JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue

JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)

An International Scholarly Open Access, Peer-reviewed, Refereed Journal

INFORMATION ON DRUG RESISTANCE TUBERCULOSIS : A SYSTEMIC REVIEW

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ABSTRACT

Three of the most deadly infectious illnesses that threaten global public health, particularly in middle- and low-income nations, are tuberculosis (TB), malaria, and acquired immune deficiency syndrome. TB brought about A third of the world's population contracts tuberculosis (TB), an infectious illness spread by the mycobacterium tuberculosis (Mtb) bacteria that causes around 16 million deaths annually. Drugs for tuberculosis are provided in various combinations of the four first-line medications (rifampicin, isoniazid, pyrazinamide, and ethambutol), which comprise the mainstay of treatment regimens throughout the first six to nine months of treatment. The failure of TB treatment can be attributed to a number of factors, including

(i) late Diagnosis,
(ii) Evolution of Drug-resistant TB strains.
(iii) Long Treatment duration
(iv) Lack of timely and proper administration of effective drugs,
(v) No adherence to drug regimen
(vi) Lower availability of less toxic, inexpensive and effective drugs,

Drug-resistant TB presents a serious obstacle to initiatives for TB treatment and control. Given the global context of the 558 000 new cases of TB that developed resistance to rifampicin in 2017—of which 82% developed multidrug-resistant TB (MDR-TB)—it is imperative that our understanding of the processes and molecular underpinnings of Mtb drug resistance be updated on a regular basis. The development of anti-tubercular medications, their mode of action, and treatment resistance mechanisms in multiple myelomavirus (MTB) is summarized in this narrative and traditional review. This review's objectives are to present current information on drug resistance mechanisms, newly produced or repurposed anti-TB drugs in the pipeline, and global guidelines for managing multidrug-resistant tuberculosis. It attempts to facilitate a better understanding of drug resistance for successful treatment and is based on latest literature and WHO standards. TB therapy and Clinical management.

INTRODUCTION

Mycobacterium tuberculosis (M2ytb) is the extremely contagious agent that causes tuberculosis (TB). Pneumonia is the primary site of infection for pulmonary TB, however other body parts can also contract the disease to develop extra pulmonary TB . It is the primary infectious agent-related cause of death, surpassing HIV/AIDS (World Health Organization, 2018). It is crucial to stop the spread of new Mtb infections and the development of TB illness. To lessen the toll that tuberculosis takes on disease and mortality. All 194 World Health Organization (WHO) and United Nations (UN) Member States unanimously decided to move toward the objective of eliminating the TB epidemic by 2030 and adopted WHO's END program in order to address this global need**.**

Face enormous expenses as a result of tuberculosis by 2035. Since 1997, the World Health Organization has released the Global Tuberculosis Report annually to present up-to-date, thorough data on tuberculosis epidemics and advancements in tuberculosis prevention at the national, international, and regional levels (Falzon. 2017; WHO 2018). 10 million TB infections (58 million men, 32 million women, and 10 million children) and 16 million TB fatalities (including 03 million co-infected HIV cases) were recorded in 2017 (WHO 2018).

Every nation on Earth has a tuberculosis epidemic. For TB, TB/HIV, and multidrug-resistant TB (MDR-TB), the World Health Organization (WHO) has established three lists of high burden countries (HBCs) for the first five years of the End TB strategy (2016–20), with at least 48 countries on each list. Fourteen nations—Angola, China, the Democratic Republic of the Congo, Ethiopia, India, Indonesia, Kenya, Mozambique, Myanmar, Nigeria, Papua New Guinea, South Africa, Thailand, and Zimbabwe—are listed in all three categories (WHO 2018). 84% of instances of TB worldwide, 83% of cases of TB/HIV, and 87% of cases of MDR-TB are caused by these HBCs each year (WHO2018).

