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The TB Enigma: Cracking the Code with a Multifaceted Approach

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Abstract

Tuberculosis (TB) is a major global health challenge, even though it is considered a preventable disease. This situation is made worse by the emergence of multidrug-resistant (MDR-TB) and extensively drug-resistant (XDR-TB) strains. In addition, there are several reasons why standard treatment efficacies are often lowered, including long courses of therapy, significant systemic toxicities, and diagnosis that is too late. The recent 2025 WHO Global Tuberculosis Report predicts that 10.6-10.8 million new cases of tuberculosis occurred world-wide resulting in 1.3 million deaths (as estimated from the disease distribution profile). In India, almost 27% of the world's TB cases occur with the yearly TB case notifications being greater than 2.4 million. Contemporary management rests on specific molecular targets (RNA polymerase transcription, cell wall synthesis using mycolic acid and inhibition of mycobacterial ATP synthase) while tackling the multidrug resistance, toxicities and numerous drug-drug interactions. The present article explores the challenging nature of the immune response and the course of TB infection, and the inadequacies of current first and second-line drugs which have, among other things, limited therapeutic windows and serious drug-drug interactions. Then again, new drugs like Bedaquiline and Delamanid are a major clinical breakthrough in the treatment of resistant strains of TB. Besides introducing new drugs to the arsenal, more sophisticated nanotechnology-based drug delivery systems designed for active targeting of infected macrophages hold a high promise as strategies to increase drug levels at the sites of infection, shorten drug half-life, reduce the frequency of administration and, most importantly, these targeting strategies will help to decrease un-wanted drug exposure of healthy cells leading to fewer side effects. In addition, natural compounds from medicinal plants and host-targeted immunomodulatory agents are very effective in strengthening the immune system and these may help to reduce the side effects of drugs. Concurrently, this comprehensive, multi-pronged approach provides a decisive roadmap to bridge current therapeutic gaps and fast-track the global elimination of TB.

Keywords: *Mycobacterium tuberculosis (Mtb), Drug-resistant TB, Plant-based Treatment, Nanotechnology, Rapid diagnosis*

1. Introduction

Today, most medications are still First and foremost focused on repairing molecular disorders and alleviating symptoms of long-term illnesses. Some of the drugs can even cure those physically disabling diseases. But traditionally the medicines are tied to a series of serious and sometimes very harsh side effects. Globally, one-fourth of the humans are infected with tuberculosis, or TB. It is a long-lasting lung disease and one of the symptoms is that the breathing becomes hard. In fact, TB is the reason why about two million people die every year. Naturally, one of the global health concerns post COVID-19 pandemic is Really TB infections can remain continuous in people whose immune systems are weakened. From the research of a group of international researchers, seems like TB-related deaths will probably see a 26% rise in the next few years, resulting in as many as 1.4 million extra deaths that can be directly attributed to the pandemic.

The issue of humans contracting TB is one of the most difficult problems and it has even got worse globally mainly after the arrival of the 21st century. The bacterium that causes tuberculosis is named *Mycobacterium tuberculosis* and, as per the knowledge that we have been able to gather, it employs various mechanisms to enable itself to live inside the different tissues of the host. The first time that the pathogen *Mycobacterium tuberculosis* was discovered was by Robert Koch in 1882. A person becomes infected with tuberculosis via the bacteria. M. leprae is one of the mycobacteria and it is the one causing human leprosy. Besides this, there are also atypical mycobacteria but their capability of infecting humans is very limited. In most cases, they infect individuals with weakened immune systems or already diseased organs. Not only lungs, but tuberculosis can also lead to an infection of other body parts. For example, the spine, brain, and kidneys are some of the areas that can be affected. Normally, TB mainly affects the lungs but it can also cause problems in other parts of the body.

The phases of TB infection are summarized in the following figure:

A : Lung macrophages ingest and absorb TB germs.

B : By adjusting to the harsh surroundings, bacteria are able to live inside macrophages.

C : To keep the infection under control, immune cells create a granuloma.

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D : Bacteria can breach the granuloma and destroy tissue if immunity deteriorates.

E : When a granuloma bursts, it released all the germs into the airways and then it can spread to other people via cough. (Figure 1)

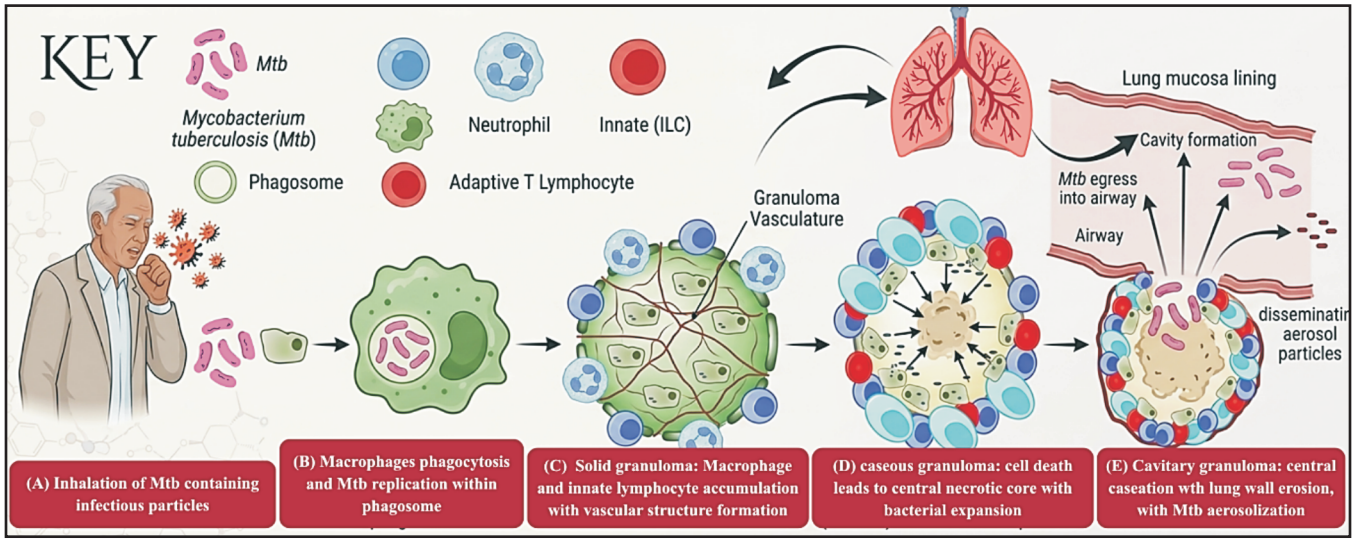


Figure 1: *Simplified depiction of the Mtb (Mycobacterium tuberculosis) lifecycle.*

The name “Tuberculosis” comes from a Latin origin which means "nodule or protrusion". Inactive or latent tuberculosis infection is a globally known yet infectious condition that occurs when an individual has the presence of bacteria inside their body but shows no symptoms. Although TB may appear to have disappeared, it is actually inactive, or sleeping, inside the body. Even though a TB infection does not usually cause sickness, therapy is necessary if it does. Despite its apparent disappearance, TB remains in the body, dormant and dormant. A person is diagnosed with active TB, also known as tuberculosis, when they are infected, exhibiting symptoms, and capable of spreading the illness.

Through the air, tuberculosis is spread. It is impossible for the illness to spread from one person to another unless the bacterial droplets are inhaled. According to this, if someone spend a lot of time with an infectious person, suffering from tuberculosis (TB), it increases the risk of contracting the disease [1].

History states that TB initially appeared in antiquity and continued to exist in an unexpected manner until the seventeenth century. Approximately 8,000,000 individuals have MTB annually, and 2–3 million of those cases end in mortality [2]. Only cases of active tuberculosis are discussed, and the adverse consequences associated with ongoing TB therapy are not addressed. In recent years, there has been a general rapid increase in the search for a new supply of TB drugs due to the rise of multidrug-resistant TB [3]. Traditional remedies utilized in South Asia and Africa represent Native American knowledge of medicinal plants and plant-based products that have been used to heal a number of ailments, including TB. The map emphasizes the significance of focused efforts as well as geographical differences in the burden of TB (Figure 2).

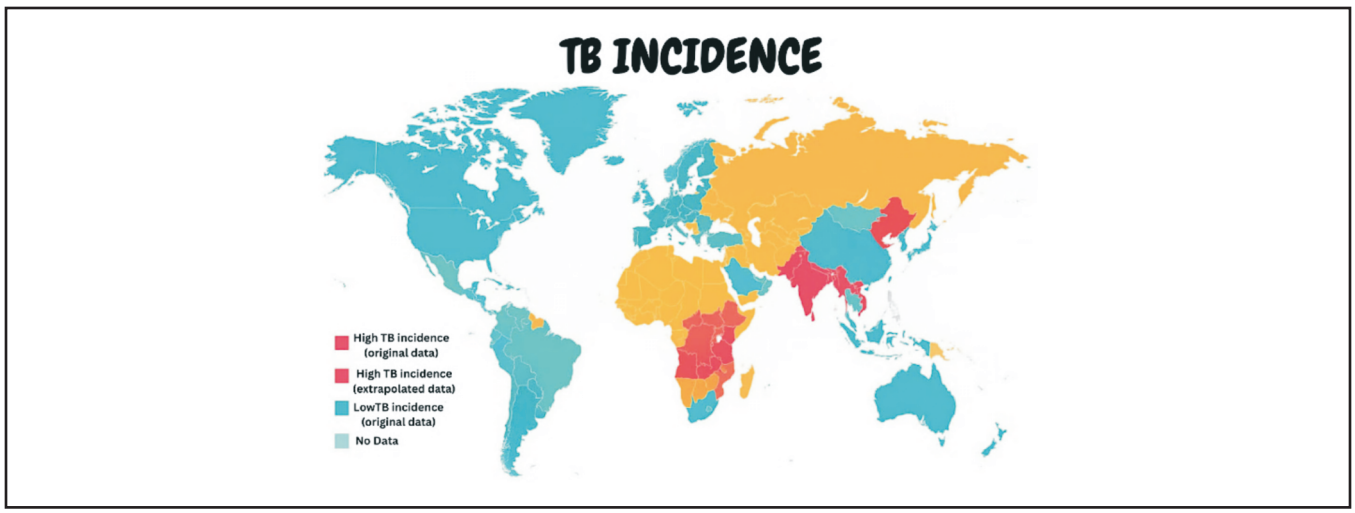


Figure 2: *The incidence of TB worldwide by nation*

2020 saw a steep decline in both America and East Asia, with a mediocre recovery rate in 2021. Ayurveda as a system of medicine is well known for its comprehensive and all-round way of healing by giving due importance to the physical, mental and emotional health of the individual Using Ayurvedic medicines for tuberculosis is based on the concept that the 3 doshas or bio-energies of the body, when disturbed, cause the disease. That means, the main objective of Ayurvedic treatment for TB is to enhance the immune status of the individual and restore the whole body to its natural state of balance. Various methods may be utilized to treat the disease, including the use of herbal medicines, changes in lifestyle and diet. Finally, lifestyle changes might include yoga meditation stress management, and getting proper sleep [4,5]. Based on the Global Tuberculosis Report (2022), the progress made so far in the fight against TB has been hampered by the emergence of the COVID-19 The coronavirus has had a detrimental effect on the diagnosis and treatment of tuberculosis. There were actually more cases of TB in 2020 than in 2019, 2020 witnessed a drastic decline in both America and East Asia, with a slow recovery rate in 2021.

