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Acquired resistance of Mycobacterium tuberculosis against antibiotics – A review

Mansi Vaghela[1], Dr. Murtaza Hajoori*[1]
[1] *Bhagwan Mahavir College of Basic and Applied Sciences,*
Bhagwan Mahavir University, VIP Road, New City Light Road, Vesu, Surat.
**Corresponding Author: Dr. Murtaza Hajoori*

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ABSTRACT: M. tuberculosis, the pathogen of tuberculosis, contains a number of fundamental attributes that permit it to prevent the action of antibiotics. It is still one of the hardest infections to treat, though the majority of current TB treatment plans involve dosages of four extremely dangerous medications for patients for six to eight months. M. tuberculosis is notable for having the ability to withstand most antibacterial medicines. The goal of these extensive treatments is to get rid of them in order to stop the emergence of mutations that are drug resistant. To understand the mechanisms of this organism's antibiotic resistance, numerous investigations have been conducted. In this article, an effort has been made to explain the many drug resistance mechanisms in M. tuberculosis, along with the innately rigid cell wall and gene mutations. Instead, it is caused by a number of genes that encode antibiotic resistance. The long latent stage's slow metabolism considerably increases the organism's resistance mechanisms, and the existence of various outlet pumps and a greasy, impenetrable cell wall is required to survive the potency of antibiotics. Enough understanding of the biological mechanisms of treatment resistance in M. tuberculosis could be used to identify potential new therapeutic targets. This understanding is essential for the development of much more powerful medications that are active toward drug-resistant M. tuberculosis strains and also contribute to reducing the length of time now needed for treating TB that is drug-tolerant.

KEYWORDS:antibiotic, drug resistance, Mycobacterium tuberculosis, multidrug resistance, XDR, TDR.

I. INTRODUCTION:

Tuberculosis (TB) is a pathogenic illness that causes by M. tuberculosis. The first therapeutic drug employed in its treatment was streptomycin, which has a significant bactericidal effect, but a few years later drug-resistant variants started to appear. Initially, this was thought to be due to the use of single antibiotic, streptomycin to cure the infection; encouraging the use of multi-drug treatment to manage the infectious disease, but in recent decades, multidrug resistance (MDR) has evolved. Moreover, the World Health Organization's data from 2010 display two further kinds of TB strains: those that are fully drug resistant (TDR) and those that are extensively drug-resistant (XDR), which are resistant to at least four of the main anti-TB medicines [1] [2]. The term "acquired resistance" refers to TB resistance that developed as a result of inadequate treatment, while "primary resistance" is a kind of TB resistance seen in persons who were initially infected by an antibiotic-resistant strain but had not received any anti-TB treatments [6] [7].

Aside from being MDR, they are also susceptible to any fluoroquinolone & at least one of the second-line medications used in vaccinations, such as kanamycin, capreomycin, or amikacin. A much more concerning scenario has lately appeared with the emergence of strains of bacteria that have been discovered to be impervious to all tested antibiotics, a condition known as fully drug-resistant (TDR)-TB[3] [4] [5].

In terms of providing insights on the molecular mechanism, adaptive characteristics, and innate mechanisms by which M. tuberculosis develops resistance to Antitubacular medications, this study will compare and contrast different pathways [8].

Characterization of Mycobacteriumtuberculosis:

Pathogenic bacteria belonging to the Mycobacteriaceae family include M. tuberculosis[9]. The combination of M. tuberculosis

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sensu stricto, M. africanum, M. Canetti, M. bovis, M. caprae, M. microtia, M. pinniped, M. fungus, & M. origins was discovered in 2019 [10]. It is non-motile, depends on oxygen to grow, and whether it generates spores is up for debate[11] [12]. M. tuberculosis divides every 18–24 hours. When compared to other bacteria, which typically have division durations measured in minutes, this is incredibly slow. It is a tiny bacillus that can tolerate ineffective disinfectants and endure for weeks in a dry environment[13] [14]. Its unique cell wall, which is rich in lipid like mycolic acid and is a major virulence component, is probably what gives it resistance to desiccation [15].

Microscopy: Auramine fluorochrome stain was used to colour fixed smear. Ziehl-Neelsen staining was used to determine acid fastness property aids vital screening of infection by M. tuberculosis[16].