Minimal prevalence of TB The least afflicted countries by tuberculosis (TB) exhibit yearly incidences of less than 10 cases of active TB disease per 100,000 people. High income nations like the United States, Canada, Australia, Western Europe, and New Zealand serve as examples of these. Smith, T., Wolff, K.A. and Nguyen, L., 2012. Molecular biology of drug resistance in Mycobacterium tuberculosis. Pathogenesis of Mycobacterium tuberculosis and its Interaction with the Host Organism, p et al. (2017), Khazaei. It is estimated that around 17 billion people, or 23% of the global population, have latent tuberculosis infections (LTBI) and are at risk of developing active TB disease at some point in their lives. The risk of contracting tuberculosis (TB) is significantly elevated in patients with immunosuppressive diseases, including HIV/AIDS, diabetes, cancer, organ transplantation, and renal Illness, misuse of alcohol, malnourishment, serious fungal infections,

Treatment with tumor necrosis factor alpha (TNF-a) antagonists, smoking, air pollution, cancers, among a population and numerous other issues Hameed et al. (2018); .A 6- to 9-month regimen consisting of a combination of four first-line medications—isoniazid, rifampicin, ethambutol, and pyrazinamide—is the current recommended treatment for drug-susceptible tuberculosis (TB) (Lienhardt et al. 2010. The 194 Member States successfully treat at least 85% of drug-susceptible TB cases, and they routinely report these cases to WHO. Nonetheless, drug-resistant strains of TB frequently evolve as a result of medication noncompliance, abuse, or incorrect administration (Nguyen 2016). Drug-resistant tuberculosis is also associated with other risk factors, Marais et al. (2013) .such as low socioeconomic position (job, education, income, poor nutrition), alcohol misuse, smoking, immigration status, co-infection with other diseases (HIV/AIDS, diabetes), and other conditions.

- TB patient living in the home, fungal infection, etc. (Singla 2017; Hameed et al. 2018; WHO 2018). Ensuring prompt and efficient TB diagnosis and sufficient infection control measures can effectively curb the progression of drug-resistant tuberculosis.
- TB treatment centers, prudent and appropriate usage of
- Therapy medications and patient adherence to medication schedule

- As well as societal knowledge about TB prevention and treatment
- (Menzies and Pinto, 2011).
- Nevertheless, drug-resistant tuberculosis continues to arise.
- Presents a significant danger to global public health and poses a challenge to effective disease management and tuberculosis therapy (Pavilions and Sulis 2016; WHO 2018). Medication resistance in
- MTB develops via a number of methods, such as
- Clonal interference, epistasis, compensatory evolution, and cell
- Drug degradation, efflux pumps, and envelope impermeability
- Drug phenotypic, target mimicking, and modification
- Understanding the biochemical, genetic and molecular
- Therefore, it is crucial to understand the basis of resistance in order to develop novel therapeutic approaches and battle medication resistance. In this analysis, the most current developments.
- Both current and upcoming novel or recycled anti-TB agents,
- How they work and how drugs develop resistance in
- This information is expected to help with improved comprehension of medication resistance for successful TB treatment and clinical management.

DRUG-RESISTANT TB

Drug-resistant tuberculosis strains that are appearing in community and hospital settings show varying degrees of drug resistance, including MDR, XDR, and rifampicin resistance (RR). Only rifampicin is resistant in RR-TB; other first- or second-line medications are not. MDR-TB is characterized by resistance to at least two of the most potent anti-TB medications, rifampicin and isoniazid. It was discovered that 82% of the 558 000 TB cases that were reported globally in 2017 were multidrug-resistant (MDR-TB) and that the cases were rifampicin-resistant (RR-TB).

Treatment for multidrug-resistant tuberculosis (MDR-TB) and recurrent tuberculosis (RR-TB) typically lasts eighteen months or longer and involves a mix of more costly and toxic second-line medications in addition to specific first-line medications. Treatment for MDR-TB has a 55% global success rate, according to WHO data. When MDR-TB is combined with resistance to at least one medication from each of the two major classes of second-line agents—fluoroquinolones and injectable—used in an MDR treatment regimen, the result is XDR-TB.

According to Seung et al. (2015), this implies that it involves resistance to any of the fluoro quinolones, including levofloxacin and moxifloxacin, as well as resistance to at least one of the three injectable second-line drugs, amikacin, capreomycin, or kanamycin. Furthermore, rifampicin and isoniazid resistance might possibly be involved. According to Migliori et al. (2007), there were reported isolated cases of tuberculosis in Europe in 2007 that did not respond to any first- or second-line anti-TB drugs. In 2009, Velayati et al. conducted a study in Iran which revealed that a group of fifteen patients had developed resistance to all anti-TB medications tested.