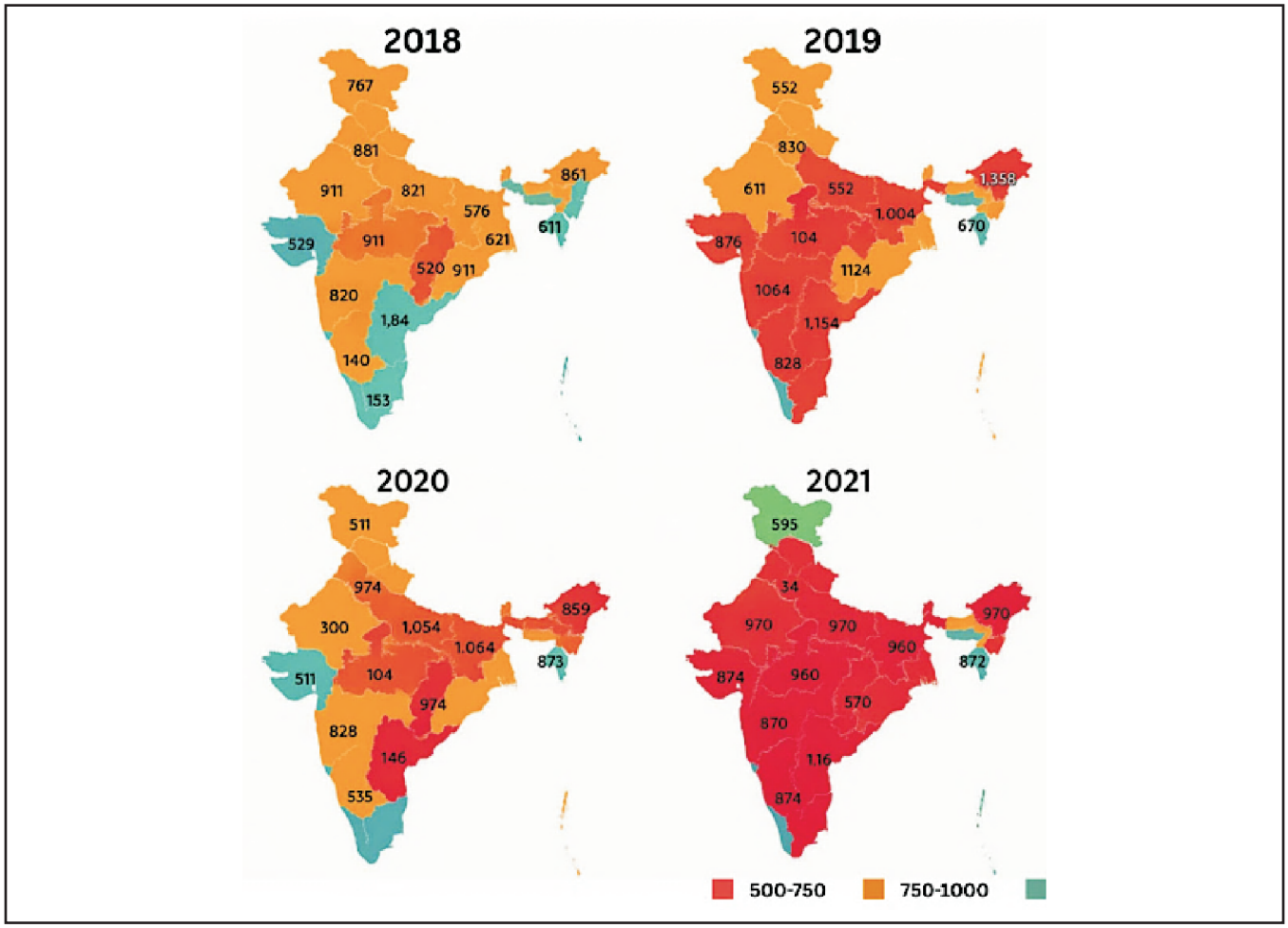


Figure 3: *Rate of Tuberculosis Testing (number of tests per lakh people)*

The image shows the annual TB case notification rates of each state in India from 2018 to 2021 revealing a steady increasing trend and expansion of areas with high TB incidence. It further draws attention to the geographic spread and mounting TB burden in particular parts of central and eastern India (Figure 3).

Multidrug resistant (MDR-TB) and extremely drug resistant (XDR-TB) strains of tuberculosis (TB) are currently making the epidemic worse, and there are fewer treatment options available because at least three effective drugs must be used in combination to successfully treat the disease while preventing the development of additional drug resistance (Figure 4). A novel method of action – combination dosing with isoniazid (INH) and rifampicin – was employed in the most recent drug therapy discovered and approved for the treatment of tuberculosis (TB). MDR-TB, however, is resistant to both RIF and INH. Either an initial infection with a drug-resistant bacterial strain or inadequate treatment durations or regimens are the causes of MDR-TB and XDR-TB infections. It is important to develop many effective medicines that can be used in conjunction with medications for other chronic illnesses, reduce treatment time, be effective against MDR-TB and XDR-TB strains, and require fewer doses. The primary objective of this review is to evaluate current therapeutic bottlenecks in TB management – specifically molecular drug resistance, treatment toxicities, and drug-drug interactions – and to synthesize how next-generation therapeutics, genomic surveillance, targeted nanocarrier drug delivery, and plant-derived host-directed immunomodulators synergize to provide a comprehensive roadmap toward TB elimination.

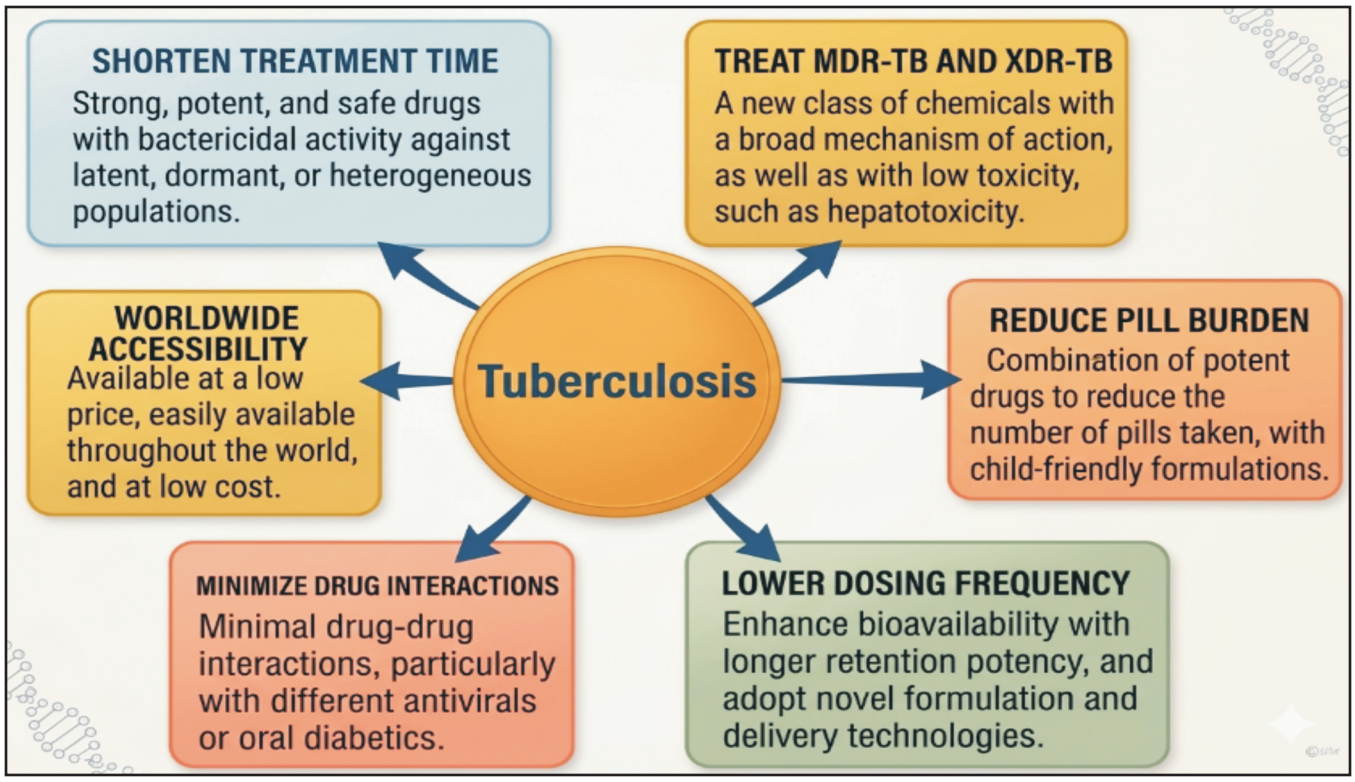


Figure 4: *The Desired efficacy profile of TB Drugs*

2. Anti-Tubercular Drugs

According to the FDA, only rifampin isoniazid pyrazinamide, and ethambutol have been officially approved for treatment of *Mycobacterium tuberculosis* infections. TB treatment usually involves a combination of different drugs, referred to as antituberculars [6]. The right combination of drugs and length of treatment depend on whether a person has an active or latent form of TB. One of the major problems in treating TB is the emergence of multi-drug-resistant TB. MDR-TB is characterized by Truth is it is resistant to both isoniazid and rifampin, which happen to be the two most important drugs in TB treatment [7]. Besides being limited in number, the treatment regimens for MDR-TB are also in a state of flux as new treatment guidelines continue to be devised. Amikacin, capreomycin, and kanamycin are injectable second-line drugs most frequently used for MDR-TB. Fluoroquinolones like levofloxacin, moxifloxacin, and gatifloxacin are the usual second line drugs that are deployed when the first-line drugs fail [8]. Recently, Pretomanid has been given FDA nod for treating multi-drug resistant tuberculosis with bedaquiline and linezolid. XDR-TB or extensively multi-drug resistant tuberculosis is a much rarer and more lethal version of MDR-TB. This disease is resistant to all fluoroquinolones, one second-line aminoglycoside, and also the major drugs isoniazid and rifampin [11].