Culture: Solid agarand eggbased culture media including Middle brook 7H11 & Lowenstein Jensen (LJ) are used for selective cultivation of M. tuberculosis [17]. The diagnostic laboratory has recently implemented matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) as an accurate and direct approach to identifying bacteria and yeasts [18] [19].

Genome: The H37Rv strains genome was released in 1998[20].In addition to using the lipid cholesterol as a carbon source, M. tuberculosis could also grow on it. Genes involved inside the cholesterol usages pathways have been proven to be crucial at different phases of the infectious disease lifecycle of M. tuberculosis, particularly during in the persistent phase of the illness when other nutrients are probably not available[21].

History: Robert Koch, who received The Nobel Prize in Physiology or Medicine (1905)for discovering M. tuberculosis, also recognized as the "tubercle bacillus," on March 24, 1882Thus, M. tuberculosisbacterium is also known as "Koch's bacillus"[22] [23].

It is simple to spread M. tuberculosis through the air by sneezing, coughing or even communicating. Anybody can respond to a contaminating droplet & become infected with M. tuberculosis. About 1.8 billion get infected and battle the aforementioned sickness on a global scaleevery year [24].

Mechanistic Innate Features of Drug Resistance

Impermeable Cell Wall:

The impermeable cell wall of M. tuberculosis is the primary cause of the organism's passive drug resistance. Mycolic acids, Wax-D and cord factors are the three main determinants of the cell wall of M. tuberculosis. The hydrophilic arabinogalactan layer assures that hydrophobic substance cannot penetrate the cell wall. Further, this layer also containshydrophobic mycolic acids, which severely inhibit the entry of hydrophilic molecules. This impermeability causes medicines to gradually accumulate around the cell, where they are then slowly detoxified by various cellular components or by the release of enzymes like lactamases; an enzyme that efficiently breaks down -lactam antibiotics, which are inhibitory to the integration of peptidoglycan (rigidity component) into to the cell wall [13].

Both M. tuberculosis and M. bovis were shown to include the outer membrane channel protein CpnT, according to researchers. This protein has a dual effect on food absorption & selective sensitivity to antibacterial drugs. According to the study, M. bovis CpnT mutant is much more resistant to most antitubercular medications[8] [13].

Slow Metabolism Mechanism:

Many antibiotics find it challenging to kill bacteria having slow metabolic pathways and lengthy generation times; therefore, bacteria that really are metabolically active & reproduce quickly make suitable targets for antibiotics. It is still unclear, nevertheless, whether the prolonged generation time in M. tuberculosis supports its antibiotic resistance. According to M. tuberculosis, the longer survival time has little effect on the organism's capacity for treatment resistance [1]. There was a link between the organism's generation time and drug resistance. However, it has been suggested that M. tuberculosis slow growth rate contributes significantly to its drug resistance. For instance, unstable antibiotics like carbapenems lose their effectiveness more quickly than mycobacterial growth[2]. Researchers have identified specific genes that enable M. tuberculosis to develop in oxygen-depleted environments, the majority of which are directly relevant to triacylglycerol production. The metabolic functions of Mycobacterium TB are slowed down by triacylglycerol. This is mostly due to the fact that the production of triacylglycerol depletes acetyl CoA, an element of the TCA cycle. The ability of the organism to grow under acidic conditions is aided genetically and is not only limited to physiological responses, as this triacylglycerol is extensively developed by Mycobacterium tuberculosis in response to varied adverse conditions such as oxygen deprivation, acidic pH and iron deficiency[5].

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Possession of Numerous Efflux Pumps:

Toxins, trash and nutrients are transported by protein channels, which also play a vital role in the regular metabolic & functioning of the organisms. It's also been demonstrated that M.tuberculosisefflux pumps are adaptable to medication resistance[30]. Multidrug efflux pumps allow antibiotics to leave the cell through to the cellular membrane. It has been discovered that M.tuberculosis medication efflux pumps contain protein encoded systems that govern their expression and specialize them for drug-resistant tasks[44] [69].

Antibiotics useful for M.tuberculosis:

Numerous antibiotics are effective against M.tuberculosis. The first line, second line & additional M.tuberculosis medications are given in Table 1[25].

