. This method allows for a much lower total dose and significantly reduces the drug's exposure to other parts of the body, which will helps to minimize the common side effects like liver damage [19].

There are two main types of inhalable formulations: dry powder inhalers (DPIs) and nebulizers. DPIs deliver a fine, dry powder containing the drug, which the patient inhales. Nebulizers turn a liquid drug solution into a fine mist that can be breathed in. Both methods have been shown in scientific studies to create a very high concentrations of drugs like rifampicin and isoniazid in the lung tissue. For example, an inhaled dose of rifampicin can lead to a concentration in the lungs that is up to 100 times higher than what it would achieved with an oral dose, all while keeping the blood levels low. This is not only makes the treatment more potent against the bacteria but also allows it to reach TB that is dormant or hidden in parts of lungs which are difficult to reach, which oral drugs often misses. This targeted approach holds immense promise for shortening of the treatment duration and improving the outcomes, especially for drug resistant TB [20].

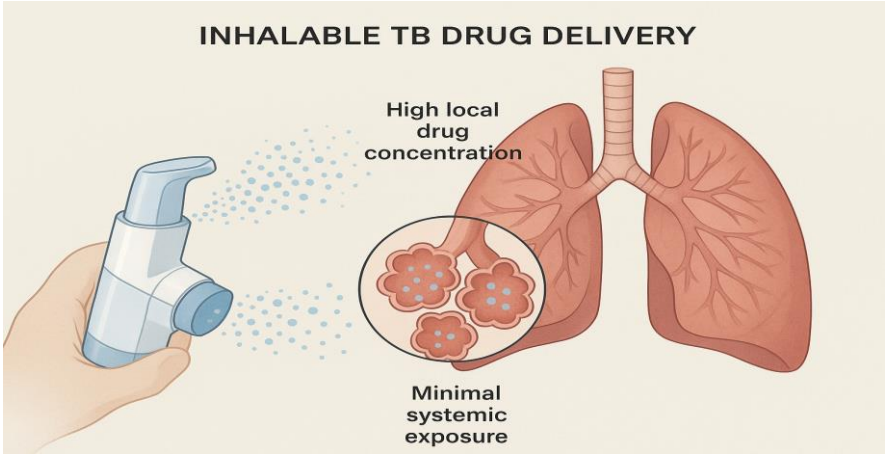

Figure 3: Inhalable Anti-TB Formulations.

Fixed Dose Combinations (FDCs)

They are a simple yet powerful innovation that has transformed the tuberculosis (TB) treatment. In a standard
TB regimen, patients have to take multiple different drugs simultaneously, often requiring them to swallow four or more pills every day. This could be confusing and overwhelming, but it may lead to mistakes in dosage or patients stopping their treatment prematurely [21]. FDCs address this problem by combining two or more anti-TB drugs into a single tablet. For example, a single FDC tablet can contain isoniazid, rifampicin, pyrazinamide, and ethambutol. This simplifies the treatment regimen dramatically, reducing the burden of taking pill from a handful of tablets to just one or two [22].

The use of FDCs has several critical benefits. First and foremost, it significantly improves patient adherence, which is a patient's ability to stick to their treatment plan. When the regimen is simpler, patients are more likely to take their medication correctly and for the full duration. This is essential for curing the TB and preventing the development of drug resistant strains. Second, FDCs could easily prevent the common problem where patients selectively stop taking one of the drugs, which can quickly lead to resistance. With an FDC, they have to take all the drugs together. Studies have consistently shown that FDCs leads to a better treatment outcomes and lower rates of drug resistance compared to when the drugs are taken as separate pills. The World Health Organization (WHO) strongly recommends the use of FDCs in national TB programs because of their proven effectiveness in simplifying care and improving patient adherence [23].

Transdermal and Injectable Routes

While oral and inhalable routes are common, scientists are also exploring other ways to deliver the anti-TB drugs, such as through the skin (transdermal) and via injections. The transdermal route, or a drug patch, works by slowly releasing medication that would absorbed through the skin into the bloodstream. This method offers a potential solution for patients who have trouble in swallowing the pills or suffer from gastrointestinal side effects. It provides a steady and controlled release of the drug over a period of time, which can maintain consistent drug levels in the body and reduces the need for frequent dosing. For TB, a transdermal patch could be designed to deliver a specific drug over a week, eliminating the need for taking pills daily and making the treatment regimen much easier for patients to manage [24].

Another important route is the use of injectable formulations, which are especially relevant for some second-line TB drugs. These are typically used for drug-resistant TB and often need to be given for a long time. The main drawback of traditional injections is that they can be painful and require a healthcare professional to administer them. However, new injectable technologies, such as long acting injectables, are being developed. These are designed to release the drug slowly over weeks or even months from a single injection, similar to some contraceptives. This could be a game-changer for drug-resistant TB treatment, as it would greatly simplify the regimen which reduces the need for daily visits to a clinic, and ensure that patients receive their full course of medication without any fail. Scientific researches are focused on creating formulations that are both long-lasting and well-tolerated by the body, which makes them a practical option for TB treatment [25].