First-line Drugs:

When it comes to treating tuberculosis, first-line therapeutic medications are the most efficient and least harmful. The term "first-line therapeutic drugs" refers to the four necessary medications used to treat mycobacterial infections.

- Ethambutol
- Isoniazid
- Rifampin
- Pyrazinamide

Second-line Drugs:

The therapeutic medications used to treat *Mycobacterium TB* infections are expensive, less effective, and more hazardous than first-line medications.

- Amikacin
- Moxifloxacin
- Streptomycin
- Kanamycin (discontinued usage in the USA)
- Levofloxacin
- Gatifloxacin
- Capreomycin

(MDR-TB)

- Pretomanid
- Delamanid
- Linezolid
- Bedaquiline

2.1 Mechanism of Action:

2.1.1 *Rifampin*

For treatment of tuberculosis infections in general, rifampin (Figure 5), rifapentine and rifabutin have been often chosen as first-line drugs in association with other medications. The use of RIF with PZA/INH to produce short therapy regimens led to the reduction of conventional TB treatment duration from a year to six months. They think that RIF acts as an inhibitor of bacterial DNA-dependent RNA polymerase. In fact, RNA polymerase consists of four subunits: α, β, β', and σ are encoded by the genes rpoA rpoB rpoC, and rpoD respectively. Through binding to the subunit of RNA polymerase and interfering with RNA synthesis, RMP leads to inhibition of transcription, death of organism. Resistance to RIF results from missense mutations in the genes. [12,13]

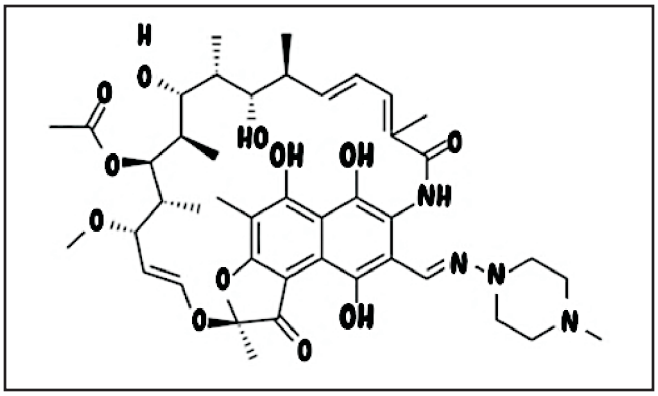


Figure 5: *Molecular structure of Rifampin*

2.1.2 *Isoniazid*

Tuberculosis (TB) and related latent infections have long been treated with Isoniazid (INH), as shown in (Figure 6) since it was released as an anti-TB medication in 1951. A pro-drug called INH is converted into its active form in the cell by the enzyme catalase-peroxidase, the gene for which is katG. The enzyme's peroxidase activity is responsible for both INH activation and its subsequent ability to interact with different toxic reactive species inside the bacterial cell. These reactive species generally contain organic fragments, hydroxyl radicals, and oxides which damage the cell wall's components leading to the loss of the cell's integrity and bacterial death. Resistance to INH develops at a much higher rate than resistance to most other anti-TB drugs. Experts say the primary target of INH is the enzyme InhA (enoyl-acyl carrier protein reductase), which plays a role in the fatty acid elongation process for mycolic acid synthesis [14].

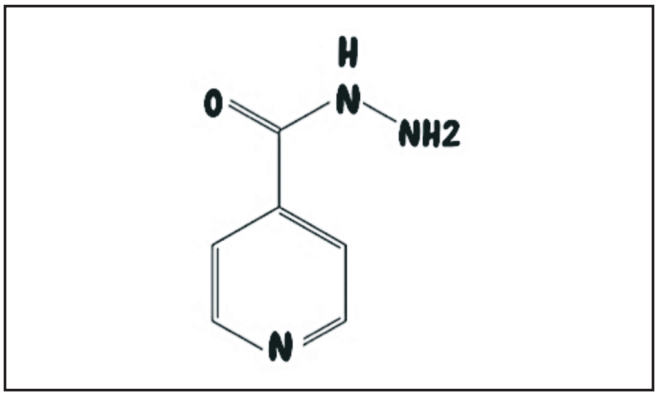


Figure 6: *Molecular structure of Isoniazid*

It seems that changing an amino acid to InhA's NADH binding site leads to INH resistance causing the inhibition of mycolic acid production to be blocked. Combining with catalase-peroxidase, isoniazid changes to its active metabolite capable of inhibiting mycolic acid formation [15].

2.1.3 *Pyrazinamide*

A major first-line drug against tuberculosis is PZA (Figure 7). one of its main effects is to kill inactive tubercle bacilli. Massive PZA buildup in the bacterial cytoplasm is made possible by the mycobacterial cell's ineffective efflux mechanism, which disrupts the membrane potential. It's still unclear exactly how PZA resistance works [16,17].

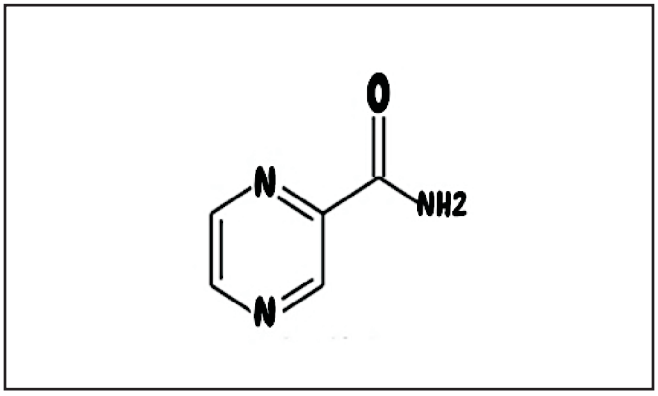


Figure 7: *Molecular structure of Pyrazinamide*

2.1.4 *Ethambutol*

Ethambutol (EMB) is one of the four first-line anti-tuberculosis drugs working with INH, RIF and PZA to avoid the emergence of bacteria that are resistant to only one antibiotic. EMB does not kill bacteria in the dormant phase and only stops multiplying bacteria from growing further. Ethambutol targets the arabinosyl-transferase enzyme involved in the production of the cell wall and because of this prevents the growth of bacilli. Ethambutol acts directly on the cell wall synthesis by disrupting the mycobacteria cell wall synthetically (Figure 8). Based on some scientist the impact of EMB on tuberculosis bacillus is through direct inhibition of arabinosyl-transferase which is the enzyme responsible for synthesizing the bacterial cell wall. Most of the time EMB resistance is caused by spontaneous random

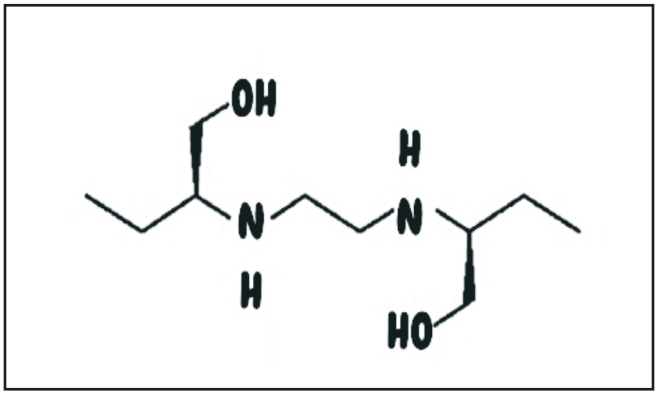


Figure 8: *Molecular structure of Ethambutol*

genetic mutation occurring at a frequency of about 1 in 107 organisms. The genetic mutation most often causes the enzymatic up-regulation of arabinosyl-transferase which in turn neutralizes the action of EMB. Ethambutol inhibits the enzyme arabinosyl transferase, which leads to the cessation of the biosynthesis of the cell wall of mycobacteria. [18].

2.1.5 *Aminoglycosides (Streptomycin, Kanamycin, Amikacin)*

The primary mechanism of action of aminoglycosides is their binding to the aminoacyl site of 16S ribosomal RNA within the 30S ribosomal subunit, leading to confusion in the decoding of genetic information and inhibition of translocation. As the fidelity of translation is compromised, elongation is stopped, even though the initial activities required for peptide synthesis, like mRNA attachment and binding of the 50S ribosomal subunit, continue normally. The antibacterial effect is usually bactericidal against aerobic gram-negative bacteria that are sensitive. Aminoglycosides accomplish this by binding to the 30S portion of ribosomes, thereby inhibiting protein production in mycobacteria [19,20].

2.1.6 *Fluoroquinolones (Levofloxacin, Moxifloxacin, Gatifloxacin)*

Fluoroquinolones disrupt bacterial DNA gyrase and topoisomerase IV, two enzymes that support the maintenance of DNA supercoiling, with different levels of effectiveness. Small doses of these drugs interfere with DNA replication; high doses but lead to cell death. Lately, the main target of fluoroquinolones in Gram-negative bacteria is DNA gyrase while topoisomerase IV is the primary target in Gram-positive bacteria. Because of this, the actual scenario depends not only on bacterial species but also on a specific drug. DNA gyrase and topoisomerase IV make enzyme DNA complexes by first creating a covalent bond with the DNA. In this reaction, the enzyme induces a transient double-strand DNA break by breaking and re-joining the DNA segments.

Adding a fluoroquinolone makes the complex a drug enzyme DNA complex (also called a ternary complex) which locks type II topoisomerase bound to DNA. A way of fluorquinolones' mechanism is to inhibit DNA gyrase and topoisomerase IV so that the bacterium is unable to synthesize new DNA. Rifampin isoniazid pyrazinamide, and ethambutol are the first-line drugs that, apart from other activities, inhibit replication of bacterial RNA, block production of mycolic acid, interfere with synthesis of coenzymes, and stop the construction of the cell wall. The main targets of aminoglycosides and fluoroquinolones, which are second-line drugs, are protein synthesis and DNA synthesis, respectively. Also, the table highlights different toxicity profiles of various drugs and, Because of this, the requirement for precise monitoring of TB treatment [23,24].

