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Drug-Resistant Tuberculosis: Molecular Mechanisms And Emerging Challenges In Mycobacterium Tuberculosis

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ABSTRACT

Tuberculosis continues to represent a major global public health concern, particularly due to the increasing prevalence of drug-resistant strains of Mycobacterium tuberculosis. Despite the availability of effective chemotherapy, the emergence of resistance to both first-line and second-line anti-tuberculosis drugs has significantly undermined disease control efforts worldwide. Unlike many other bacterial pathogens, M. tuberculosis primarily acquires antibiotic resistance through spontaneous chromosomal mutations rather than horizontal gene transfer. These mutations affect drug targets, drug-activating enzymes, transcriptional regulators, and metabolic pathways, leading to reduced drug susceptibility and treatment failure.

This review comprehensively examines the molecular mechanisms underlying antibiotic resistance in M. tuberculosis. Resistance to first-line drugs such as isoniazid and rifampicin is largely attributed to mutations in genes including katG, inhA, and rpoB, which impair drug activation or alter target binding. Resistance to second-line agents, including fluoroquinolones and injectable aminoglycosides, is associated with mutations in gyrA, gyrB, and ribosomal components, as well as enzymatic drug modification. In addition, the role of efflux pump systems in mediating multidrug tolerance and contributing to unexplained resistance phenotypes is discussed. These pumps enhance bacterial survival by reducing intracellular drug concentrations and promoting phenotypic heterogeneity.The review also outlines the classification of drug-resistant tuberculosis, including mono-drug resistant, multidrug-resistant, pre-extensively drug-resistant, extensively drug-resistant, and totally drug-resistant tuberculosis, highlighting their clinical and epidemiological significance. Furthermore, emerging evidence on metabolic adaptations, persister cell formation, and stress response pathways that facilitate drug tolerance is addressed. A detailed understanding of these resistance mechanisms is essential for improving molecular diagnostics, optimizing treatment regimens, and guiding the development of novel therapeutic strategies aimed at curbing the global burden of drug-resistant tuberculosis.

Keywords: Antibiotic resistance, Mechanism, Mycobacterium Tuberculosis

1.Introduction And Background :-

A significant worldwide public health concern is still tuberculosis (TB) [1]. Mycobacterium tuberculosis, the slow-growing bacterium that causes tuberculosis (TB), has been associated with humans since the early stages of human colonisation from east Africa [2]. Airborne infections that move from person to person are the microorganisms that cause tuberculosis (TB). However, TB mostly affects the brain, kidneys, spine, lungs, and other organs. Although TB is usually treatable, people may not live if treatment is not received. whenever someone with tuberculosis (TB) of the throat or lungs sings, speaks, coughs, or sneezes. These microbes can infect neighbours if they breathe them in [3]. Every region of the world is affected by

tuberculosis (TB), and numerous cases have been reported from all over the world. Every year, millions of people die from tuberculosis (TB), which affects around one-third of the population. Mycobacterium tuberculosis (MTB), which mostly affects the lungs but can sometimes infect other organs, is the source of the illness. The rise of multidrug resistance (MDRTB) and extensive drug resistance (XDRTB) strains is currently the greatest obstacle to treating this illness, and it is still a serious but mostly unsolved problem [4].Robert Koch discovered the causative agent of human tuberculosis (TB) more than a century ago [5].The World Health Organisation designated human tuberculosis (TB), a deadly illness brought on by the gram-positive, acid-fast eubacterium Mycobacterium tuberculosis, as a global health emergency in 1993. With an estimated 1.8 million fatalities annually, mostly in underdeveloped nations, tuberculosis (TB) continues to be one of the deadliest infectious illnesses (World Health Organisation) [6].Drug-tolerant persisters, which withstand antibiotics without undergoing genetic alterations, are frequently the source of drug-resistance (DR) in bacteria. The bacteria that causes tuberculosis (TB), Mycobacterium tuberculosis (Mtb), may go through a similar transitional process. According to recent research, persister development and medication resistance are mostly dependent on modifications in trehalose metabolism. Here, we find that fewer DR mutants were present in mutants lacking trehalose catalytic shift activity because of fewer persisters. This change increases medication tolerance and metabolic heterogeneity, which promotes drug resistance and improves Mtb survival after antibiotic treatment. [7] Four medications (isoniazid [INH], rifampicin [RIF], ethambutol [EMB], and pyrazinamide [PZA]) are used as the usual treatment for drug-susceptible tuberculosis (TB) for two months, followed by INH and RIF for four months. Even among patients with verified drug-susceptible tuberculosis, there is interpatient variability in the responsiveness to this standardised treatment regimen. The time to culture conversion, or the interval between the start of treatment and the first of two consecutive negative cultures, is a crucial indicator of the responsiveness to treatment. This varies from patient to patient, with 95% confidence intervals between 41 and 83 days (4–6). Additionally, some patients relapse even if they were completely compliant with treatment, even though the majority of patients are cured and remain free of TB after completing a 6-month treatment plan [8].