Pharmaceutical Technology Enhancing Bioavailability

Bioavailability is a scientific term that describes the fraction of a drug that is absorbed by the body and becomes available in systemic circulation to have its intended effect. For many tuberculosis (TB) drugs, bioavailability is a major challenge. The drugs are often poorly soluble or get metabolised by the body before they could reach the TB bacteria. This means that a large portion of the medication a patient takes is essentially wasted, and higher doses are needed to compensate the drawback, which on the other hand increases the risks of side effects [26]. Pharmaceutical technology is constantly innovating to overcome this problem by improving how the drugs are absorbed and utilized. These technologies aim to protect the drug from degradation, increase its solubility, and ensure it is delivered to the right target site in the body, ultimately making the drug more potent and the treatment more effective. One of the most important ways by which technology enhances bioavailability is by changing the physical form of the drug [27]. For example, with the using of tiny nanoparticles can increase the surface area of a drug, allowing it to dissolve and be absorbed much more quickly than the traditional tablet. Another approach is to use special coatings or matrices that protects the drug from the acidic environment of the stomach. By preventing this early breakdown, more part of the drug can reach the intestines to be absorbed. These technological advancements are not just about making drugs work better, they are also about making the treatment safer and more efficient. By improving bioavailability, we can potentially lower the required dose, with reducing the duration of treatment, and minimize the severe side effects that often make it difficult for patients to complete their full course of therapy [28].

Microencapsulation and Sustained Release Formulations

Microencapsulation and sustained release formulations are the two key pharmaceutical technologies that designed to improve how drugs work in the body, particularly for diseases like TB that require long-term treatment. Microencapsulation involves wrapping tiny particles of a drug in a protective coating or polymer. This is like putting a drug in a tiny, biodegradable capsule [29]. This coating serves several important functions. First, it can protect the drug from the harsh environment of the stomach, which might otherwise break it down before it can be absorbed. Second, it can mask the drug's taste, which is especially useful for pediatric patients. Most importantly, microencapsulation can be used to control the release of the drug over time. The coating could be designed to dissolve slowly and releasing a steady amount of medication into the body over several hours or even days [30]. This leads to sustained-release formulations, which are a direct result of technologies like the microencapsulation. Traditional pills give the body a large, immediate dose of a drug, which can lead to a spike in the drug concentration followed by a rapid drop-off. This can cause side effects which means that the patient needs to take multiple doses throughout the day to maintain a specific therapeutic level. Sustained-release formulations, however, could ensures a slow and steady release of the drug [31]. This maintains a more consistent drug concentration in the bloodstream, which is ideal for killing the slow growing bacteria like M. tuberculosis. A more consistent drug level not only reduces the risk of side effects but also helps to prevent the bacteria from developing resistance against the drug, as they are constantly exposed to a therapeutic dose. Scientific studies have shown that the sustained-release versions of TB drugs like rifampicin could leads to a better outcomes by maintaining drug levels for longer periods and reducing the need for taking the pills daily, thus improving the patient adherence [32].

Mucoadhesive and Targeted Delivery Systems

Mucoadhesive and targeted delivery systems are advanced pharmaceutical technologies that aims to deliver drugs with a high degree of precision, which is a crucial factor in diseases like TB. Mucoadhesive systems are specially formulated to stick to the mucosal surfaces moist linings of the body's cavities, such as the inner linings of the nose, mouth, or lungs. When a drug is formulated with mucoadhesive properties, it can stay at the site of absorption for a longer time, which increases the amount of drug that is absorbed and enhances its local effect. For example, a mucoadhesive inhaled formulation for TB would stick to the lining of the lungs and slowly releasing the drug directly where the infection is, rather than being cleared quickly. This will improve the drug's efficiency and allows it to show therapeutic effects at a lower dose [33].

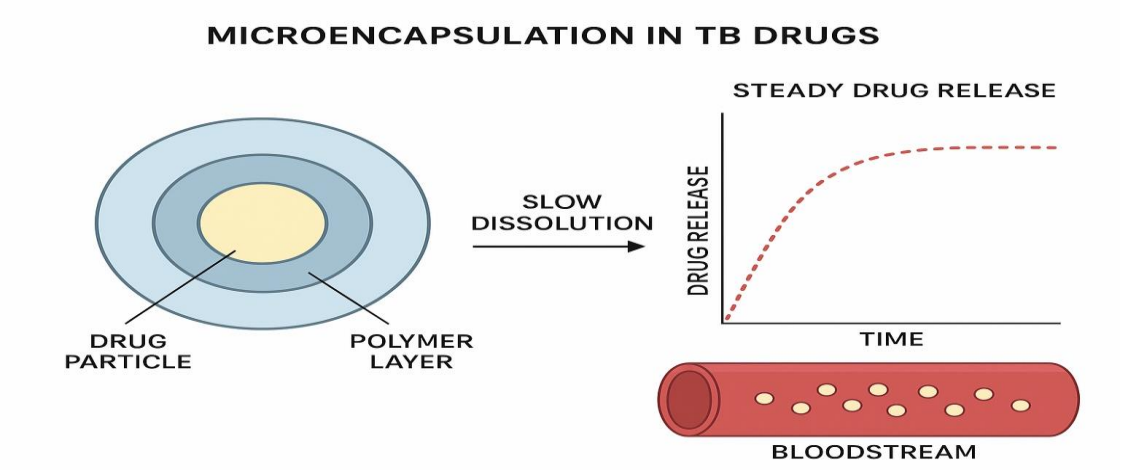

Figure 4: Microencapsulation and Sustained Release Formulations.

Targeted drug delivery systems take this concept a step further by using specific biological triggers to deliver the drug to a particular cell type or tissue. This is incredibly useful for TB, where the bacteria hide inside the macrophages. So instead of releasing the drug throughout the body, a targeted delivery system could be designed to specifically seek out and enter these macrophages where the bacteria hide and then release the drug. For example, nanoparticles can be coated with a substance that is recognized by receptors on the surface of macrophages [34]. When these targeted nanoparticles enter the body, they are specifically taken up by the macrophages, and the drug is released directly inside the cell. This means the drug could reach the bacteria with much greater efficiency. Scientific evidence has demonstrated that this approach could increases the drug concentration inside the infected cells by a factor of ten or more, which significantly improves the drug's ability to kill the bacteria and shortens the time it takes to see results. These systems offer the potential for more effective treatment with fewer side effects by precisely controlling where the drug goes in the body [35].