Table 1: *Table depicts the TB medications along with their mechanism and effects*

Drugs	Treatment	Molecular Formula	Mechanism of Action	Adverse Effect
Rifampin	First Line	C43H58N4O12	DNA-dependent RNA polymerase is inhibited reversibly, which also hinders the synthesis of bacterial proteins.	Liver toxicity, Low platelet count, Neutropenia, orange/red tint in bodily fluids, CYP450 inducer.
Isoniazid	First Line	C6H7N3O	Stop the production of mycolic acid and change it to its active metabolite form through catalase peroxidase.	Hepatotoxicity, VitaminB6 deficiency, Peripheral Neuropathy
Pyranzinamid	First Line	C5H5N3O	Inhibits coenzyme synthesis and trans-translation, both of which are essential for bacterial survival.	Hepatotoxicity, Hyperuricemia, Arthralgia
Ethambutol	First Line	C10H24N2O2	Inhibits arabinosyltransferases and stops the bacterial cell wall from being biosynthesised.	Optic neuropathy, Hepatotoxicity
Aminoglycosides (Streptomycin, kanamycin, Amikacin)	Second Line	C38H64N8O14	Binds to the ribosome's 30s subunit and prevents mycobacterial protein production.	Ototoxicity, Nephrotoxicity
Fluoroquinolones (Levofloxacin, Moxifloxacin, Gatifloxacin)	Second Line	C9H6FNO	Inhibits bacterial DNA synthesis as well as DNA gyrase and topoisomerase IV.	Tendonitis, Tendon rupture, Arthropathy

2.2 Drug Resistance Mechanism

Resistance to INH has an important primary component due to mutations in the katG gene (most commonly the Ser315Thr SNV) which causes structural loss of the catalase-peroxidase enzyme activity necessary for pro-drug activation into the reactive acyl radical. Another effect of promoter region mutations (like c-15t) in inhA is to cause InhA target overexpression, thereby producing low-level resistance, while secondary mutations in ahpC and kasA also cause drug tolerance. Resistance to RIF is first and

foremost and unequivocally caused by a SNV in an 81-base-pair section of the rpoB gene (codons 425452), the RIF Resistance-Determining-Region (RRDR). Point mutations at codons Ser531Leu, His526Y/D, and Asp516V modify the steric binding cavity of the bacterial RNA -subunit, rendering the method of transcription inhibition futile. These resistance determinants have profound implications, causing treatment failures, requiring lengthy second-line regiments, and helping the evolution of Multidrug-Resistant (MDR-TB) and Extensively Drug-Resistant TB (XDR-TB).

3. National Initiatives for TB Elimination in India

In response to a major disease burden in the country, the NTEP has aimed for worldwide elimination of TB as a public health threat through comprehensive feasibility projects. A few essential elements of this national program are:

- Ni-kshay Portal: an integrated web-based platform for patient management, which gives a set of online modules for case reporting, direct benefit transfers, and drug adherence monitoring in real time, among others.
- Ni-Kshay Poshan Yojana (NPY):is a Direct Benefit Transfer scheme of providing financial nutritional support of 500/month to the registered TB patients till the duration of their treatment.
- Nikshay.org Pradhan Mantri TB Mukt Bharat Abhiyaan: a community-led programme that empowers the community and organizations/individuals (Ni-kshay Mitras) to adopt TB patients and provide them with nutritional, diagnostic, and vocational support.
- Expanding Access: Self-coined "Fox-guarded henhouse" needing the creation of a spreadout network of the precision lab across all level of healthcare by the rapid, effective deployment of the automated cartridge-based nucleic acid amplification test (CBNAAT / GeneXpert) stations and the home-grown chip-based Truenat assay.

4. Challenges to Treatment

To properly treat all types of active TB disease, several antibiotics have to be given for quite a few months. Drug-susceptible, MDR, and XDR TB cases are treated with first-, second-, and third-line drugs correspondingly, which are authorized ones. On one hand, disease progression variability, host reactions, and drug resistance patterns not only make treatment and drug development very challenging but also provide chances to classify patient populations, and therapeutic and preventive strategies may be improved. Presently, infrastructure is capable of only moderately complex interventions since tuberculosis mostly affects poor countries. It makes the already difficult study even more difficult to undertake and carry out. One of the ways to get faster and long-lasting treatment is to pay attention to persistent and drug-resistant bacterial populations that are responsible for the features of active disease and drug-resistant nature of LTBI. Although scientists know quite well microenvironments and stress conditions at disease sites, treatment outcomes' dependence on these and also their clinical relevance are not fully understood. Based on assays developed by us, which can simulate immunological pressure, environmental factors and drug stress *in vitro* as well as *ex vivo*, it is known that *M. tuberculosis* changes itself to such conditions and this leads to lower drug susceptibility [25,26].

Ex vivo models achieve the closest mimic of *in vivo* conditions through methods utilizing explanted cavity caseum from rabbits and variously culturable *M. tuberculosis* obtained from patient sputum. These techniques are resource-heavy and mainly suitable for profiling authorized drugs and compounds in clinical development. Drug tolerance in intracellular *M. tuberculosis* remains inadequately understood for two main reasons. In experiments involving *M. tuberculosis* infection, different immortal cell lines and occasionally macrophages derived from primary blood or bone marrow monocytes are utilized, leading to differing levels of potency. Although *M. tuberculosis* exhibits approximately 100 times lower sensitivity to rifampicin in hypoxic lipid-loaded macrophages compared to normoxic THP-1-derived macrophages, immortalized macrophage-like cell lines are often used due to their cost-effectiveness and ease of upkeep [27,28]. A comparison of the efficacy of anti-TB medications in standard cell lines and infected primary macrophages does not exist. Secondly, it is increasingly recognized that polymorphonuclear leukocytes are vital and supportive in the persistence and growth of bacteria. Neutrophils seem to provide a secure haven and convey mycobacteria to macrophages while they can still damage host tissue, rather than eliminating them. The drug tolerance of *M. tuberculosis* residing within and around neutrophils and other granulocytes has not been assessed through any *in vivo* or *ex vivo* studies [29-32].

Drug-Drug Interactions (DDIs) probably the most important pharmacological hurdle in current TB drugs management, the potent host hepatic Cytochrome P450 (mainly 3A4) and P-glycoprotein (P-gp) induction by Rifampicin. At this level, as well as reduce by significant extent systemic bioavailability of protease inhibitors and non-Nucleoside reverse transcriptase inhibitors (NNRTIs) given as co-treatment of HIV+ TB patients, or oral hypoglycemics and extension newer anti-TB drugs such as Bedaquiline. Host Response: effective host defenses to infection with Mycobacterium tuberculosis depend on effective cell-mediated immune responses driven by a balanced Th1/Th17 response. Activation of alveolar macrophages by interferon-gamma (IFN-γ) and TNF-α induce phagolysosomal fusion and contain the infection by granuloma formation. Knowledge of host pathogen microenvironments informs strategies to develop Host Directed Therapies, which can augment macrophage autophagy and reduce host destructive pathology.

Simplifying and Improving Treatment of Drug-resistant Disease

The strong clinical drug candidate pipeline enables a movement toward developing pan-TB or universal treatment regimens for all forms of drug-susceptible and drug-resistant TB. An encouraging progression toward this ambitious goal is the success of the NIX-TB trial (NCT02333799), a six-month regimen involving three drugs that achieved notable cure rates in specific patient populations infected with MDR and XDR strains2. New diagnostic technologies are continually being developed to help doctors and health services understand data and treat patients more quickly and accurately, making drug-resistance profiling easier or

more precise. The WHO recently published a compilation of 17,000 mutations of *M. tuberculosis* and their association with drug resistance. The document provides a benchmark for understanding mutations that lead to resistance against various second-line drugs as well as all first-line drugs. It is utilized alongside SplitStrains, an advanced method that employs whole-genome sequencing data to identify and differentiate mixed *M. tuberculosis* infections with genetically varied strains. This event can lead to hetero-resistance and the subsequent treatment challenges [33]. The new toolbox allows for the detection, identification, and quantification of multiple infecting strains within a sample with increased precision. The primary challenge in eradicating drug-resistant TB, beyond the development of enhanced diagnostics, is pinpointing and formulating universal treatment plans that consist solely of medications featuring distinct mechanisms of action and limited side effects. These treatments might be employed for resistant TB and could potentially replace the first-line regimen. To achieve this, the Tuberculosis Drug Accelerator was created in 2011 as a project aimed at dismantling obstacles between competing labs and organizations to encourage collaboration in anti-TB drug development.

The Tuberculosis Drug Accelerator is a unique collaboration among universities, pharmaceutical firms, international NGOs, and government agencies that aims to reduce medication costs for those in need, enhance understanding, and strive to develop shorter, safer, universally applicable treatment protocols that can deliver a rapid, enduring cure irrespective of drug resistance [34].

XDR and MDR

The major obstacles now encountered by the community of drug developers are centered on substantially enhancing therapies for active MDR-TB and XDR-TB. Currently, MDR-TB is managed through a mix of various medications, with treatment durations ranging from 18 to 24 months, and only four of these drugs specifically created for TB treatment. Ineffective treatment results in nearly 30% of MDR-TB patients facing failure in therapy. The choices for treating XDR-TB are quite restricted since XDR-TB bacilli resist not only INH and RIF but also fluoroquinolones and injectable medications like aminoglycosides. Moreover, significant side effects are noted with many MDR-TB and XDR-TB medications, such as nephrotoxicity and ototoxicity from aminoglycosides, hepatotoxicity from ethionamide, and dysglycemia caused by gatifloxacin [35-37].

5. Evolving Treatment Protocols

Due to the combined efforts of government initiatives, non-profit organizations, and pharmaceutical companies, the initial approvals of new antitubercular drugs in nearly half a century have taken place recently. Recent years have seen the approval of new Mtb drugs, including bedaquiline and delamanid, marking the first regulatory clearances in decades. Both medications have obtained conditional approval due to documented side effects [delamanid by the European Medicines Agency (EMA) of the European Union] [38]. Bedaquiline for MDR-TB and delamanid as a compassionate care choice for XDR-TB and TDR-TB infections have received approval from the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), respectively (Figure 9). The reality is that these drugs present significant issues, including hERG toxicity challenges and various ADME concerns due to their elevated lipophilicity. The state of drug discovery in this field is indicated by the shortage of effective alternatives in advanced clinical development stages, highlighting an urgent requirement for innovation to drive new initiatives [39]. This research focuses on new classes of medications that have demonstrated efficacy in vivo and are set to commence clinical trials.

We emphasize the possible advantages of focusing on MDR-TB in replicating and more dormant forms, the uniqueness of their mechanisms of action, and their potential for clinical application.