Very drug-resistant (XXDR)-TB and entirely drug-resistant (TDR)-TB are the names used by the authors of these reports, respectively, to describe their respective research findings. Subsequently, it was reported that four patients from India had TB that was completely drug-resistant (Udwadia et al. 2012). Nevertheless, the WHO has not yet approved a phrase such as “totally drug resistant” for tuberculosis (TB) since it is not well defined.

Currently, due in part to the limitations and technical difficulties of in vitro drug susceptibility testing (DST), these patients are also classified as XDRTB by the WHO. For traditional DST, a consensus has been obtained solely for medications that define MDR-TB and XDR-TB, following extensive research on suitable methodologies, critical drug concentrations defining resistance, reliability, and repeatability of results

(WHO/HTM/TB/2008a). For the other second-line medications, the repeatability and reliability of DST have not been proven and are still to be associated with the clinical outcome of treatment. As a result, the WHO does not recommend using these results to guide treatment (WHO/HTM/TB/2008b).

DRUGS AND STRATEGIES FOR IMPROVING TREATMENT OUTCOME OF TB

To meet the End TB Strategy targets set for 2030 and 2035, there will need to be an extraordinary acceleration in the rate of TB incidence drop after 2025. Only if the 1 to 7 billion people who are now infected globally have significantly less LTBI to Active TB disease will this faster rate—an average of 17% annually between 2025 and 2035—be conceivable. (WHO 2018). A state of persistent immune response to Mtb without the clinical signs of active TB disease is known as long-term benevolent immunity (LTBI). More effective LTBI medication therapies and the creation of a vaccine to stop adult LTBI reactivation are two medical approaches that reduce the probability of LTBI progression to active TB illness. Three priority groups for Testing and treatment of LTBI have been recommended By 2018 guidelines of WHO and these include HIV individuals, children below 5 years coming in contact with Confirmed pulmonary TB cases and clinical risk groups With anti-TNF treatment, dialysis, organ or hematological transplantation, silicosis etc (WHO 2018).

The Lack of access to interferon gamma release assay, tuberculin skin testing, or chest radiography should not impede treatment for long-term brain injury. The advantage of this shorter length is patient adherence to treatment regimen. The guidelines for LTBI treatment include four choices with varying combinations of dosages of rifampicin and/or isoniazid for 3-6 months (WHO 2018). Preventive medication should never be prescribed before active tuberculosis has been ruled out by screening for symptoms. There are two main types of anti-TB medications, according to WHO guidelines: Group-1, which consists of four first-line medications, and Group-2, which consists of second-line medications Isoniazid, rifampicin, pyrazinamide, and ethambutol are the four first-line anti-TB medicines that make up the mainstay of treatment for drug-susceptible TB in new patients (with active TB illness but who have not received prior TB treatment) (Tiberi et al. 2018; WHO 2018). Ethambutol is bacteriostatic, while rifampicin, isoniazid, and pyrazinamide are bactericidal first-line medications.

Using oral administration of combinations of first-line medications, more than 90% of patients with drug-sensitive tuberculosis remain cured after six months (Tiberi et al. 2018). The two-month intense phase of the drug-sensitive tuberculosis treatment regimen is followed by a four- or seven-month continuation phase, for a total of six to nine months of treatment. Mtb resistance to rifampicin and/or other anti-TB medications presents a risk to patient survival and public health. WHO classification of medications used in treatment regimens for susceptible-TB and MDR-TB recommendations 2016 (Da Silva 2011) is provided in The WHO's Guideline Development Group (GDG), which is composed of an international team of specialists with a wide range of technical knowledge, updates treatment guidelines for drug-resistant tuberculosis. In patients with RR/MDR-TB, the current guidelines prescribe a shorter, standardized treatment schedule of 9–12 months (Falzon et al. 2017). Revisions to the GDG's classification of the medications used to treat MDR/RR-TB and XDR-TB are based on the current evaluations of the safety and efficacy of the evidence (World Health Organization, 2016). There are now four groups (A, B, C, and D) for the Group-2 medications that make up the "core" second-line parts of a lengthier MDR-TB therapy regimen (WHO 2016; Hoagland et al. 2016). While some second-line medications are just bacteriostatic, the majority of them have bactericidal activity (Mpagama et al. 2013). Three subgroups, D1 (first-line anti-TB medications), D2 (bed aquiline and delaminate), and D3 (other agents of unknown role in MDR-TB treatment), comprise Group-D pharmaceuticals, which are add-on agents not part of the core MDR-TB regimen.