Dry Powder Inhalers (DPIs) in Pulmonary TB

They are a specific and highly effective technology for delivering the medication directly to the lungs, making them an excellent tool for treating pulmonary tuberculosis (TB). Unlike a typical tablet that has to be swallowed and travel through the entire body, a DPI delivers a fine, dry powder containing the anti-TB drugs straight into the lungs. This is a very efficient way to get the medication to the primary site of infection. The patient would simply inhale deeply, and the powdered drug is carried into the deep regions of the lungs, known as the alveoli. This targeted delivery is a major advantage because it allows for a much higher concentration of the drug at the infection site [36].

By delivering the drug directly to the lungs, a DPI can achieve therapeutic concentrations that are orders of magnitude higher than what is possible with oral pills, while simultaneously keeping the drug levels in the rest of the body like the bloodstream, liver, and kidneys very low, leading to minimum drug loss [37]. This is a crucial benefit for patients, as it can drastically reduces the systemic side effects, which are a common reason for stopping the treatment. For example, one of the main side effects of anti-TB drugs is liver toxicity, and by minimizing the drug's exposure to the liver, DPIs can make the treatment much safer. Scientific studies have shown that inhaled formulations of drugs like rifampicin and isoniazid are highly effective in killing the TB bacteria in the lungs. This technology holds greater potential for shortening the duration of treatment, improving patient adherence by reducing the side effects, and offering a potent new weapon against drug resistant forms of Tuberculosis [38].

Formulation Challenges and Patient Centric Solutions

Developing new drug formulations is not just about making a drug work better; it's about making it work for real people, with all their individual needs and challenges. For a global disease like tuberculosis (TB), which affects a wide range of patients from children to the elderly, one size fits all drug formulations are often not effective. A major challenge in designing drugs that are suitable for different patient populations. For example, a tablet designed for an adult is often too large for a small child to swallow, and the dose can be difficult to adjust correctly. Similarly, elderly patients might have difficulty with a complex regimen of

multiple pills, or they might have other health conditions that make them more susceptible to side effects. Therefore, pharmaceutical research is increasingly focused on patient centric solutions, which means designing formulations with the patient's specific needs and limitations in mind [39].

A core part of this approach is making the treatment more tolerable and easier to follow. Long-term treatment with multiple pills often leads to patients feeling overwhelmed and stopping their medication early. This not only puts their own health at risk but also contributes to the global problem of drug resistance. By creating the formulations that reduce the number of doses, simplify the regimen, and minimises side effects, we can help ensure that more patients would complete their full course of treatment [40]. Technologies like fixed dose combinations (FDCs), which combine multiple drugs into a single pill, are an excellent example of this patient-centric approach. They simplifies the regimen and have been proven to improve adherence and the treatment outcomes. Other solutions include creating palatable liquid formulations for children and easy to swallow tablets for the elderly [41].

Pediatric and Geriatric Dosage Design

The needs of children and the elderly are vastly different when it comes to medication, and ignoring these differences is a major challenge in creating effective TB treatments. For pediatric patients, having the right dose is critical. Their bodies are smaller, and their metabolism is also different from adults, so a standard adult dose is not appropriate them. A common practice is to crush adult pills and estimate a fraction of the dose, but this can lead to the inaccurate dosing, which is both ineffective and could be dangerous. The ideal solution is to develop a specific formulation for children, such as chewable tablets, liquids, or dissolvable granules. These are not only ensuring accurate dosing but also make the medication easier and more palatable for children to take, which is a key factor in ensuring for them to complete their long-term treatment [42].

Geriatric patients, or older adults, face their own set of challenges. They often have multiple health conditions and are taking other medications, which can lead to complex drug interactions. Their bodies also process drugs differently, and they might be more sensitive to side effects like liver toxicity or kidney problems. For these patients, a simpler, lower-dose regimen that minimizes side effects which is crucial [43]. Formulations that are easy to swallow, such as liquid suspensions or smaller tablets, are also important. Furthermore, technologies that can maintain a consistent drug level with less frequent dosing, like sustained release formulations or transdermal patches, they would be particularly beneficial. By designing treatments specifically for these two populations, we can make TB treatment safer, more effective and more manageable for all patients, which is a vital step in controlling the disease [44].

Cost Effective and Scalable Technologies

A major challenge in drug development for a global disease like tuberculosis (TB) is not just creating an effective treatment, but making it affordable and accessible to the millions of people in low and middle income countries who needs it most. Many of the innovative drug delivery systems, such as complex nanoparticles or advanced sustained-release technologies, can be expensive to research and manufacture. If these new treatments are too costly, they will not being widely adopted, and the public health benefits will be limited. Therefore, a significant focus of pharmaceutical research is on developing a cost-effective and scalable technologies [45]. This means finding the ways to produce an advanced formulations using the inexpensive materials and simplified the manufacturing processes that can be ramped up to produce the large quantities quickly and cheaply [46].

One approach is to use the commonly available and well-understood materials in new ways. For example, instead of using a complex, expensive polymer for a sustained-release formulation, researchers can explore more readily available and affordable alternatives. Another strategies are to simplify the manufacturing process itself. For example, developing an one-step process to create a fixed dose combination pill, rather than a multi-step process, which could significantly reduces the cost of production. Furthermore, there could be a push to develop formulations that don't requires a cold chain the expensive and complex process of keeping the drugs refrigerated [47]. A TB treatment that can be stored at room temperature is far more practical for delivering to remote areas with a limited access to electricity. By prioritizing the cost-effectiveness and scalability from the very beginning of the research and development process, we can ensure that the next generation of TB treatments will be both scientifically advanced and universally accessible [48].