6. Next-Generation Drugs

a. Diarylquinolones and respiratory chain antagonists

The diarylquinolones represent the most advanced category of new antitubercular drugs. This group encompasses the newly approved bedaquiline. Bedaquiline significantly inhibits the essential ATP synthase function in both replicating and dormant mycobacteria, exhibiting high selectivity without impacting other prokaryotic or eukaryotic cells [40] [41]. The F0F1 ATP synthase rotor ring of the organism was found to be the target, specifically interacting with the c subunit, via the creation of drug-resistant mutants [42]. Mtb utilizes a pool of ATP produced by the F0F1 ATP synthase to maintain an energetic membrane for survival in a nonreplicating state [43]. Bedaquiline is, thus, an outstanding agent for eradicating the inactive Mtb subgroup. Bedaquiline is an important addition to an MDR-TB regimen as it operates differently from RIF and INH, as revealed by Janssen's phenotypic screening.

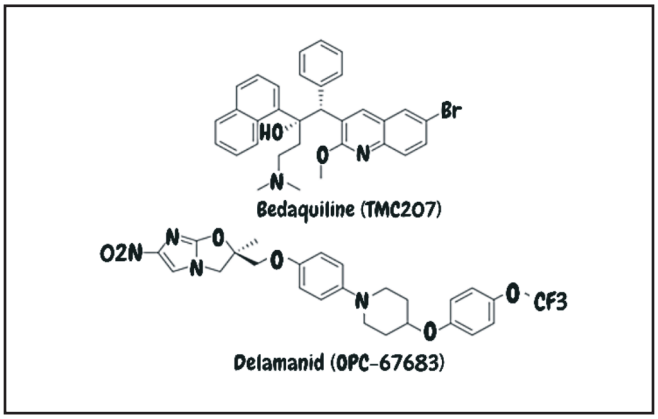


Figure 9: *Recently approved antitubercular agents developed specifically for MDR-TB infections*

The progress on the next-generation diarylquinolones, aimed at improving the drug's physicochemical properties and eliminating its cardiac risk, is still ongoing. Recent studies have been facilitated by the co-crystal structure of bedaquiline bound to its ATP synthase active site, which should enable structure-guided development of less toxic and more potent analogs [46]. Q203, an imidazopyridine drug for tuberculosis that also impacts

the respiratory chain, has recently started Phase I clinical trials as of this writing. In the cytochrome bc1 complex, Q203 interacts with the cytochrome b component (QcrB) (Figure 10). These values account for Q203's remarkable efficacy in chronic Mtb infection models and outshine bedaquiline's metrics. Q203, sponsored by Qurient Therapeutics (Gyeonggi-do, Korea), was discovered through a high-throughput screening (HTS) targeting infected human macrophages and subsequent medicinal chemistry refinement [47]. This screen identified 96 substances that might permeate and accumulate in the macrophage sufficiently to show growth inhibition based on the chemical's concentration. The imidazopyridine framework was selected due to its efficacy against clinical MDR-TB isolates and demonstrated activity in both free media and macrophages [48].

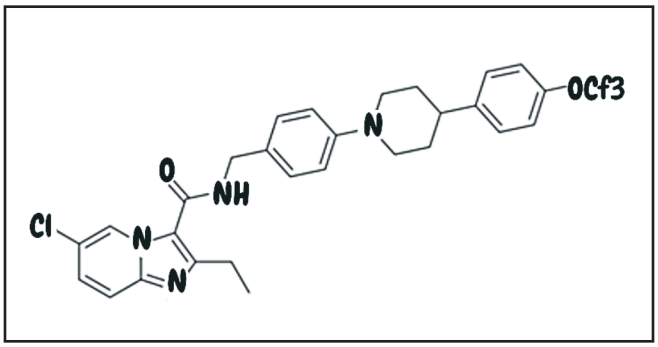


Figure 10: *Structure of Q203, shows strong efficacy against latent Mtb and is a promising candidate for inclusion in MDR-TB treatment protocols.*

b. InhA inhibitors

A key component of frontline TB therapy is isoniazid. The enoyl reductase InhA in mycobacteria, essential for producing mycolic acids—the main feature of the lipophilic—serves as its molecular target. Fatty acid biosynthesis (FAS) occurs via two distinct pathways; bacteria employ the FAS II mechanism, while humans utilize the FAS I route. Both pathways exist in mycobacteria, and FAS II comprises a distinct assortment of enzymes that contribute to the synthesis of very long mycolic acids. FASII enzymes can be utilized to develop drugs targeting Mycobacterium specificity, which is essential for formulating an MDR-TB treatment. The prodrug INH must be activated by the catalase–peroxidase KatG to inhibit InhA. During this bioactivation phase, Mtb primarily acquires resistance by inactivating this nonessential enzyme (Figure 11). Consequently, if the bioactivation process of new prodrugs for MDR-TB is similar to that of INH or other prodrugs currently utilized in TB treatment, like EMB and PZA, it is possible that these will encounter cross-resistance in patients with Mtb. Due to a structural alteration in helix 6 that occurs post the initial binding and does not occur with fast reversible inhibitors of InhA, the resulting INH–NAD adduct obstructs the enzyme and shows an impressive residence time [49–56].

According to Peter Tonge and others [57–59], residency duration is vital for drug development and lead optimization. Having a strong binding affinity alone is not enough. The biological activity *in vivo* is typically better demonstrated by how quickly the inhibitor dissociates from the enzyme [60]. In S. aureus, the ortholog of InhA, FabI, has been a major target for antibacterial structure-based drug studies, with at least two candidates progressing to clinical trials (NCT02426918) [61]. This data provides a valuable foundation for ongoing research aimed at discovering direct-acting InhA inhibitors that are resistant to cross-resistance associated with KatG. Scientists have developed lead compounds containing a methyl thiazole core (Figure 12) that act as nanomolar InhA inhibitors at GSK (Middlesex, UK) and subsequently at AstraZeneca. Both exhibit acceptable preclinical toxicity profiles, minimal CYP450 activity, and promising initial PK characteristics, coupled with outstanding MIC values against Mtb. The MIC for the GSK compound is 0.48 μM for intracellular application and 1 μM for whole cells in previous research. However, the series does not exhibit the *in vivo* effectiveness of INH and requires additional refinement to be clinically beneficial. A thorough examination of the 4-hydroxy-2-pyridones (Figure 12), another group of compounds that directly block InhA, was recently published by the NITD. NITD-916 is the foremost member of this group of orally active medications, demonstrating potent bactericidal effects against several INH-resistant Mtb strains and showing *in vivo* efficacy in models of both acute and chronic infections. Like the MmpL3 series, the primary concerns with this group of inhibitors involve their significant lipophilicity and effectiveness against dormant bacteria, in addition to the unfavorable physiochemical properties stemming from inhibitors that target mycolic acid-binding sites [62-65].

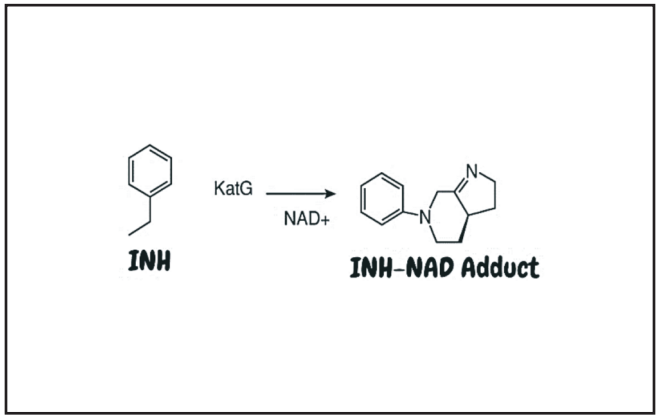


Figure 11: *INH bioactivation of the NAD adduct that is responsible for InhA inhibition.*

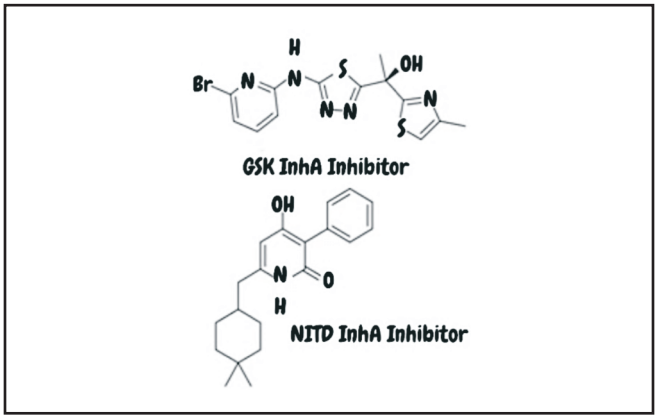


Figure 12: *Direct InhA inhibitors that are under development by GSK and the NITD.*

WGS and targeted NGS have revolutionised TB surveillance and drug-resistance detection. WGS can distinguish the old from the modern *M. tuberculosis* lineages (e.g., Lineage 2/Beijing against Lineage 3/CAS), and trace infection sources at the resolution of TB outbreaks. Coupling accurate detection with rapid results, modern detection platforms can screen a comprehensive panel of SNPs not only across the core first-line drugs (*katG*, *inhA*, *rpoB*, *embB*, *pncA*), but also other resistance loci (*atpE* for bedaquiline, *rv0678* for clofazimine, *ddn* for delamanid/pretomanid), thus negating the need for slow and labour-intensive culture-based DST. Bioinformatic algorithms can be used to detect heteroresistance and mixed-strain infections from deep within a single genome.

7. Phytoproducts: An Emerging Alternative

Employing Nanoparticles for Drug Delivery in Tuberculosis Nanotechnology-based medication delivery systems have significantly improved healthcare and enabled disease prevention at the molecular level [66]. Owing to their remarkable stability and ability to carry substances, nanoparticles serve as advanced drug delivery systems (Figure 13). Studies are underway to explore how nanotechnology can assist in tackling these issues in India, believed to have the highest estimated count of TB patients [67-69]. Polymers, which may be synthetic (such as polylactides and polyalkylcyanoacrylates) or natural (for example, gelatin and albumin), as well as solid lipids (including SLNR and NLCR), serve as examples of biocompatible and biodegradable materials in nanoparticles [70]. Utilizing nanoparticles for medication delivery offers multiple benefits, such as enhanced stability resulting in extended shelf life, a significant capacity to carry drug molecules, the possibility of encapsulating both hydrophilic and hydrophobic compounds, and versatility in administration methods like oral consumption and inhalation [71]. The creation of silver nanoparticles (AgNPs) influenced by an endophytic fungus such as Aspergillus fumigatus has amplified antimicrobial effectiveness. The bactericidal effect was significant against Salmonella typhi, Shigella dysenteriae, and Staphylococcus aureus by breaking the cell membrane and releasing the cell's contents [72,73].