Despite being more costly and hazardous, only medications falling under groupings A, B, C, and D are useful for treating MDR-TB, according to the WHO (Tiberi et al. 2018). Group A medications, which include oral fluoroquinolones like levofloxacin, moxifloxacin, and gatifloxacin, are advised for the treatment of MDR-TB. Second-line injectables such aminoglycosides (e.g., kanamycin, amikacin), cyclic peptides (e.g., capreomycin), and aminoglycosides (e.g., streptomycin) are examples of Group-B medicines for MDR-TB.

Other essential second-line medications, such as isonicotinic acid derivative/ethionamide medicines (ethionamide/prothionamide), comprise group-C therapies for the treatment of MDR-TB.

D-cycloserine is a derivative of oxazolidinone (linezolid), iminopherazine (clofazimine), and cycloserine (terizidone). Nicotinamide derivatives (pyrazinamide), ethylene diimino di-1-butanol (ethambutol), and nicotinic acid hydrazide (high-dose isoniazid) are the subgroup-D1 medicines used in the treatment of MDR-TB. The MDR-TB regimen's subgroup-D2 consists of nitroimidazole (delamanid) and diarylquinoline (bedaquiline). Para-amino salicylic acid, meropenem, semi-synthetic thienamycin (imipenem), b-lactam antibiotics with blactamase inhibitors (Amoxicillin b-lactam antibiotic with clavulanate b-lactamase inhibitor), and thiacetazone are the drugs that make up Subgroup D3.

During the intense phase of the MDR/RR-TB treatment regimen, pyrazinamide and four second-line TB medications—one from Group-A, one from Group-B, and at least two from Group-C—are among the at least five effective TB medications. If the minimum quantity of potent TB medications cannot be combined as described above, additional Group-D3 agents and an agent from Group-D2 may be added. If further medications are discovered to be safe, they may be added to improve the likelihood of a cure (Falzon et al. 2017). Additional agents from Group-C or Subgroup-D2 may be used in place of an injectable drug (Group-B) in the event of nephrotoxic or hearing loss.

According to Falzon et al. (2017), the order levofloxacin, moxifloxacin, and gatifloxacin is preferred for oral fluoroquinolone usage. Because there is little data to support the effectiveness of ciprofloxacin and ofloxacin in MDR-TB regimens, it is advised that both be phased out. If the other three injectable medicines are not effective, streptomycin can be administered in their place. During the intensive phase of the MDR-TB core regimen, two or more of the following Group-C second-line agents, namely ethionamide (or prothionamide), cycloserine (or terizidone), linezolid, and clofazimine (Falzon et al. 2017), should be included. This will ensure that there are at least four effective second-line TB medications overall. The lengthier MDR-TB treatment plan may include bedaquiline or delamanid in addition to other second-line medications.

Bolster it. In combination, clavulanate and carbapenems are utilized in therapy. Only in patients of TB that are HIV-negative is Thioacetazone utilized (Falzon et al. 2017). With information on their therapeutic targets and cellular processes blocked, Table 2 enumerates the novel or repurposed medications in pipeline (undergoing clinical trials) and compounds under in vitro/preclinical development for the treatment of tuberculosis (TB) (Silva et al. 2018). From 17 in August 2017, to 20 in recent months, there are now more medications in the pipeline.

These include medications for the treatment of drug-susceptible TB, MDR-TB, or LTBI, and are now in various levels of clinical trials (I, II, or III). Out of these twenty medications, eleven are novel compounds: pretomanid, sutezolid, GSK-3036656, macozinone, OPC167832, pretezolid, delpazolid, Q203, SQ109, and TBI-166.Silva and associates (2018) The market is already filled with more recent fluoroquinolones, like gatifloxacin (authorized by the FDA in May 2010) and moxifloxacin (approved by the FDA in 1999). The US Food and Drug Administration (FDA) authorized bedaquiline in 2012 for the treatment of XDR-TB and MDR-TB. Delamanid, also marketed as Deltyba and formerly known as OPC-67683, was the first medication in a new family of medications known as nitroimadazoles to get conditional clearance from the European Medicines Agency (EMA) in April 2014.