Mechanism of Action of Anti-TB Drugs

Understanding how anti-TB drugs work at a molecular level is crucial for the development of new treatments and combating drug resistance. These drugs don't just kill bacteria as they target specific parts of the Mycobacterium tuberculosis bacterium to disrupt its life cycle. The drugs often interfere with the essential processes that bacteria need to survive, such as building a cell wall, making proteins, or creating the genetic

material. By targeting these specific mechanisms, the drugs could kill or stop the growth of the bacteria. However, the bacteria can evolve and develop new ways to survive, which leads to drug resistance. This is why a combination of drugs is always used to attack the bacteria from multiple angles and reduce the chances of resistance [49].

First Line Drugs: Isoniazid, Rifampicin, Ethambutol

First line anti tuberculosis (TB) drugs are the initial and most important medications used to treat TB. These include Isoniazid (INH), Rifampicin (RIF), Pyrazinamide (PZA), Ethambutol (EMB) and Streptomycin. These drugs are known for their high effectiveness, relatively low toxicity, and broad action against Mycobacterium tuberculosis. They are usually given for a period of 6 months an initial intensive phase of 2 months using INH, RIF, EMB, and PZA, followed by a 4 month continuation phase with INH and RIF [50].

Table 1: Key Characteristics of First Line Anti-TB Drugs.

Name	Drug Class	Mechanism	Stage of Development	Major Advantages Over Existing Treatments
Pretomanid	Diarylquinolone	Inhibits mycobacterial cell wall synthesis	Approved	Shorter treatment duration, improved efficacy
Bedaquiline	Diarylquinolone	Inhibits mycobacterial ATP synthase	Approved	Effective against drug-resistant TB
Delamanid	Nitroimidazole	Inhibits mycolic acid synthesis	Phase 3	Improved safety profile, efficacy against MDR-TB
SQ109	Diarylquinolone	Inhibits mycobacterial membrane	Phase 2	New class, potential for combination therapy

Isoniazid (INH)

INH is a highly active drug that blocks mycolic acid synthesis, which is crucial for the bacterial cell wall. It is a prodrug, activated by the bacterial enzyme KatG. INH can be taken orally or intramuscularly and distributes well into tissues, including the brain. It is broken down in the liver by acetylation. People vary as either fast or slow acetylators, which affects drug metabolism and dosing. Common side effects include liver damage and peripheral nerve problems. A toxic overdose can cause a triad of symptoms seizures, metabolic acidosis, and coma [51].

Rifampicin (RIF)

RIF plays a vital role in shortening the duration of TB treatment. It blocks DNA dependent RNA polymerase, stopping bacterial protein production. It works against both TB bacteria and also other microbes like Staphylococcus and E. coli. RIF is given orally or intravenously. It is metabolized in the liver, and its absorption decreases with fatty meals. RIF has a short half-life and is eliminated through bile and urine. Common side effects include liver toxicity and orange-red staining of urine, sweat, and tears [52].

Ethambutol (EMB)

EMB is used to stop bacterial cell wall synthesis. It works by blocking the enzyme arabinosyl transferase, affecting the arabinogalactan production. EMB is usually taken orally and works against both TB and non TB mycobacteria. A significant adverse effect is optic neuritis, which could lead to vision changes, such as color blindness or blurred vision. Regular eye check-ups are recommended during the therapy [53]. Together, these first-line drugs form the core of TB treatment and are highly successful when used properly. Ensuring adherence to the full treatment course is essential to prevent the development of resistance and relapse [54].

Second Line and Reserve Drugs

Second line anti-TB drugs are used when first-line treatments fail due to resistance or intolerance. These drugs are often less effective, more toxic and expensive. They are generally reserved for treating the multidrug-resistant TB (MDR-TB), where the bacteria are resistant to both Isoniazid and Rifampicin [55].

These drugs include several classes:

1. **Fluoroquinolones**

These are oral antibiotics that include Ofloxacin (Ofx), Levofloxacin (Lfx), Moxifloxacin (Mfx), and Ciprofloxacin (Cfx). They works by inhibiting bacterial DNA gyrase, an enzyme essential for DNA replication. Fluoroquinolones are among the most effective second-line options, but they can cause joint pain, dizziness, and heart rhythm disturbances like QT prolongation [56]

2. **Injectable Drugs**

These include Kanamycin (Km), Amikacin (Am), and Capreomycin (Cm). These aminoglycosides work by binding to the bacterial ribosome, interfering with protein synthesis by misreading of protein signals. They are given by injection and can cause hearing loss and kidney damage [57].

3. **Oral Bacteriostatic Drugs**

These include Ethionamide (Eto), Prothionamide (Pto), Cycloserine (Cs), Terizidone (Trd), Para-aminosalicylic acid (PAS), Thiacetazone (Thz), and Rifabutin. They have different mechanisms from disrupting cell wall synthesis to inhibiting protein synthesis — and are typically used in combination regimens [58].

The World Health Organization classifies these drugs into Groups A, B, C, and D:
Group A: Levofloxacin and Moxifloxacin are prioritized for MDR-TB. They are the most effective second-line drugs.
Group B: Cycloserine is used with Group A drugs for its additive effect. It is bacteriostatic.
Group C: Amikacin and PAS are used to supplement Group A and B drugs.
Group D: Kanamycin and Capreomycin are now less favored due to toxicity and lower effectiveness.