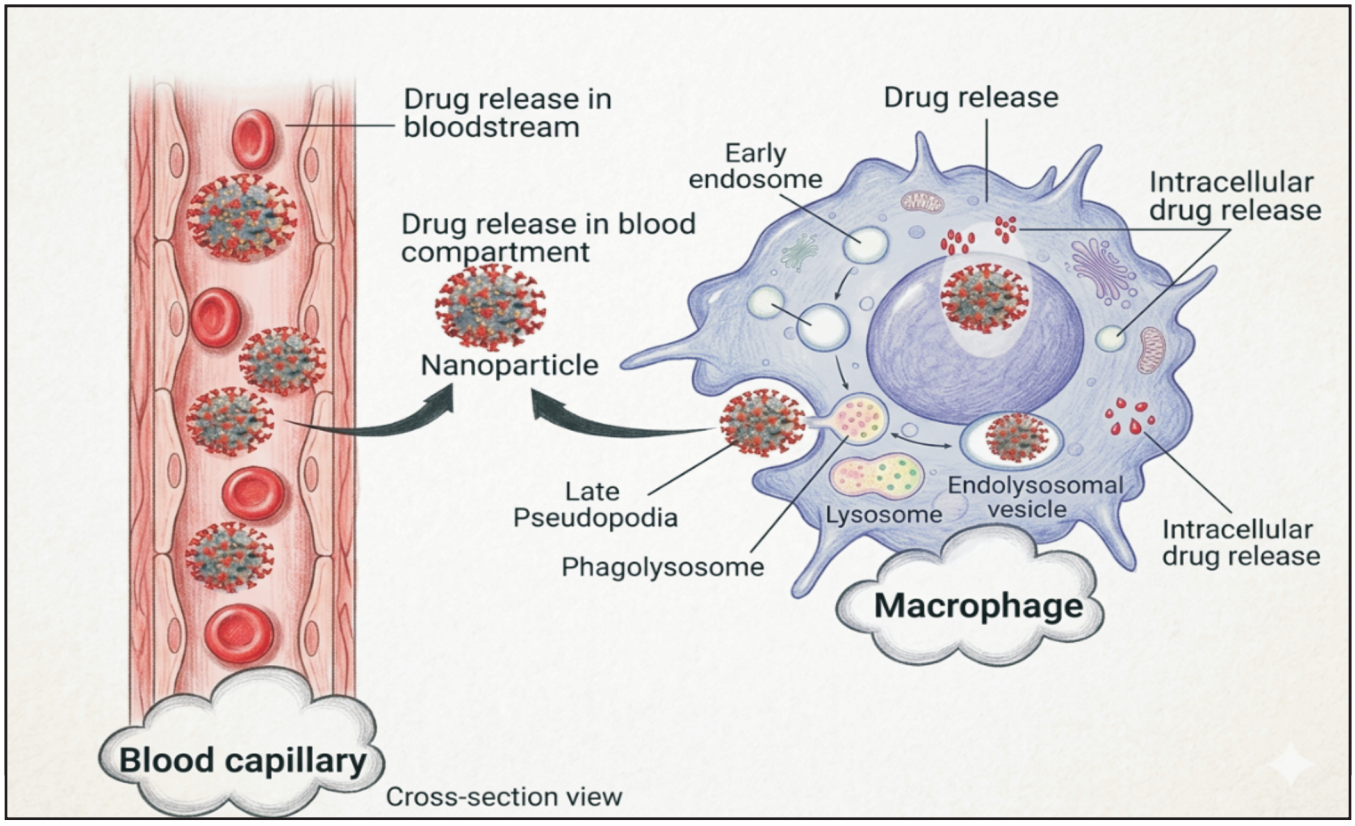


Figure 13: *Method of drug delivery via nanoparticles. The release of the encapsulated drug happens within the infected macrophages. The medication is discharged into the blood compartment of the capillary. The infected macrophage engulfs nanoparticles from the blood capillary, releasing the drug internally.*

7.1 Exploration of Therapeutic Delivery Mechanisms for Tuberculosis

Liposome-Driven Techniques for Drug Delivery: Small, enclosed vesicles known as liposomes form when phospholipid and water layers merge. They have been extensively researched as a promising drug delivery platform for bioactive compounds due to their remarkable capacity to encapsulate both hydrophilic and hydrophobic drugs (Figure 14). Liposomes exhibited improved positive anti-TB effectiveness in both acute and chronic conditions and notably diminished the drug's toxicity in both *in vitro* and *in vivo* experiments [74]. Total bacilli eradication from the lungs, liver, and spleen was noted in mice with chronic infection that received treatment with liposome-encapsulated PZA (pyrazinamide) and RFB (rifabutin).

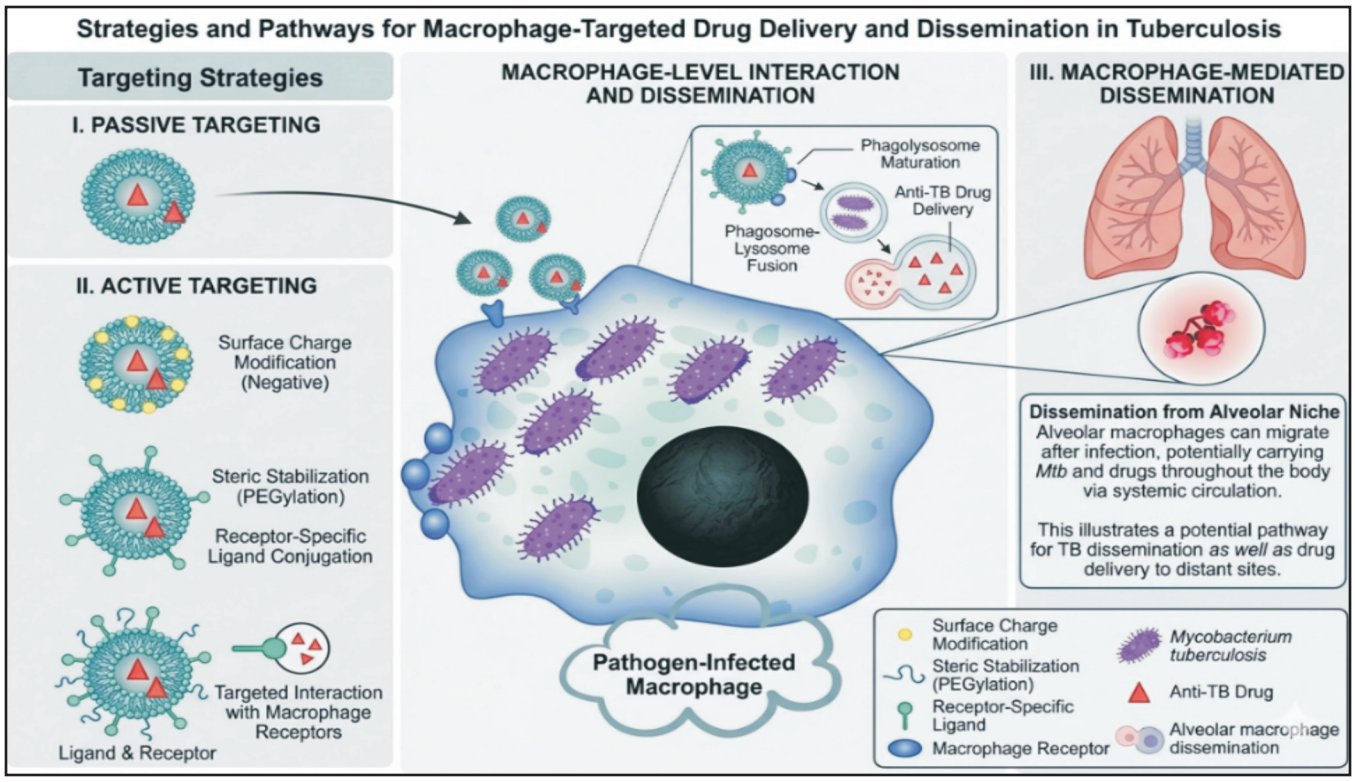


Figure 14: *Liposomes utilized for delivering drugs to alveolar macrophages. PEG: Polyethylene Glycol*

7.1.1 *Passive Targeting*

Nanocarriers for drug delivery are selectively directed to the target area through passive targeting, removing the necessity for ligand modifications for specific receptor interactions. Two main methods have been utilized in the management of tuberculosis (TB).

Initially, dendritic cells, monocytes, and macrophages, as key components of the mononuclear phagocyte system (MPS), possess phagocytic capabilities that nanocarriers exploit. These immune cells are strongly attracted to infection areas, particularly granulomas, where they utilize endocytosis or phagocytosis to take up nanocarriers. To enhance absorption, the properties of nanocarriers such as size, charge, rigidity, and form can be modified. Due to the slight negative charge of the cells, macrophages exhibit increased uptake of positively charged nanoparticles. Additionally, MPS-mediated phagocytosis is enhanced by opsonization and the formation of a protein corona, ensuring delivery to infected areas. Secondly, a mechanism for infected tissues has been proposed that resembles the enhanced permeability and retention (EPR) effect observed in tumor microenvironments. Heightened microvascular permeability triggered by inflammatory reactions may assist in the accumulation of nanocarriers at infection locations like granulomas. Extended circulation durations for nanocarriers are preferable to enhance their effect and raise the likelihood of reaching these areas [75-79].

7.1.2 *Active Targeting*

Active targeting has become an important strategy to enhance the precision of drug delivery via nanocarriers targeting *Mycobacterium tuberculosis* (Mtb) microenvironment. It relies on the very selective attachment of nanocarrier ligands to cell receptors of the targeted cells. Typically, receptor-mediated endocytosis is triggered and more drugs can enter the cells. The receptors on mononuclear phagocyte system (MPS) cells - which are the primary host cells for Mtb - are the focus for targeting in tuberculosis (TB).

The major targets are phagocytes' pattern recognition receptors (PRRs), which bind to the pathogen-associated molecular patterns (PAMPs) of microbes. Both C-type lectin receptors (CLRs) and Toll-like receptors (TLRs) – two types of membrane-associated PRRs – are very significant [80,81]. CLRs recognize microbial carbohydrates such as mannose and – glucans, while TLRs can detect many ligands including heat shock proteins and lipopolysaccharides. Apart from membrane PRRs, macrophages also have a unique set of PRRs known as scavenger receptors, which are capable of binding many ligands including oxidized lipoproteins as well as bacterial components. That is why they are considered great targets for drug delivery.