In July 2014, the Japanese Regulatory Authority approved Delamanid. October 2014 saw the publishing by WHO of the interim policy guidelines for the use of delamanid for MDR-TB (Sloan and Lewis 2016). For those with fewer treatment options, certain trials conducted since 2016 have validated the use of bedaquiline and delamanid in combination (Ferlazzo et al. 2018). Clofazimine, linezolid, levofloxacin, moxifloxacin, nitazoxanide, rifampicin (high dose), and rifapentine are seven repurposed medications that are undergoing additional testing (Tiberi et al. 2018). There are already Rifamycin derivatives on the market, such as rifabutin (authorized by the FDA in December 1992) and rifapentine (approved by the FDA in June 2009).

Various combinations of treatment regimens using these new or repurposed drugs are under clinical trial phase II or III. Other new strategies currently under active investigation for improving outcomes of TB treatment include development of next-generation nano-based drug delivery vehicles using biodegradable polymers, liposomes and microspheres (Hari et al.) nano-based drug delivery systems, their properties, administration mode and present status of development. Nanocarrier-based drug

DRUG RESISTANCE MECHANISMS IN MYCOBACTERIUM

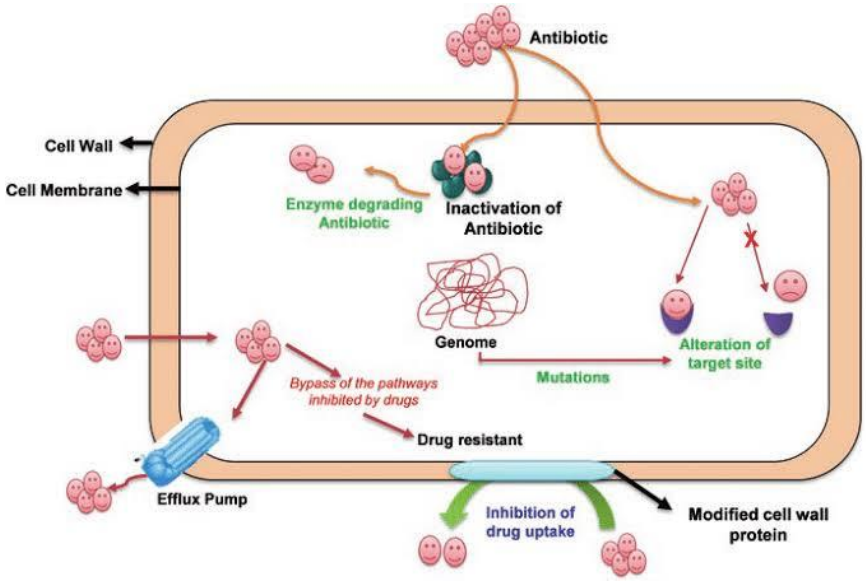

Fig No 1 :- Mechanism of drug resistance in Mycobacterium tuberculosis

Drug resistance is a problem to global public health and therapeutics and is a major barrier to the treatment of tuberculosis. Even while anti-TB medications are effective, drug-resistant Mtb isolates are starting to emerge. Drug degradation and modification, target mimicry, clonal interference, compensatory evolution, efflux pumps, cell envelope impermeability, and phenotypic drug tolerance are some of the mechanisms that promote the evolution of drug resistance in Mtb (Rojas et al. 2019). Both extrinsic (recently acquired mutations) and intrinsic (naturally present high levels of antibiotic resistance) antibiotic resistance may be the cause of treatment failure for tuberculosis.