Second line treatment usually involves a longer duration, often 18 to 24 months. Drug resistance testing is essential before beginning therapy. Adherence and monitoring for side effects are crucial because these drugs often cause more serious toxicities than first-line treatments [59].

Drug Synergism and Combination Therapy

The treatment of tuberculosis (TB) is almost never done with a single drug. Instead, doctors use a powerful strategy called combination therapy, where a patient takes a regimen of multiple drugs at the same time. This approach is the cornerstone of modern TB treatment and is far more effective than by using any single drug alone. To understand why, we need to look at the bacteria itself. Mycobacterium tuberculosis is a clever and resilient pathogen. It can exist in different states within the body some bacteria are actively growing and multiplying, while others are in a dormant or "sleeping" state, making them much harder to kill. A single drug is often only effective against one of these states. With the using of a combination of drugs, the treatment could launch a multi-pronged attack, targeting the bacteria in all their different forms and ensuring that none could survive. This multi drug approach works due to a principle known as drug synergism [60]. This means that the combined effect of the drugs is much greater than if each drug were used individually. Think of it like a team of superheroes, each with a different power, working together to defeat a villain. One drug might attack the bacteria's cell wall, another might stop it from making the proteins, and a third might prevent its DNA from replicating. By hitting the bacteria from different angles, the combination makes it incredibly difficult for the bacteria to survive the assault. For example, isoniazid is a very potent drug against fast-growing bacteria, while rifampicin is effective against a broader range of bacteria, including those that are growing more slowly. When these are used together, they create a much more comprehensive and powerful attack, leading to a faster and more complete cure [61].
Perhaps the most critical reason for combination therapy is to prevent the development of drug resistance. TB bacteria can naturally develop random genetic mutations that allow them to survive a specific drug. When a patient takes a single drug, there is a chance that a few bacteria with this resistance mutation would survive, then multiply, and eventually takes over the entire infection, rendering the drug useless. However, the probability of a bacterium developing two or three different resistance mutations at the exact same time is extremely low. With the using of combination of four drugs, the chance of the bacteria becoming resistant to all of them is virtually zero. This strategy would make sures that any bacteria that might be resistant to one drug would quickly killed by the other drugs in the regimen. This is why it is so important for patients to take all their pills, every day, for the entire duration of their treatment.
Historically, the use of single drugs like streptomycin in the 1940s quicklyled to widespread resistance, which was a major setback in the fight against Tuberculosis [62]. This experience taught scientists the absolute necessity of combination therapy. The standard initial treatment today involves a combination of at least four drugs isoniazid, rifampicin, pyrazinamide, and ethambutol to ensure a swift and complete killing of the bacteria. This approach not only cures the patient but also prevents the spread of drug-resistant strains to the others. While this multi-pill regimen could be challenging for patients to adhere to, newer innovations like the Fixed-Dose Combinations (FDCs), which combines multiple drugs into a single tablet, that are helping to simplify the treatment and makes it easier for

patients to follow. In the end, the principle of synergism and combination therapy remains the most effective scientific strategy we have for defeating this resilient pathogen [63].

Emerging Pharmacological Agents

For decades, the drugs used to treat tuberculosis (TB) remained largely unchanged. However, with the rise of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB, the need for new, more effective drugs became urgent. The last decade had seen a breakthrough with the approval of several new pharmacological agents that works differently from the older drugs and are specifically designed to combat with drug resistant strains. These emerging drugs represents a new hope for patients with the resistant forms of the disease, offering a shorter and more tolerable treatment regimen than older second-line therapies. They are a critical part of the global effort to eradicate the Tuberculosis [64].

Bedaquiline and Delamanid

Bedaquiline (BDQ) and Delamanid (DLM) are two newer drugs which are developed for treating multidrug-resistant tuberculosis (MDR-TB). They are used when the traditional first- and second-line treatments are no longer effective. It belongs to the diarylquinoline class and works by targeting ATP synthase, a crucial enzyme for energy production in Mycobacterium tuberculosis. By stopping the ATP production, the bacteria will losses energy and die. This unique mechanism makes bedaquiline highly effective against the resistant strains. It is taken orally, and its absorption improves with fatty meals. It is mainly metabolized in the liver by the enzyme named CYP3A4 [65]. Caution is needed when using it with drugs like rifampicin, which induce CYP3A4 and reduce bedaquiline's effectiveness by metabolising it more quickly. The drug stays in the body for a longer duration of time, its half-life is about 160 to 165 days, indicating slow elimination. The usual dose is 400 mg once daily for the first two weeks, followed by 200 mg three times a week for the next 22 weeks. Common side effects includes nausea, liver toxicity, and QT interval prolongation, a heart rhythm disturbance that needs monitoring through ECG [66].

Delamanid belongs to the nitro dihydroimidazooxazole class. It works by blocking the synthesis of mycolic acid, a vital component of the mycobacterial cell wall. It is a prodrug and becomes active after undergoing bioreduction of its nitro group, releasing reactive species that kill the bacteria. It's also used orally and is recommended in MDR-TB and pulmonary TB. The typical dose is 100 mg daily. Like bedaquiline, delamanid can cause QT prolongation, nausea, and liver problems. However, it is generally well-tolerated when combined with other anti-TB drugs. Both drugs are often used together or alongside other medications in specialized regimens. They offer hope for better treatment outcomes in MDR-TB and reduce reliance on long and toxic injectable therapies [67].