Table 1: Different antibiotics useful for Mycobacterium tuberculosis

Antibiotics	Drugsname	References
First line Anti – TB drugs	1. Rifampicin 2. Isoniazid 3. Ethambutol 4. Pyrazinamide 5. Streptomycin	[25] [26]
Second line Anti – TB drugs	1. Fluoroquinolone 2. Kanamycin, Capreomycin, Amikacin, Viomycin 3. Ethionamide 4. Para – Amino Salicylic Acid 5. Cycloserine 6. Thioacetazone 7. Macrolides 8. Clofazimine 9. Linezolid	[25][48][49]
New Anti – TB drugs	1. Bedaquiline 2. Delamanid 3. SQ – 109 4. PA – 824 5. Benzothiazinones	[25][65][67]

Proposed mechanism for acquiring resistance against different antibiotics:

Molecular mechanism:

Using antibiotics it has been demonstrated that M. tuberculosis resistance results from spontaneous mutation in a number of chromosomal genes. This recurring mutation has been found to impact the necessary interaction between each anti-tuberculosis treatment and its specified target.

First-Line Anti-TB Drugs:

Rifampicin:

Rifampicin is a rifamycin analog that was first marketed in 1972 to treat tuberculosis. This is among the most powerful anti-TB medications and along with isoniazid; it forms the core of the multi-drug approach to treating TB. Rifampicin works by attaching to the RNA polymerase's subsidiary & blocking messenger RNA synthesis in M. tuberculosis. The majority of M.tuberculosis strains isolated that are rifampicin-resistant have alterations in the rpoB gene, which produces the β-subunit of RNA polymerase. As a result, conformational modifications take place, which lower the drug's affinity and lead to the emergence of tolerance. When treating tuberculosis, it is typically combined with isoniazid as the first-line chemotherapy[26]. Rifampicin has a slow-acting inhibitory impact on tuberculosis.

The lowest level of resistance to rifampicin has been linked to mutations in portions of codons (for example, 518 or 529) while remaining susceptible to other rifamycin, including such rifabutin or rifalazil[27]. Moreover, nonresistance to rifampicin is silent, rare and nearly all rifampicin-resistant strains are also resistant to other drugs, exclusively to isoniazid. That is the reason why rifampicin resistance is observed as a surrogate marker for MDR-TB.

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Mode of action: It inhibits the elongation of mRNA by attaching to the subunit of RNA polymerase. Due to their resistance to all of the other tubercular medications, rifampicin-resistant MTB strains frequently serve as a sign of MDR tuberculosis[27]. The majority of the rifampicin-resistant individuals have missense mutations and nucleotide substitutions at codons 526 & 531 of rpoB, according to a report. It is hypothesized that nucleotide alteration at positions 516, 526, or 531 of the rpoB locus is related to rifampicin susceptibility in tuberculosis[28] [29].

Pyrazinamide:

Early in the 1950s, pyrazinamide was suggested as a potential TB treatment; it is now a staple of the first-line treatment protocol[32]. Pyrazinamide, a nicotinamide correlate, was introduced to shorten the treatment plan to six months. It has the capacity to suppress dormant bacteria living in acidic conditions, such as those present in TB lesions [30]. Another study discovered that Mycobacterium TB, one of the kinds of bacilli, can be inhibited from multiplying by pyrazinoic acid as well as its n-propyl ester[32].

Mode of action: pyrazinamide involves the conversion of Pyrazinamideto pyrazinoic acid by the enzyme pyrazinamide/ Nicotinamidase coded by the pncA gene[33] which disturbs the bacterial membrane's energetics & prevents membrane transport. Owing to an ineffective efflux, protonated pyrazinoic acid would have been reabsorbed into the cell & constructed inner lining in acidic circumstances, causing cellular harm [31].

Isoniazid:

It serves as the main antibiotic in the fight against tuberculosis. Isoniazid is typically present in the inactive form, but the body transforms it into the active form through metabolism. Gene mutations in the katG&inhA or its regulatory domain are linked to the two main underlying pathways of isoniazid resistance[34]. Indeed, multiple investigations have discovered that the two genes most frequently related to isoniazid susceptibility contain alterations in them. The majority of them have been found to have the gene mutation S315T in katG, which prevents isoniazid products from creating the isoniazid-NAD combination necessary to exert their antimicrobial property. This variant is more common in Multi - drug resistant strains and it has repeatedly been associated with high susceptibility to isoniazid. The second most prevalent mutation affects InhA's active site, which less quality and variety in a mutation that reduces InhA's sensitivity to the isoniazid-NAD combination. Both of these mutations cause overexpression of InhA. The most frequent mutation discovered is at position 15C/T and is frequently linked to modest levels of isoniazid tolerance[36].