For instance, Mtb has intrinsic resistance to the b-lactam class of antibiotics since its genome encodes for a blactamase enzyme (Nguyen 2016). Prolonged tuberculosis treatment frequently results in patients not adhering to their prescribed regimen and Mtb has rapidly evolved from being mono-drug resistant to being MDR and XDR. Understanding the mechanisms underlying antibiotic resistance is the first step towards combating drug resistance in Mycobacterium (Kurz et al. 2016).drug resistance that has been acquired Antibiotic resistance in bacteria is typically acquired by mutations or horizontal gene transfer via phages, transposon elements, or plasmids. However, there are no reports of horizontal gene transfer via mobile genetic elements in MTB. Rather, chromosomal mutations that encode drug targets or drug-activating genes are the main cause of treatment resistance in Mtb.

In order to control fitness, these resistance mechanisms may evolve through compensatory evolution. The acquisition of a second mutation, which lessens the negative effects of the first mutation and enables Mtb to preserve the resistant phenotype while increasing its fitness, mediates compensatory evolution. Additional or different mutations at intra-extragenic loci can lead to compensatory evolution (Saeedi and Hajoj-A 2017). In a guinea pig model, isoniazid-resistant Mtb isolates displayed reduced virulence (Koch et al. 2014).

Additionally, research showed that the co-occurrence of secondary mutations made up for Mtb's decreased fitness.

Alkyl hydroperoxide reductase (AhpC) overexpression resulting from a mutation in ahpC is an illustration of compensatory evolution linked to isoniazid resistance. According to Koch et al. (2014), a mutation in ahpC may have made up for the fitness cost of the Ser315Thr mutation in katG, which codes for catalase peroxidase and is involved in the bioactivation of isoniazid. In a similar vein, compensatory evolution that produced RR was also documented. Change 95% of clinical isolates with rpoB, which codes for the RNA polymerase b-subunit, showed high Level RR at the expense of fitness. On the other hand, MDR isolates with little to no cost fitness had the mutation S531L.

Following whole genome analysis, it was discovered that 0% of MDR-TB cases in HBCs carried mutations in rpoA and rpoC, which compensated for the fitness loss caused by mutation S531L. (Koch et al. 2014). According to a different study, an intragenic V615M mutation in the gene increased the rate of transcription elongation, compensating for the S531L mutation's reduced RNA polymerase activity and resulting in RR. There may be other fitness compensation methods available in addition to these Changes in gene regulation may mitigate compensatory mutations and the harmful impact of mutations (Dookie et al. 2018).

IMPERMEABILITY OF CELL ENVELOPE

Mycobacterial cell envelope has an unusual lipid composition and structure which contributes to virulence and Intrinsic drug resistance (Nguyen 2016). The most recent Model for mycobacterial cell envelope subdivides it into Three distinct entities namely outermost layer called capsule, cell wall and cell membrane (Nasiruddin et al.2017). The outer capsule is mainly formed of proteins, Glycan and little amount of lipids. The cell wall consists Of outer mycomembrane (MM), arabinogalactan (AG) And inner peptidoglycan (PG). MM has two leaflets, the Outer one formed of lipids such as phospholipids, treehouse mycolates, glycopeptidolipids and lipoglycans and The inner leaflet composed of long-chain mycolic acids(MA) (Nguyen 2016). The mycolic acid-arabinogalactan PG polymer forms a hydrophobic layer in association With other lipids and cytoplasmic membrane.

The Periplasmic space separating the cell wall from the membrane lipid bilayer protects the cells from environmental Stresses and acts as permeability barrier for antibiotics (Nguyen 2016). Furthermore, presence of wide array of Lipids makes the Mtb cell envelope extremely thick, highly Hydrophobic and hinders the diffusion of even hydrophobic molecules, which include antibiotics such as Rifamycin, macrolides, fluoroquinolones and tetracyclines (Gygli et al. 2017). It is speculated that the rate of diffusion is a function of hydrophobicity of the molecule only till certain Extent and beyond a limit, even highly hydrophobic Molecules cannot diffuse readily through Mtb cell envelope (Nasiruddin et al. 2017).