Pretomanid and Novel Agents in Pipeline

Pretomanid (PA) is one of the latest drugs approved for treating MDR-TB and extensively drug-resistant TB (XDR-TB). It belongs to the nitro-imidazooxazine class and was developed by the non-profit TB Alliance. Approved by the US FDA in 2019, Pretomanid is used only in combination with other drugs, such as bedaquiline and linezolid not as a standalone treatment. Its mechanism is similar to delamanid it interferes with the mycolic acid synthesis and disrupting the cell wall of M. tuberculosis. It also releases nitric oxide under low oxygen conditions, which would help kill dormant bacteria in lesions where oxygen is scarce. This dual mechanism gives it both bactericidal (kills bacteria) and bacteriostatic (stops bacterial growth) properties. It is usually given as part of the BPaL regimen (Bedaquiline, Pretomanid, Linezolid) for treating highly resistant TB. The dose is 200 mg once daily. Like the other new agents, it can cause QT prolongation, liver issues, and gastrointestinal discomfort, but it is considered as relatively safe and effective in short-course regimens [68].

Novel Agents in the Pipeline are despite advances, TB treatment still faces many challenges. Lile resistance, long treatment duration, and side effects continue to cause problems. As a result, there is an urgent need for newer drugs with better activity, fewer side effects, shorter treatment duration, and effectiveness against resistant strains. Several new compounds are in preclinical and clinical development [69].

These include:

- Oxazolidinones (like Sutezolid): More tolerable alternatives to linezolid.
- DprE1 inhibitors (like BTZ-043, OPC-167832): Target bacterial cell wall synthesis.
- Q203 (Telacebec): Inhibits cytochrome bc1 complex, blocking bacterial respiration.
- TBA-7371 and others: Target enzymes in cell wall synthesis and energy pathways [70].

Screening Efforts

Early diagnosis is critical. Modern tests like interferon-gamma release assays (IGRAs) such as QuantiFERON Gold and T-SPOT.TB are replacing older tests like the tuberculin skin test due to better accuracy. These tests

help identify latent TB infection (LTBI), reducing the transmission and improving the public health. Continued investment in research, global partnerships, and rapid clinical testing are the key to overcoming TB in the future [71].

Table 2: Comparing First Line Anti-TB Drugs.

Name	Mechanism of Action	Route of Administration	Key Side Effects	Special Notes
Isoniazid	Inhibits mycolic acid synthesis	Oral	Peripheral neuropathy, hepatotoxicity	Vitamin B6 supplementation recommended
Rifampicin	Inhibits RNA polymerase	Oral	Hepatotoxicity, orange-red discoloration of body fluids	Potent inducer of drug-metabolizing enzymes
Ethambutol	Inhibits arabinosyl transferase	Oral	Optic neuritis	Requires dose adjustment in renal impairment
Pyrazinamide	--------	Oral	Hepatotoxicity, hyperuricemia	Caution in patients with gout

Immunomodulators and Adjunctive Therapy

While most TB research focuses on drugs that directly kill the bacteria, another promising area is immunomodulators and adjunctive therapy. These treatments don't kill the bacteria themselves but instead help the patient's own immune system to fight against the infection more effectively. The TB bacteria have evolved in a clever ways to hide from and manipulate the host's immune system, often living inside the immune cells called macrophages. An immunomodulator is a substance that can change or regulate the immune response. By using immunomodulators, scientists hopes to create an environment where the body's immune system could better recognize and destroy the TB bacteria. For example, some immunomodulators could enhances the function of macrophages, making them more effective at killing the bacteria they have engulfed [72].

Adjunctive therapy refers to any treatment that is given in addition to the primary anti-TB drugs to improve the outcome. The goal is to help the primary drugs work better or to reduce the harm caused by the infection. For example, some adjunctive therapies might help reduce the inflammation in the lungs caused by the TB infection, which can lead to permanent damage even after the bacteria are gone. Other therapies are focused on boosting the overall immune response. A scientific example is with the use of vitamin D, which has been shown in some studies to have immunomodulatory effects that could help the body to fight TB. The use of these therapies in combination with traditional drugs holds great a promise for not only curing the disease more quickly but also for preventing the long-term damage to the lungs and improving the overall health of the patient [73].

Resistance and Pharmacokinetics

The global fight against tuberculosis (TB) is severely complicated by the rise of drug resistance. Resistance occurs when the TB bacteria evolve it's genetic mutations that allow them to survive the drugs which are designed to kill them. This happens most often when patients don't complete their full course of treatment, which gives the few surviving bacteria a chance to multiply and pass on their resistance genes. Understanding the molecular functioning mechanisms behind this resistance is crucial for developing new drugs. For example, resistance to the drug isoniazid often results from a mutation in a gene called katG, which is needed to activate the drug. Similarly, resistance to rifampicin is most often caused by mutations in the rpoB gene, which codes for the enzyme that rifampicin targets [74].

The rise of MDR-TB (multidrug-resistant TB), which is resistant to at least the two most powerful first-line drugs, and XDR-TB (extensively drug-resistant TB), which is resistant to a wider range of drugs, poses a major public health crisis. These resistant forms are much harder to treat, also require longer and more toxic drug regimens, and have lower cure rates. To combat this, researchers are developing new drugs that are not affected by the common resistance mutations and are also creating rapid diagnostic tests that can identify resistance mutations in a matter of hours, allowing doctors to quickly prescribe the correct treatment [75].

MDR and XDR TB: Molecular Mechanisms

Multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant TB (XDR-TB) are major global health challenges. MDR-TB is resistant to at least isoniazid and rifampicin, the two most powerful first-line TB drugs. XDR-TB is resistant to these plus any fluoroquinolone and at least one second-line injectable drug, such as amikacin, kanamycin, or capreomycin. These resistant forms of TB arise due to genetic mutations in the Mycobacterium tuberculosis genome. The improper use of TB drugs such as incorrect dosing, early discontinuation, or poor-quality medications increases the risk of this type of mutations [76].