Apart from phagocytic receptors, complement receptors (CRs) and Fc receptors (FcRs), which play a role in opsonin-mediated phagocytosis, can also be utilized for target-specific delivery [82]. This is one of the reasons why, by looking at a figure of macrophage receptors, one can more clearly see those used in active targeting rather than passive targeting and free drug approaches.

Table 2: *Plants and their parts used in TB treatment.*

Scientific Names	Plant Part Used	Active Substituents
Nerium oleander	Leaf extract	Oleandrin (cardiac glycoside), Neritaloside, Flavonoids
Butea monosperma	Bark	Butrin, Isoflavonoids (Butin), Saponins, Tannins
Pea nut	Skin and seed	Isoflavones, Saponins, Flavonoids (Genistein, Daidzein)
Hibiscus cannabinus	Stem extract	Cannabinol, Tannins, Flavonoids, Alkaloids (Hibiscusin A, B)
Sesbania grandiflora	Leaf extract	Flavonoids (Quercetin, Kaempferol), Tannins, Saponins
Salix alba	Leaf extract	Salicin (a glucoside), Tannins, Flavonoids (Salicortin)
Eucommia ulmoides	Bark	Iridoid Glycosides (Geniposide), Phenolic acids, Lignans
Galaxaura elongata	Powder or extract	Polysaccharides, Alkaloids, Flavonoids, Phenolic compounds
Ocimum sanctum	Leaf extract	Eugenol, Rosmarinic acid, Flavonoids, Essential oils (e.g., Ocimene, Linalool)
Torreya nucifera	Leaves and bark	Flavonoids (Quercetin), Alkaloids, Tannins, Terpenoids
Olea europaea	Leaf extracts	Oleuropein, Hydroxytyrosol, Flavonoids, Phenolic compounds (Tyrosol, Lignans)
Rosa indica	Rose petals	Flavonoids (Anthocyanins), Tannins, Phenolic acids (Gallic acid, Ellagic acid)
Pistacia integerrima	Galls extract	Tannins, Gallic acid, Flavonoids, Polyphenolic compounds
Terminalia arjuna	Fruit	Arjunolic acid, Tannins, Flavonoids, Saponins (Arjuna inositol)
Euphorbia hirta	Leaf extract	Euphorbin, Flavonoids, Alkaloids, Triterpenoids
Morinda citrifolia	Root extract	Anthraquinones, Flavonoids, Iridoids, Phenolic compounds
Zizyphus mauritiana	Extract	Alkaloids (Zizyphine), Saponins, Flavonoids (Kaempferol, Quercetin), Triterpenoids

Phytochemical compounds naturally occurring in medicinal plants are considered primary and secondary metabolites. Many articles about the therapeutic roles through biological means of these constituents which are divided into chemical families (Table 2) including flavonoids carotenoids indoles isothiocyanates monoterpenes, and phenolic acids have been reported. The abbreviation "DOTS" (Directly Observed Treatment Short-course) is the term for the use of antibiotics in the therapy of tuberculosis. Its negative effects and extreme toxicity are well documented. MTB infection blocks the Th1 immune response resulting in higher production of anti-inflammatory cytokines and lesser production of proinflammatory cytokines [83-87]. Patient are prone to re-infection and reactivation of old infections because of the side effects of DOTS treatment and the decrease in protective CD4+ T cell levels. Addition of anti-inflammatory drugs to the routine treatment can improve the overall efficacy of

Table 3: *Phytocompounds and their anti-TB mechanisms of action*

Plant Species / Phytocompound	Active Chemical Class	Primary Mechanism of Action / Anti-TB Effect	Key References
Curcuma longa (Curcumin)	Polyphenol	Induces host macrophage autophagy; inhibits NF-κB inflammatory cascade	91,92
Allium sativum (Allicin)	Organosulfur	Disruption of bacterial cell wall lipids; thiol-dependent enzyme inhibition	93,94
Piper nigrum (Piperine)	Alkaloid	Bacterial efflux pump inhibitor; enhances bioavailability of Rifampicin	95,96
Adhatoda vasica (Vasicine)	Quinazoline Alkaloid	Mucolytic property; disrupts biofilm architecture and intracellular survival	97
Withania somnifera (Withanolides)	Steroidal Lactones	Modulates Th1/Th2 cytokine balance; enhances phagocytic activity	98

anti-tubercular therapy. Yet, these drugs may cause quite severe side effects if used continuously, so their use is not recommended. So, scientists are examining substances capable of modulating the immune system by mainly promoting the Th1 response and at the same time suppressing the Th2 immune response. Compounds from plants are good candidates for immunomodulatory activity.

The alcohol-based extract of Coleus scutellarioides (Miana leaves) influences the immune system by increasing the activity of proinflammatory T-lymphocytes and the production of IFN- γ and TNF- α [88-90].

Plant-derived phytoconstituents represent an attractive adjunctive and alternative approach to current treatment strategies with M. tuberculosis attributable to their wide-ranging bio-activities and novel targets. Evident from the values presented in (Table 3), the natural bioactive molecules have a demonstrated potent anti-TB activity mediated via diverse robotic pathways including the induction of host macrophage autophagy, cell metabolism disruption, bacterial efflux pump inhibition as well as immunomodulation.

Combination therapies employing any of the bioactive molecules and standard drug protocols may provide a useful adjunct in the increased management of TB.

In mouse models, bergenin, a secondary metabolite found in various plant parts, suppresses bacterial growth and activates the Th1 and Th17 responses. Furthermore, the combination of bergenin and isoniazid reduces the duration needed for MTB clearance while promoting the formation of enduring, central memory T-cell responses and mitigating the immunological damage associated with isoniazid [99-101].

Similarly, silymarin extracted from Sylibum marianum seeds leads to an enhanced Th1 response in both drug-sensitive and drug-resistant strains.

Examples of plant-derived immunomodulators include allicin from garlic, piperine, an extract of Chanca piedra (Phyllanthus niruri), curcumin from turmeric, gingerol from ginger, and extracts from Rubiaceae species, all of which possess anti-oxidant and anti-inflammatory effects [102-104]. To control inflammation, they could be utilized alongside DOTS as a substitute for steroids. A variety of phytocompounds exhibiting anti-TB properties have been documented.

These compounds include terpenoids, flavonoids, and alkaloids. (Figures 15, 16, and 17) below depict the essential process of these photoproducts [105-108].

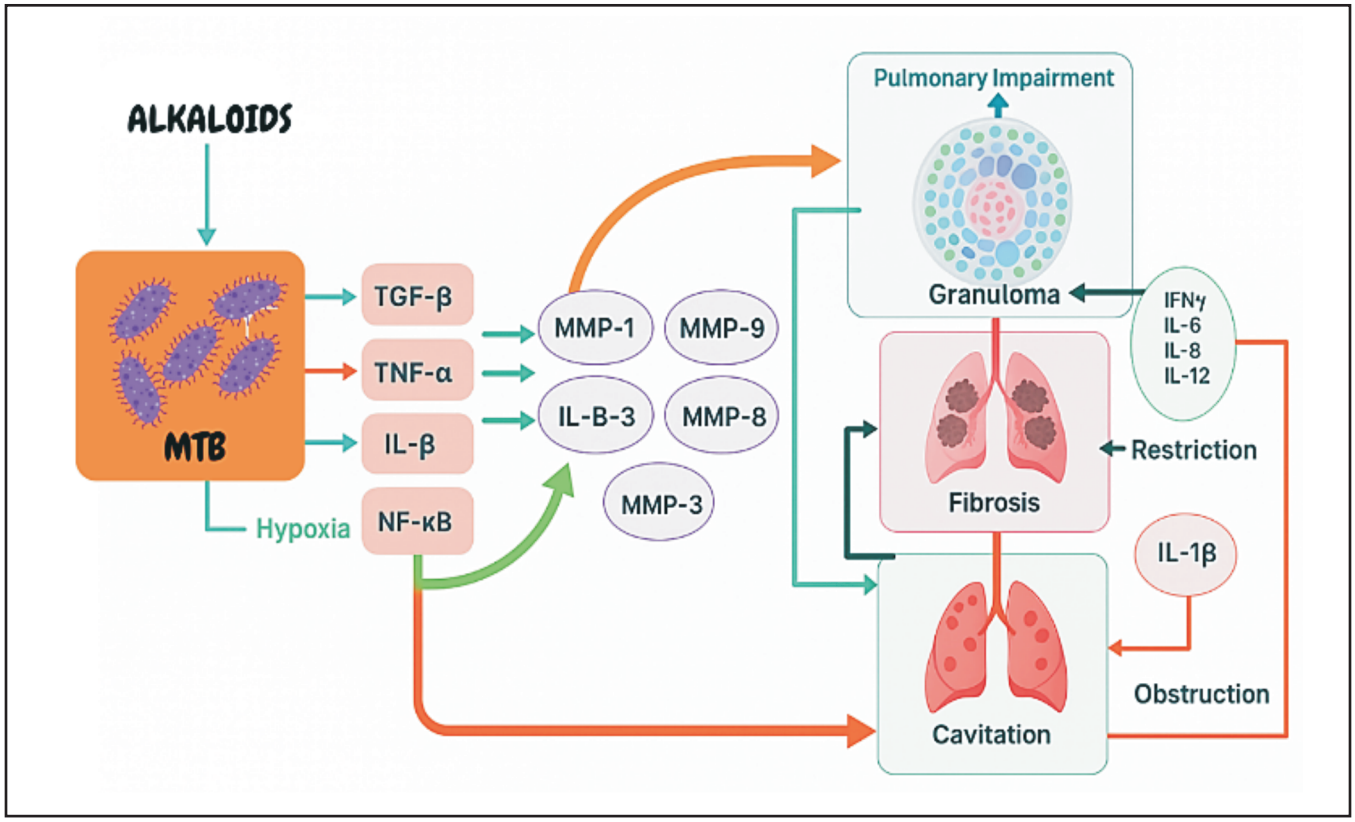


Figure 15: *The chemical extracted from the plant possesses properties that inhibit MTB. In hypoxic conditions, MTB cells produce HIFA, NF-κB, IL-1B, and TNF-α. These proteins subsequently activate the production of inhibitors for MMP-12, MMP-3, MMP-1/ MMP-8, and MMP-9. The synthesis of these matrix metalloproteinases leads to lung cavitation, while MMP-12 and MMP-1 collaborate to create granulomas that harm or necrotize the lungs, resulting in cavitation and obstruction. Cavitation leads to fibrosis among the processes of abnormal tissue healing.*