Mode of action:MTB-resistant strain with katG&inhA mutations. MTB isolates from patients inside the Republic of Moldova with (MDR) & (XTR) tuberculosis have a katG 315T mutation[35] [36].A recent intriguing discovery suggested that the dihydrofolatereductase (DfrA) in M.tuberculosis is inhibited by the 4R isomer of the isoniazid-NADP crosslinking, suggesting that dfrA mutations may contribute to isoniazid resistance. In addition, proteome analysis of isoniazid assaults in M. tuberculosis revealed sixteen additional proteins which were cross-linked with[37] greater affinity in addition to InhA&DfrA, suggesting that the drug may have other, as yet unidentified effects on the bacteria. Despite this, no mutation in dfrA linked to isoniazid tolerance has been found in two recent studies[38]. It was first proposed that mutations in the promoter of ahpC might be employed as representational indicators for isoniazid-resistantM. tuberculosis because ahpC transcripts an alkyl hydro peroxidase reductase that is linked to resistance to reactive oxygen intermediates. Genetic polymorphisms in additional genes, such as kasA& also the oxyR-ahpC&furA-katGintragenicareas have been discovered in strains isolated of M. tuberculosis that are resistant to isoniazid[39].

Ethambutol: Ethambutol, which is a feature of the new first-line TB treatment regimen, was initially used to cure the infection in 1966[42]. Ethambutol is four-drug regimen anti-tuberculosis drug, PZA, rifampicin, and isoniazid.

Mode of action: Development of the cell wall, suppression of the sperm dine and phospholipid synthesis and spermicide synthesis[40].Ethambutol resistance has been linked to polymorphism in embA, embC, alterations in embB497 & embB406 and a variant in codon 306 in embB[41].

Furthermore, a study using a large number of M. tuberculosis isolates discovered that variations in embB306 were not only associated with an increased propensity to become resistant to ethambutol but also with the ability to spread[42]. In actuality, allelic exchange experiments revealed that ethambutol resistance was caused by distinct mutations leading to amino acid conjugation, whereas other amino acids conversation had little to no impact on ethambutol resistance. The same researchers have reported mutations in the genes Rv3806c and Rv3792 of the decaprenyl phosphoryl-B-D-arabinose (DPA) biosynthetic &

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application pathway along with mutations in embB and embC, assemble, increasing a variety of ethambutol MICs depending on the type and number of mutations. These results might affect how correctly current molecular techniques analyze ethambutol resistance. Therefore, different levels of ethambutol resistance are caused by mutations in embB306, which are necessary but insufficient to produce high levels of ethambutol resistance[40].

Streptomycin: The first antibiotic to treat tuberculosis effectively was streptomycin, which was initially obtained from the soil bacterium Streptomyces griseus. Unfortunately, resistance to it quickly developed as a result of being treated as immunotherapy. An aminocyclitol glycoside that works against bacteria that are actively developing is streptomycin.

Mode of action:

Streptomycin also affects the ribosomal proteins S12 and 16S rRNA, which are both encoded by distinct genes at the region of the 30S Subunit of the ribosome[43].The most frequent mutation found in rpsL has been a conversion in codon 43 from lysine to arginine. High-level and low-level resistances to streptomycin are produced via mutation[44].

Second-Line Anti-TB Drugs:

Fluoroquinolones:

Currently, fluoroquinolones are used as 2nd medication to treat MDR-TB. Ofloxacin and ciprofloxacin both are synthetic variations of the nalidixic acid parent substance, which was found to be a by-product of the parasite chloroquine. In order to reduce the period of TB treatment, newer generation quinolones including moxifloxacin & gemifloxacin are now being tested in clinical studies and suggested as the first antibiotics. Fluoroquinolone majorly the Ciprofloxacin is a chemotherapeutic agent used in the treatment of tuberculosis.

Mode of action:

Fluoroquinolones act by inhibiting two enzymes gyrase and topoisomerase IV involved in bacterial DNA synthesis. Resistance gyrA or gyrB mutation[45].Fluoroquinolone resistance develops through two main mechanisms involving alterations in the drug target viz., gyrase and topoisomerase IV and alterations in getting access to the drug target enzymes.In Mycobacterium TB, the bacterial cell wall also contributes to fluoroquinolone resistance[46].