Mutations can occur in various genes:

- katG and inhA mutations cause resistance to isoniazid.
- rpoB mutations result in rifampicin resistance.
- gyrA/gyrB mutations affect fluoroquinolones.
- rrs and eis genes contribute to resistance against aminoglycosides [77].

In 2023, about 10.8 million people were affected by TB over the whole world. India alone contributed around 2.8% of MDR-TB cases among new TB patients and 12–17% in retreatment cases. Cases of totally drug-resistant TB (TDR-TB), also called XXDR or XXXDR-TB, have been reported, particularly in India, Russia, and South Africa [78]. These cases does not respondes even to the newer drugs like bedaquiline and delamanid. Resistance spreads due to improper treatment, lack of adherence, and failure of health systems to diagnose and monitor TB effectively. Molecular tests like GeneXpert and Line Probe Assays (LPA) helps in the early detection of drug-resistant TB by identifying the resistance-conferring mutations directly from the sputum samples [79].

MDR and XDR-TB are life-threatening and often requires prolonged treatment with second-line or new drugs. The treatment is expensive, more toxic, and less effective than first-line therapy. Patients might often experience severe side effects, and success rates are much lower in compared to drug-sensitive TB. The World Health Organization (WHO) recommends rapid diagnosis and use of shorter, all-oral regimens when ever its possible. Strengthening TB control programs, ensuring patient adherence, and investing in new drug development are essential to stop the spread of drug-resistant TB [80].

Drug Metabolism and Enzyme Interactions

The effectiveness of anti-TB drugs is not only about how they kill bacteria, but also about how the human body processes them, a science known as pharmacokinetics. A key part of pharmacokinetics is drug metabolism, which is the process by which the body breaks down a drug. Many drugs are metabolized by enzymes in the liver, such as the cytochrome P450 (CYP450) family of enzymes [81]. For example, rifampicin is a powerful inducer of these enzymes, which means it speeds up the rate at which the body breaks down the other drugs. This can be a significant problem for patients on TB treatment, as they often have other health issues and may be taking other medications. Rifampicin can cause a interaction with drug that they are taking for HIV, diabetes, or epilepsy, leads to broken down too quickly and speeds up their elimination, making them ineffective [82].

These enzyme interactions could be a serious clinical challenge. Doctors needs to be aware of all the medications a patient is taking to adjust the doses and prevent possible dangerous interactions. For example, a patient on rifampicin may need a higher dose of their other medications to compensate for the faster breakdown. Similarly, some drugs can inhibit these enzymes, causing other medications to accumulate in the body to toxic levels [83]. This is why a complete drug history is essential for every TB patient. Research into new anti-TB drugs are now focused on finding agents that have fewer interactions with the body's metabolic enzymes. This would simplify treatment, reduce the need for dose adjustments, and make TB therapy safer for patients with other health conditions [84].

Therapeutic Drug Monitoring (TDM)

Even when a patient is taking their medication correctly, the amount of a drug in their body can vary widely from person to person. This is due to differences in metabolism, body weight, genetics, and other factors. Therapeutic Drug Monitoring (TDM) is a scientific practice that helps the doctors to ensure that the drug concentration in a patient's blood is within the ideal range, it should be high enough to be effective but not so high as to cause toxicity. For TB, TDM involves taking a blood sample at a specific time after a patient has taken their medication and then measuring the concentration of the drug. If the concentration is too low, the patient might not be getting a full therapeutic effect, and the bacteria could develop resistance [85]. If it's too high, they are at a greater risk of severe side effects. TDM is especially important for patients with drug-resistant TB, children, the elderly, and those with other health conditions like HIV or liver disease. In these cases, the standard dose may not be appropriate. For example, a child has faster metabolism which might break down the drug more quickly, leads to requirements for a higher dose. TDM allows doctors to personalize the dose for each patient based on their individual needs, rather than relying on a one-size-fits-

all approach. While it is not a standard practice for all TB patients due to its cost and logistics, TDM is becoming an increasingly valuable tool for managing the complex cases, helping to improve the cure rates and reduces side effects by optimizing drug dosages based on scientific data [86].

Host Pathogen Interaction and Drug Efficacy

The battle against tuberculosis is not just about a drug killing a bacterium; it is a complex interaction between the host (the human patient), the pathogen (M. tuberculosis), and the drug. The effectiveness of a drug is heavily influenced by this interaction. The bacteria's ability to survive and multiply plays a major factor, but so is the patient's immune response. For example, if the TB bacteria can live inside the patient's immune cells, which make it difficult for the drugs to reach them. A weak or compromised immune system, which are seen in patients with HIV, can also make it much harder for the body to control the infection, even with proper drug treatment [87].

Drug efficacy, therefore, is not simply a scale to measure how well a drug kills the bacteria in a test tube. It is a measure of how well it works in the patient's body, where the bacteria are hidden and the patient's immune system is also responsible [88]. Researchers are now looking at ways to use this knowledge to develop new treatments. For example, some research is focused on developing drugs that can better penetrate the immune cells where the bacteria are hiding. Other research is focused on host-directed therapies, which are treatments that don't kill the bacteria directly but instead it strengthens the patient's immune response to help them fight against the infection more effectively. Understanding this complex host pathogen drug dynamic is critical for the development of next generation of TB treatments that are more effective and can lead to a faster cure [89].

Future Directions in Pharmacological Research

The future of pharmacological research for tuberculosis (TB) is moving beyond simply finding any new drugs to kill the bacteria. Scientists are now focusing on more sophisticated and personalized approaches that take into an account of the unique genetic makeup of each patient and the complex interaction between the human body and the TB bacteria [90]. This new direction is driven by the need to combat drug resistance, shorten treatment, and create therapies that are safer and more effective for every individual. It involves integrating advance genetic information, with the using of new technologies to deliver drugs, and developing treatments that work with the patient's own immune system to clear the infection [91].