The function of mycobacteria Lipids In the cell envelope that confer inherent drug resistance was effectively illustrated by employing mutants with impaired cell envelope lipids, which showed elevated susceptibility to antibiotics (Nguyen 2016). Furthermore, the physical arrangement and chemical makeup of the lipids may have an impact on the fluidity of the cell envelope, which may have an impact on drug susceptibilities. According to Nasiruddin et al. (2017), fluidity in Mtb is thought to be a result of mycolic Acid structure and is influenced by the length of mycolic Acid and the presence of functional groups. Exposure to sub inhibitory concentrations of ethambutol has been shown to increase the fluidity of the cell envelope and the simultaneous transport of chemicals across it in M. smegmatis. This, in turn, increases the susceptibilities of the drug to combination therapy (Nasiruddin et al. 2017).

Consequently, any increase in fluidity brought on by a medication—like ethambutol, for instance—can make a previously resistant Mtb cell vulnerable to other drug classes. A malfunction in any of the proteins and enzymes that support the integrity of the Mtb cell wall can make a patient more vulnerable to various medications. Important biosynthetic enzymes for the production of PG include MurA and MurB (Nasiri et al. 2017). Fosfomycin, an antibiotic found in nature, inhibits MurA specifically and forms a covalent adduct with

a cysteine residue in the active sites. Aspartic acid replaces the equivalent cysteine residue in Mtb, displaying intrinsic

Fosfomycin resistance (Smith et al. 2013). Trehalose dimycolate (TDM) synthesis is dependent on proteins of antigen 85 (Ag85) complexes and is essential for maintaining the integrity of the Mtb cell wall. Ag85 gene inactivation changes the permeability of the Mtb cell membrane and its mycolate content, which increases susceptibility to first-line medications and other broad spectrum antibiotics (Smith et al. 2013). Consequently, Ag85's synthesis of TDM is necessary for Mtb's inherent resistance. Ag85-specific inhibitors by themselves, or in combination with additional antibiotics, may be a useful TB therapy approach.

GlmU, MurX, Alr, RmlC, Ddl, Pks12, and accD6 are additional examples of Mtb proteins that are involved in cell wall integrity. It has been shown that these proteins are desirable targets for the development of anti-TB drugs. It is well known that b-lactam antibiotics deactivate the crucial transpeptidase function of traditional penicillin binding proteins. Like other bacteria, mtb has D,D-transpeptidases in its structure. Additionally, it has been found that Mtb possesses five L,D-transpeptidases (LdtMt1 to LdtMt5), which are in charge of the resistance to b-lactam antibiotics like carbapenems and amoxicillin. Mtb that lacked LdtMt1 and LdtMt5 shown susceptibility to vancomycin and amoxicillin. PonA2 and PonA1, the two proteins that bind penicillin, are involved in the biosynthesis and homeostasis of cell wall components. Studies have shown that ß lactam sensitivity is increased four to eightfold in ponA2 mutants (Smith et al. 2013; Nasiri et al. 2017).According to Smith et al. (2013), porins are pore-forming proteins found on the outer layers of cell walls that allow hydrophilic compounds, nutrients, and tiny molecules to enter and support Mtb survival and replication. Numerous antibiotics are only able to pass through cell walls through porin. Hydrophilic chemicals cannot enter bacterial cells due to the lipidic composition of the cell wall and the reduced number of water-filled pores in the wall (Nguyen 2016). Despite Mtb encoding two

IMPERMEABILITY OF CELL ENVELOPE

The atypical lipid composition and structure of the mycobacterial cell membrane is linked to both intrinsic drug resistance and virulence (Nguyen 2016). According to Nasiruddin et al. (2017), the most recent model for the mycobacterial cell envelope splits it into three separate entities: the cell wall, the cell membrane, and the outermost layer known as the capsule. Proteins and glucan make up the majority of the outer capsule, with trace amounts of lipids. The components of the cell wall are inner peptidoglycan (PG), arabinogalactan (AG), and outer mycomembrane (MM). MM consists of two leaflets: an inner leaflet made up of long-chain mycolic acids (MA) and an outside leaflet made up of lipids such as phospholipids, treehouse mycolates, glycopeptidolipids, and lipoglycans (Nguyen 2016).

Mycolic acid-arabinogalactan PG polymer interacts with other lipids and the cytoplasmic membrane to generate a hydrophobic layer. The periplasmic gap, which divides the membrane lipid bilayer from the cell wall, serves as an antimicrobial permeability barrier and shields the cells from external stresses (Nguyen 2016). Additionally, a broad range of lipids contribute to the Mtb cell envelope's exceptional thickness and hydrophobicity, which prevents even hydrophobic molecules—such as tetracyclines, macrolides, fluoroquinolones, and antibiotics like rifamycin—from diffusing (Smith et al. 2013).