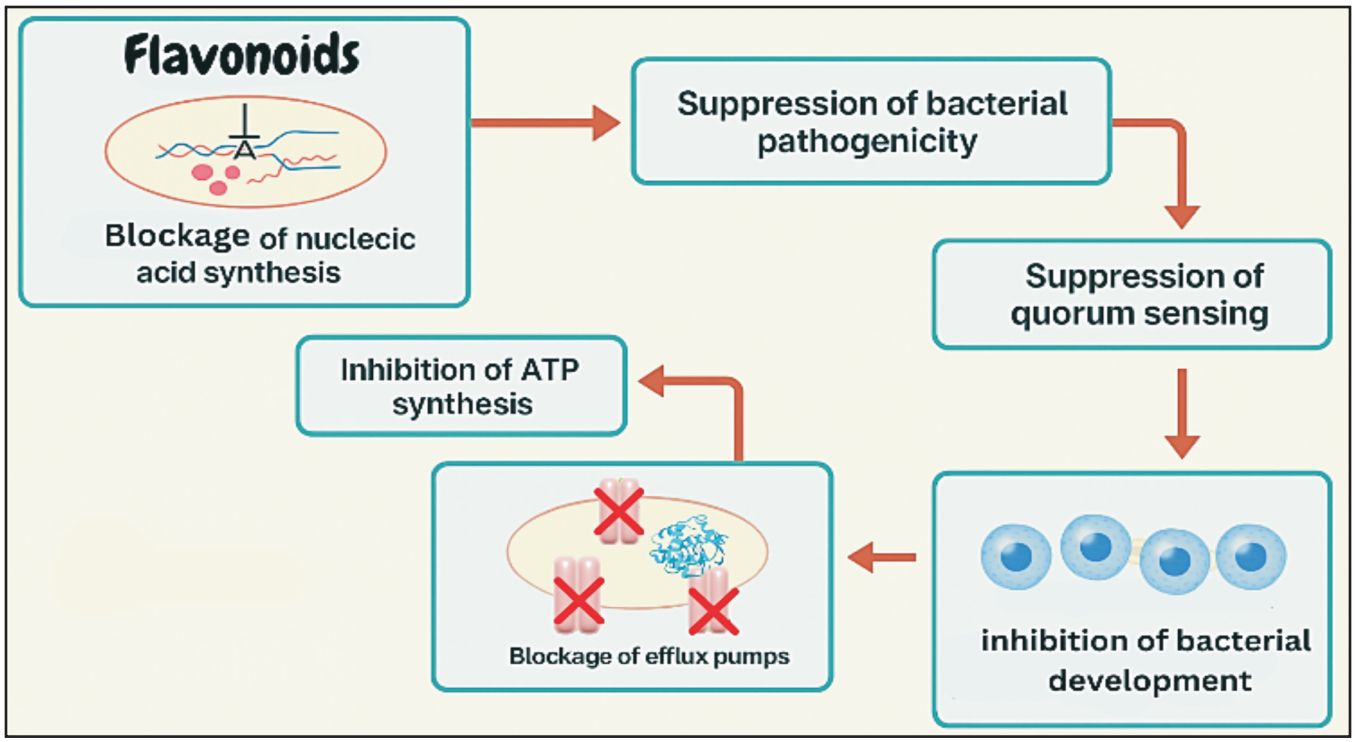


Figure 16: *Flavonoids negatively affect bacterial pathogenicity by inhibiting it. Toxins, gyrase/topoisomerase inhibitors, helicases, quorum sensing, and dihydrofolate reductase (DHFR) all inhibit nucleic acid synthesis. The capacity to create biofilms consequently inhibits the synthesis of the cell membrane. This involves blocking the fatty acid synthase (FAS-5) enzyme along with the synthesis of peptidoglycan (preventing peptidoglycan cross-linking and reducing Ala-Ala dipeptide production). Additionally, flavonoids can block efflux pumps, potentially reversing antibiotic resistance. The activities of NADH-cytochrome c reductase and ATP synthase in the bacterial respiratory chain are subsequently inhibited.*

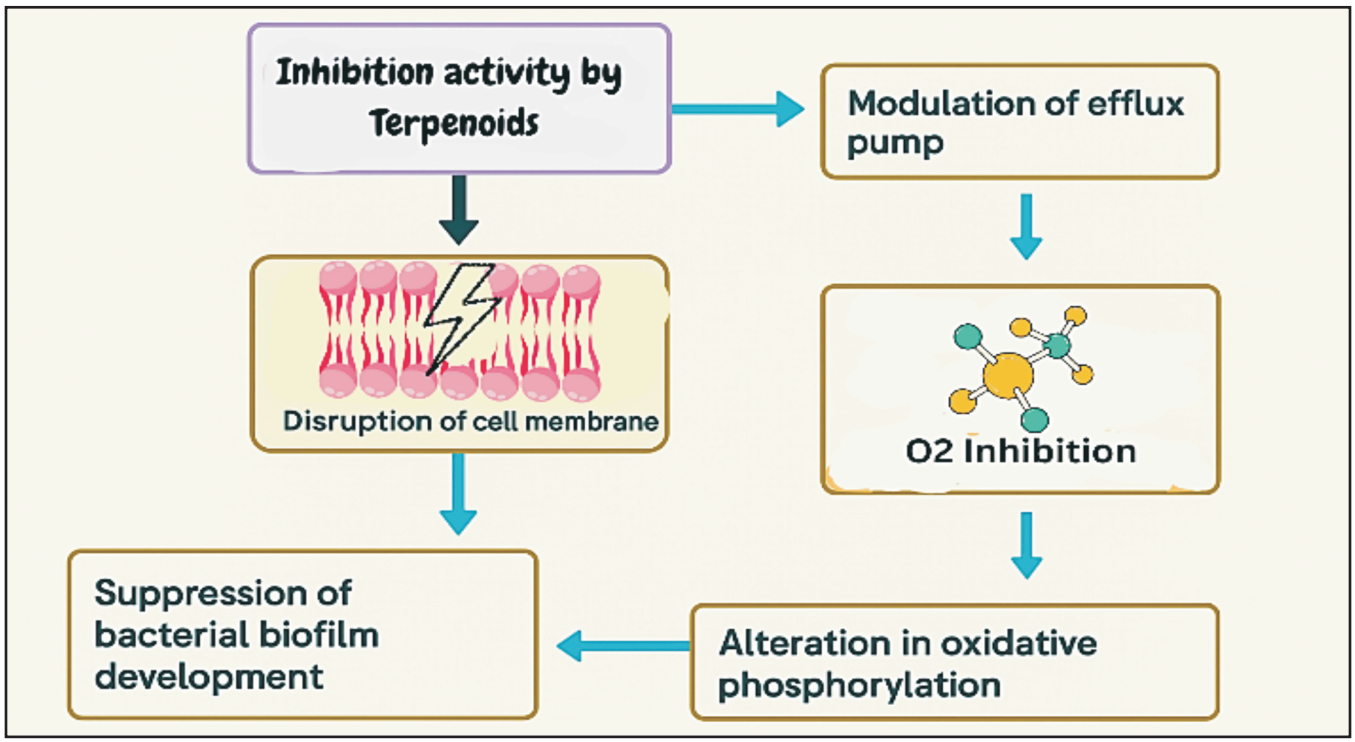


Figure 17: *The action mechanisms of terpenoids. Terpenoids disrupt the cell membrane. Altering the efflux pump could potentially counteract antimicrobial resistance. Oxygen is restricted as the process of oxygen uptake is blocked. There is a modification in the oxidative phosphorylation process.*

8. Conclusion

Besides, another major problem with the fight against the worldwide tuberculosis epidemic is the emergence of drug resistant strains and the social and economic factors that determine health, which negatively influence the access to healthcare facilities. If only we want to do something effective, comprehensive plans should be laid out. This means we should mix medical interventions with social and policy ones. Although diagnosis, treatment, and prevention of TB have Much changed in recent times and still global efforts to eliminate TB are constantly challenged by the appearance of drug resistant strains, social and economic factors which are influencing health, and unequal access to healthcare. To genuinely win the fight against TB, all stakeholders, including governments, worldwide health organizations, and local communities must be able to come together in enhancing the early diagnosis, upgrading the healthcare infrastructure, enforcing the treatment compliance, and increasing public awareness. In fact, approaches like personalized therapy and vaccine development are also allies in the war against drug-resistant TB. Lastly, a multi-dimensional approach encompassing not only health-related but also socio-economic factors will be the ultimate weapon in the fight against TB globally. However, the health goal of a world free of tuberculosis will depend on persistent political will, availability of resources, and global cooperation.

Combining the use of conventional, traditional, and palliative therapies is truly an integrated and therapeutic way to manage and treat diseases. Conventional medicine allows for accurate diagnosis and treatment based on results obtained through technological examination and testing. However, identified and healing methods based on age-old knowledge and cultural wisdom, historically referred to as traditional medicine, emphasize treating the whole person that is mind, emotions and spirit. Palliative care is concerned with alleviating symptoms and providing psychological comfort, which is in particular beneficial in minimizing suffering and improving the quality of life of individuals with chronic or terminal conditions. The combination of these three approaches can transform healthcare into more patient-oriented and holistic system while at the same time increasing patient satisfaction and health outcomes. This integrative method respects the complexity of human health and acknowledges that dealing with both the mental and physical aspects of illness is usually necessary for a successful result. If research is conducted into the benefits of combining these medicines, the simultaneous utilization of these treatment methods might lead to a major change in patient care and the creation of a healthcare model that is more efficient, inclusive, and compassionate. *Mycobacterium tuberculosis* (MTB) cannot be effectively managed with just one method either conventional, traditional or palliative. Due to the complexity of the disease in particular with the emergence of drug-resistant strains, a diversified strategy is required. Traditional therapies that effectively target the pathogens may be compromised by drug resistance and typically need long-term compliance. Conventional therapies may be used but alone they are not potent enough to affect the desired therapeutic outcome. Palliative care contributes only as a means of symptom control and quality of life enhancement but does not offer cure for the disease. This fact emphasizes the necessity of a comprehensive strategy that incorporates many therapy techniques. The best chance to successfully manage the illness, reduce suffering, and enhance patient outcomes is with a holistic approach that builds on the advantages of each therapy. In the continuous worldwide effort to treat *Mycobacterium tuberculosis,* a multidisciplinary strategy is still crucial by addressing both the biological and psychological aspects of MTB.

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