Personalized Medicine in TB

Personalized medicine, also known as precision medicine, this an innovative approach to healthcare that tailor's medical treatment to the individual characteristics of each individual patient. For tuberculosis, this means moving away from a one size fits all approach and instead using a patient's genetic information, we take the specific strain of TB they have, and their individual health profile to design the most effective treatment plan. The goal is to maximize the drug's effectiveness while minimizing the side effects [92]. For example, a genetic test could identify a patient who metabolizes a certain drug too quickly, allowing a doctor to prescribe a higher dose from the beginning, or a different drug entirely. This prevents the patient from receiving an ineffective dose and potentially developing drug resistance [93].

Another aspect of personalized medicine is to using rapid molecular diagnostics to quickly identify the specific genes that makes a TB strain resistant to the certain drugs. This allows doctors to bypass the long, multi-drug regimen and immediately start a more targeted and effective treatment [94]. In the future, a patient could have their genetic profile and the genetic profile of their TB strain would analyzed, and a computer program could recommend the optimal combination and dose of drugs suitable for them. This would not only lead to better cure rates but also shorten the treatment duration and reduces the burden on the patient [95].

Pharmacogenomics and Individual Response

Pharmacogenomics is the study of how a person's genes affect their response to drugs. This field is a cornerstone of personalized medicine and holds great promises for improving TB treatment. For example, some people have genetic variations that might cause their liver enzymes to break down a drug much faster or slower than the average rate [96]. A person with a genetic variation that will lead them to break down a drug too quickly may not have enough of the medication in their system to kill the bacteria, which leads to treatment failure. Conversely, someone who breaks down the drug too slowly could have it accumulate to toxic levels, causing severe side effects like liver damage [97]. By understanding these genetic differences, doctors can use pharmacogenomic testing to predict how a patient will respond to a specific drug. Scientific studies have already identified some of the key genes involved in the metabolism of anti-TB drugs like isoniazid and rifampicin. In the future, a simple blood test could

identify these genetic variations, which allow doctors to adjust the dose of a drug to make it safer and more effective for that specific patient. This would reduce the trial and error approach of modern medicine, minimize side effects, and improve the chances of a successful cure for all patients [98].

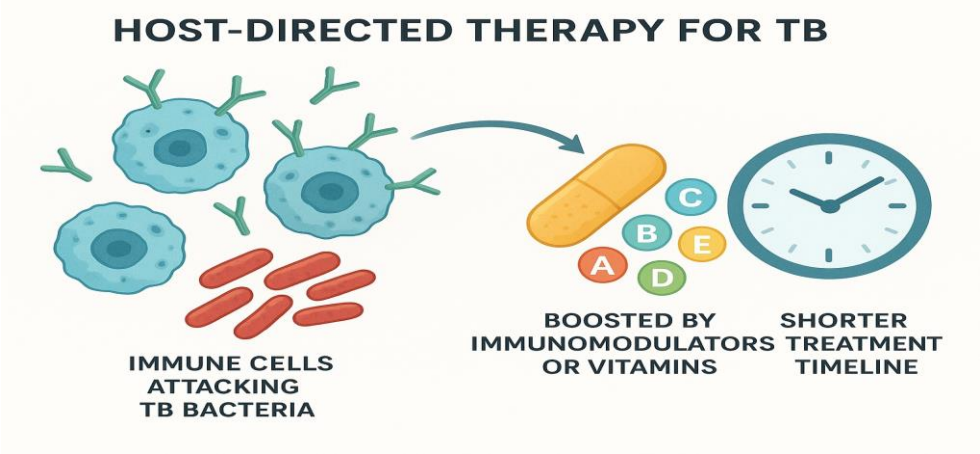

Figure 5: Host Directed Therapy and Immune Boosters

Host Directed Therapy and Immune Boosters

Instead of just focusing on drugs that directly attack the TB bacteria, there is an emerging area of research is host-directed therapy (HDT). HDT is a strategy that aims to improve the patient's own immune response to the infection, which makes the body a more hostile environment for the bacteria. The TB bacteria are very good at manipulating the immune system to survive, they often hides inside immune cells called macrophages. HDT aims to reverse this by boosting the function of these immune cells, making them more effective at killing the bacteria they have engulfed. For example, some research is exploring the use of vitamins or other natural compounds to modulate the immune response [99].

Immune boosters are a part of this strategy. They are substances that could enhance the patient's immune system to help fight against the infection. For example, a patient with a weakened immune system could be given an immune booster in addition to their anti-TB drugs. This combined approach could lead to a faster cure and reduce the chance of a relapse. The ultimate goal of HDT and immune boosters is to shorten the duration of treatment, reduce the reliance on long courses of antibiotics, and prevent the long-term damage that the infection could cause. By working with the body's own natural defenses, these therapies offer a new and exciting way to fight TB [100].

Abbreviations

TB: Tuberculosis; MDR-TB: Multidrug-Resistant Tuberculosis; XDR-TB: Extensively Drug-Resistant Tuberculosis; TDR-TB: Totally Drug-Resistant Tuberculosis; INH: Isoniazid; RIF: Rifampicin; PZA: Pyrazinamide; EMB: Ethambutol; Km: Kanamycin; Am: Amikacin; Cm: Capreomycin; PAS: Para-Aminosalicylic Acid; BDQ: Bedaquiline; DLM: Delamanid; PA: Pretomanid.

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