Ethionamide:

These antitubacular medications, which structurally resemble isonaizid, are chemotherapeutic entities that are inactive in their natural states; however, when their metabolisms are activated, they become pharmacologically active. The above activation invites for a monooxygenase that is encoded by the ethA gene. [47].

Mode of action: On the production of mycolic acid, it is inhibitory.Additionally, it has been discovered that resistant strains possess etaA/ethA &ethR mutations[48].

Kanamycin, Capreomycin, Amikacin, Viomycin:

Antitubercular medications are the ones that prevent protein production. Cyclic polypeptides, amikacin and kanamycin are examples of aminoglycoside antibiotics[49], along with viomycin and capreomycin. Bacteriostatic antiseptics include capreomycin &viomycin. The 50S ribosomal subunit is used as the mechanism to stop translational processes.

According to reports, mutations in the tlyA gene are a major factor in the development of cross-resistance among Capreomycin &Viomycin. Resistance to amikacin and kanamycin coexists with mutational changes in the RRs gene[50] [51].

Para-Amino Salicylic Acid:

A course of treatment for MDR-TB is called PAS. Clinical isolates that were resistant to PAS were likewise found to have changed in the gene associated with PAS resistance, as was the case with transposon mutagenesis. In a recent investigation, experimental isolates of M. tuberculosis have a missense mutation in the gene for Dihydrofolate synthase that made them resistant to PAS[52].

Cycloserine:

Cycloserine inhibits the production of peptidoglycan, making it a mouth bacteriostatic. Additionally, it can prevent the D-alanine racemase (AlrA) enzyme from converting L-alanine to D-alanine[53]. More significantly, it was demonstrated that Cycloserine tolerance in M. bovis BCG was substantially caused by a single mutation in the D-alanine transporter gene, cycA[54].

Thioacetazone:

It is an outdated medication that was used to treat TB at a really minimal cost. It is a member of WHO group 5 medications and mycolic acid production inhibit its synthesis[55].

Macrolides:

Due to the inadequate activity against M. tuberculosis, macrolides are advised for the diagnosis of other mycobacterial infections. Reduction in cell wall transparency and the availability of emr37, a gene that codes for a methylase at a specific location in the 23S rRNA and prevents the medication from binding have

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been linked to innate resistance to macrolides[56]. Additionally, research using strains isolated of M. tuberculosis revealed that ethambutol reverses resistance to clarithromycin, indicating a barrier function as the root of the macrolide's resistance development[57].

Clofazimine:

It is indeed a riminophenazine molecule that was long known to have anti-TB efficacy as well as certain adverse side effects, including skin discoloration.

Mode of action: Clofazimine's potential target could be the outer membrane. Clofazimine is decreased by NADH dehydrogenase in M. tuberculosis, and then, upon spontaneous oxidation, free bactericidal quantities of reactive oxygen species are produced (ROS)[58].

Linezolid:

This is an oxazolidinone and therefore is clinically used to treat nosocomial pneumonia and skin disease.Linezolid works by inhibiting the binding of the 50S ribosomal subunit, which is the first step in the combining of proteins.In vitro-selected mutants, clinical isolates of Mycobacterium TB resistant to linezolid, as well as the variant T460C in response, encoding the 50S ribosomal L3 protein, have all been discovered in a more recent investigation employing next-generation sequencing[59].

New Anti-TB Drugs:

Bedaquiline:

A brand-new antibiotic from the diarylquinoline family with particular action against Mycobacterium tuberculosis, bedaquiline is also referred to as TMC207 or R207910. The medication entered clinical evaluation for drug-susceptible & MDR-TB[60] after demonstrating both in vitro&in vivo activity towards Mycobacterium tuberculosis.

Mode of action: It prevents M. tuberculosis from producing ATP synthase.The sole change found in these mutants' genomes by sequencing them and comparing them to the genomes of the affected strains was also in the top gene that encodes the c subunit of the F0 component of ATP synthase[61].

Delamanid:

It was formerly known as OPC-67683 and is a nitro-dihydric-imidazooxazole derivative that has anti M. tuberculosis efficacy by preventing the production of mycolic acid.

Mode of action: Demand is fulfilled by suppressing the production of mycolic acid; however, it varies from isoniazid in that it only suppresses the production of methoxyand keto-mycolic acid. The Rv3547 gene was discovered to have a mutation, which raises questions about how the medicine is activated by it[62].