It is hypothesized that, up to a certain point, a molecule's hydrophobicity determines the diffusion rate; after that, even very hydrophobic molecules are thought to be less likely to diffuse easily through the Mtb cell membrane (Nasiruddin et al. 2017). The function of lipids in the mycobacterial cell membrane in granting innate resistance to drugs was effectively illustrated by employing mutants with impaired cell envelope lipids, which showed elevated susceptibility to antibiotics (Nguyen 2016).Furthermore, the lipids' physical arrangement and makeup are probably going to have an impact on the fluidity of the cell envelope, which can then have an impact on drug susceptibilities.

According to Nasiruddin et al. (2017), fluidity in Mtb is thought to be a result of mycolic Acid structure and is influenced by the length of mycolic Acid and the presence of functional groups. According to

Nasiruddin et al. (2017), it has been shown that exposure to subinhibitory concentrations of ethambutol increases the fluidity of the cell membrane and the simultaneous diffusion of substances across it, boosting drug susceptibilities in combination therapy. Consequently, any increase in fluidity brought on by a medication, like ethambutol, can render

CONCLUSION

Treatment for tuberculosis and worldwide public health are seriously threatened by the sharp rise in tuberculosis cases around the world and the advent of drug-resistant strains of Mtb. Mtb is naturally resistant to the majority of antibiotics, but it also frequently develops resistance in reaction to them. The Mtb cells are resistant to the majority of antibiotic classes due to a combination of intrinsic and acquired drug resistance mechanisms, including genetic mutations, chromosomal changes, cell envelope impermeability, drug efflux, drug degradation and modification, target alteration, and target mimicry. The bacteria develop resistance to the antibiotics that are now on the market thanks to newly acquired mutations and the progressive chromosomal accumulation of such alterations. Through acquired compensatory mutations, MDR strains further stabilize transmissibility by regaining fatness. The rise of MDR and XDR strains poses a constant concern, especially with the introduction of new anti-TB medications into the market. The change from the metabolically active, replicating form of Mtb to the dormant, nonreplicating form results in phenotypic drug tolerance and acts as a recalcitrant component in TB therapy, in addition to inherent and acquired drug resistance. Due to recent developments in biology and genetics, we now have a far better understanding of the remarkably diverse range of antibiotic resistance pathways found in Mtb. Even still, there is still room for more research to fully understand the molecular causes of antibiotic resistance in this particular class of bacteria, despite significant advancements. The use of current antibiotics in therapy is restricted by these drug resistance and drug tolerance processes, which also obstruct the creation of novel anti-TB medications. To further enhance the therapeutic outcomes for TB patients, a deeper understanding of the precise mechanisms underlying Mtb antibiotic resistance is the best hope for the future. The development of anti-tubercular drugs (old/new/repurposed), their mechanism of action, and the mechanisms of Mtb drug resistance are all summed up in this review. It was created with the goal of facilitating a better understanding of drug resistance for efficient TB therapy and clinical management. It is based on latest literature and WHO guidelines.

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ACKNOWLEDGEMENT

Every great work is supported by diligence and sincerity. We are able to learn a great deal of theoretical and practical information over this period of work. Without the assistance of my esteemed advisor, Dr. Neha N. Rajpurohit, our project work would not have been feasible. I appreciate your unwavering encouragement, inspiration, zeal, leadership, and support. We are incredibly appreciative of everyone who has supported us throughout our project work on “information on drug resistance tuberculosis : a systemic review” We appreciate you. The facilities to carry out this work were provided by Dr. K Raja Rajeshwari, Principal of Vardhaman College of Pharmacy, Koli Karanja (Lad). We would also like to thank All of our esteemed teachers for sharing their knowledge, working with us, and inspiring us throughout this Effort. We are grateful to Dr. Varsha Rathod ma’am the Hon. President and Dr. Manoj Jain Sir, the Hon. Secretary, for providing the necessary facilities for us to complete this task.