PA-824:

It is a nitro imidazole bicyclic derivative that has demonstrated particular anti M. tuberculosis action. Additional clinical testing is now being done on PA-824[63].Protein and lipid production in cell walls is inhibited. Loss of a particular glucose-6-phosphate dehydrogenase is primarily responsible for the mechanism of PA-824 resistance (FGD1)[64].

SQ-109:

It is a synthetic analogue of ethambutol with action towards drug-susceptible & drug-resistant M. tuberculosisin vitro&in vivo. A two stages clinical trial is now evaluating SQ-109[65].

Mode of action: SQ-109 works by preventing mycolic acids from forming the core of the bacterial cell wall, which leads to the formation of trehalosemonomycolate, the parent compound of trehalosedimycolate.The iniBAC operon's transcription, which is necessary for the efflux pump to operate, is impacted by SQ-109. SQ-109 signals MmpL3 as its target and identifies MmpL3 as a Trehalosemonomycolate transporter[66].

Benzothiazinones:

It was also found to be active against drug susceptible and MDR clinical isolates of M. tuberculosis[67].

Mode of action: Benzothiazinones was firstly spotted at the biogenesis level. The target of the medication was found by further research using in vitro mutants. The genes rv3790 and rv3791 encode proteins that catalyze the epimerization of decaprenyl phosphoryl ribose (DPR) to decaprenyl phosphoryl arabinose (DPA), a predecessor for the synthesis of arabinan required for the bacterial cell wall. These two important enzymes were given the names DprE1 and DprE2, respectively. BTZ043's mechanism of action is demonstrated by demonstrating how the drug is activated in bacteria by removing a crucial nitro group to create a nitroso analogue, which can then interact with such a cysteine residue in DprE1 [68].

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Involvement of genes in resistance:

Table 2: Genes involved in acquired drug resistance in M. tuberculosis

Sr. No.	Gene	Encoded protein	Protein function	Affected drug	Drug's mode of action	Reference
1	katG	Catalase – peroxidase	Prodrug activation	Isoniazid	Inhibiting mycolic acid biosynthesis and other metabolic processes	[34]
2	inhA	Enoyl ACP reductase	Drug target	Isoniazid		[36]
3	rpoB	β-Subunit of RNA polymerase	Drug target	Rifampicin	Inhibiting transcription	[28] [29]
4	pncA	Pyrazinamidase	prodrug activation	Pyrazinamide	Inhibiting trans-translation	[33]
5	embB	Arabinosyl transferases	drug target	Ethambutol	Inhibiting arabinogalactan synthesis	[40]
6	rpsL	S12 ribosomal protein	drug target	streptomycin	Inhibiting protein synthesis	[44]
7	rrs	16S ribosomal RNA	drug target	Amikacin/kanamycin	Inhibiting protein synthesis	[49]
8	ethA	Flavin monooxygenase	prodrug activation	Ethionamide	Inhibiting mycolate biosynthesis	[48]
9	gyrA gyrB	DNA gyrase subunit A, DNA gyrase subunit B	Drug target, drug binding	Fluoroquinolone	Inhibiting DNA gyrase	[45]
10	alrA, cycA	D-Alanine racemase, D-Alanine-D-alanine ligase	Drug target	D-Cycloserine	Inhibiting peptidoglycan synthesis	[69]
11	thyA	Thymidylate synthase A	dTTP synthesis	p-Amino salicylic acid (PAS)	Inhibiting folate biosynthesis	[52]
12	ribD	Dihydrofolate reductase analog	Replacement of drug target activity	p-Amino salicylic acid (PAS)	Inhibiting folate biosynthesis	[52] [69]

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13	tlyA	rRNA methyltransferase	Ribosome protection	Capreomycin	Inhibiting protein synthesis	[49]
14	rrs	16S ribosomal RNA	Drug target	Capreomycin	Inhibiting protein synthesis	[50]

REMEDY FOR TREATMENT:

Among the most challenging infections to treat is tuberculosis. The issue has been made worse by mycobacteria's characteristics, such as slow proliferation and internalized placement of the bacilli. In order to reduce virulence, delay the emergence of resistance, and shorten the duration of treatment, a combination of medications is utilized for tuberculosis. The majority of cases respond well to first-line medications[1]. Drugs with the greatest impact should be used in rigorous initial treatment. Considerations such as excellent patient compliance and therapeutic costs are also important. The first and second stages of chemotherapy are also employed. Additionally employed is short-term therapy, which has lower failure rates, fewer chances of encountering resistance, and higher patient compliance. If you already have dormant TB and are at a greater risk for developing active TB, your doctor may advise pharmaceutical treatment. Drugs and treatment duration are determined by your age, general health, potential drug resistance, and the location of the illness in your body[7].

The above-mentioned 6-month regimen is the accepted treatment for first-time cases of TB in Spain based on the fundamental bacteriological principles of TB treatment: First-line medications are isoniazid, rifampicin, pyrazinamide, & ethambutol for two months, then isoniazid and rifampicin for four months[70]. A patient is defined as a first-time case if they have never received therapy (new case) or if they have only had prophylactic treatment for a little less than one month. In situations of silico tuberculosis, the guideline advises extending this schedule to 9 months, and in patients with TB effect on the central nervous, to 12 months. During the initial period, the patient should be given a dosage of 20 to 40 milligrams of corticosteroids[71].

For logistical reasons and to protect the impact of potential initial resistance to isoniazid as the generalization of such resistant throughout Spain has still not been accurately determined, ethambutol is included with the standard authorization for all patients. However, it is very likely that the majority of TB patients of Spanish descent would benefit from the usual regimen without ethambutol as a viable therapy choice. Once drug susceptibility has proven that the first-line medications are successful, ethambutol may be withdrawn from the list of approved pharmaceuticals. When taking the medication in the morning while fasting, just one dose should be taken, and for the following 30 minutes, neither liquids nor solids should be consumed. Ethambutol dosage for children under age of five should have been 15 mg/kg per day[40] [41].

There are currently commercially marketed formulations that combine predetermined dosages of the first-line medications. Combination pills increase treatment compliance by lowering the required dosage and halt the development of resistance by preventing preferential immunotherapy in individuals who quit taking their medication[13]. The widespread usage of combination medication compositions has been permitted by current TB treatment recommendations. As an alternative to the 6-month regimen, the accompanying 9-month treatment plan may be used: 2 months of isoniazid, rifampicin, & ethambutol followed by seven months of isoniazid and rifampicin. Patients with gout are especially advised to use this authorization[24].

Commonly used drugs for tuberculosis:

When treating active tuberculosis, especially if it is a drug-resistant type, numerous medications must be taken at once. Isoniazid, Rifampin, Ethambutol, and Pyrazinamide are the most often prescribed antibiotics for the treatment of tuberculosis. A combination of antibiotics known as fluoroquinolone and injectable drugs, including such Amikacin or capreomycin, are typically used for more than two years if you have drug-resistant TB[27] [30] [35]. Additionally, certain TB strains are becoming resistant to these medications. Bedaquiline and Linezolid are two medications that may be added to therapy to combat drug resistance[59] [60], however they come with side effects such sickness or vomiting, loss of appetite, jaundice, dark urine, bleeding, and blurred vision.

II. CONCLUSION:

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Mycobacterium tuberculosis resistant strains are not the result of a single uniform genetic unit. Instead, it is the result of a recurrent mutation in a number of genes that code for bacterial resistance. Additionally, the thick impermeable cell wall and the presence of many efflux pumps are crucial for enduring the effectiveness of antibiotics. The slow metabolism throughout a protracted latent state also considerably increases its resistance to drugs. It may be useful to look at novel aspects of drug development if one has a sufficient understanding of the molecular underlying mechanisms of resistant strains in M. tuberculosis.

Antibiotic resistance in TB is still a result of human activity. It develops as a result of M. tuberculosis's spontaneous gene alterations, which make the bacterium resistance to some of the most widely used anti-TB medications. The initial cause of this is identified as non-compliance with the prescribed therapeutic interventions. The usual treatment regimen for TB entails a 6 prescription of four medications, which is prolonged to 18–24 months when second-line treatments are involved in MDR-TB. This makes adhering to treatment plans exceedingly difficult, as well as the levels of non-adherence may be significant, leading to subpar results and the spreading of MDR strains.

Despite the fact that resistance to antibiotics in M. tuberculosis is unquestionably linked to changes in a variety of genes, resistant strains frequently lack any known alterations. A deeper understanding of the relationship between active efflux systems and the emergence of therapeutic drug resistance, as well as the potential contribution of pores to the responsible for resistance to specific antibiotics, is also necessary. Therefore, it's crucial to increase our understanding of new drug resistance pathways to the present anti-TB medications. It could have a significant effect on how TB spreads and the research & establishment of innovative anti-TB medications.

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