Etiology :

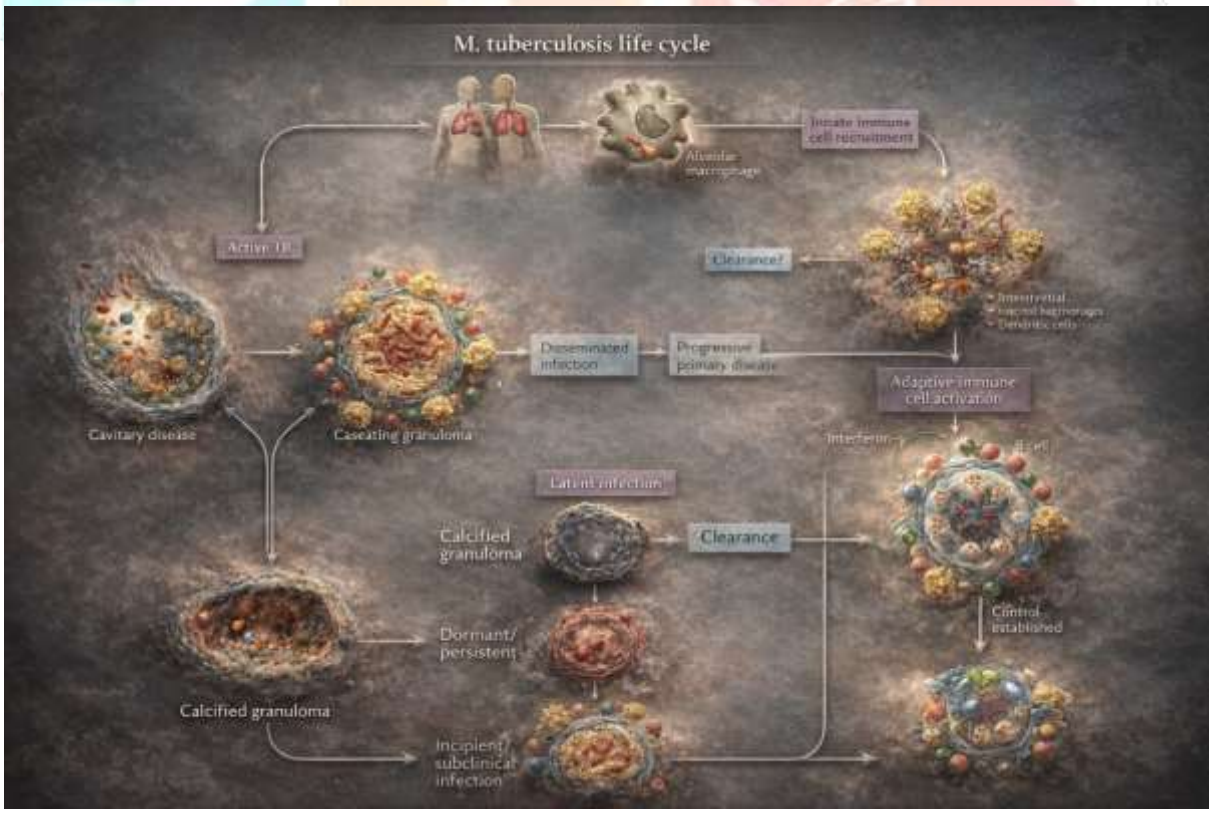

Fig1: Mycobacterium tuberculosis life cycle (9)

3.Mechanisms of drug resistance in M. tuberculosis:-

Mycobacterium tuberculosis's resistance to anti-TB medications is man-made. Clinical resistance is almost never present in wild isolates of M. tuberculosis that have never been exposed to anti-TB medications. Although there are a few outliers, it is not believed that they significantly add to the total burden of resistance. For example, isolates of M. tuberculosis from patients in the United Kingdom were shown to have a lower average level of resistance to para-amino salicylic acid (PAS) than isolates from Madras (Chennai), India. We refer to this resistance as natural resistance[10]. Antibiotics may be rendered ineffective by enzymatic cleavage after entering the cell wall as a first line of defence. The enzymatic breakdown of β-lactam antibiotics by β-lactamases, which hydrolyse the antibiotics' β-lactam ring, is one of the most notable instances. Early research on penicillin showed that M. tuberculosis is inherently resistant to this family of antibiotics (Abraham et al. 1941). One class A β-lactamase, known as BlaC, is encoded in the genome of M. tuberculosis and is believed to be located in the periplasmatic space, either unbound or attached as a lipoprotein in the outer leaflet of the plasma membrane. Despite having different affinities, the M. tuberculosis β-lactamase exhibits broad substrate specificity, including carbapenems, and is regarded as an extended-spectrum β-lactamase. The β-lactamase inhibitor clavulanate inhibits BlaC irreversibly (Wang, Cassidy, and Sacchettini 2006; Hugonnet and Blanchard 2007). There has been a resurgence of interest in the use of β-lactam antibiotics in the treatment of tuberculosis due to the rise in cases caused by MDR/XDR M. tuberculosis strains. When treating patients infected with MDR M. tuberculosis strains, a salvage regimen (a regimen of last resort with unknown effectiveness) that included an amoxicillin/clavulanate combination had no positive effects, according to an early, small research (Yew et al. 1995). Since then, a number of in vivo (Payen et al. 2012; De Lorenzo et al. 2013) and in vitro (Chambers et al. 1995; Hugonnet et al. 2009) investigations have shown promising findings on treatment outcomes with different regimens by combining β-lactam antibiotics with clavulanate Nevertheless, certain MDR/XDR M. tuberculosis isolates still seem to be resistant to amoxcicillin/clavulanate or mereponem/clavulanate without carrying any changes that would account for the observed variation in sensitivity to these medications (Cohen et al. 2016). More research is needed to determine the actual efficacy of β-lactam antibiotics in treating drug-resistant M. tuberculosis variations. The limited treatment choices for MDR/XDR TB and the proven safety profile of β-lactam antibiotics/β-lactamase inhibitors call for more research into treatment regimens that include this class of antibiotics, given the favourable outcomes in several trials. Antibiotics can be rendered inactive by alteration, such as methylation or acetylation, in addition to drug breakdown. The most well-explained method of medication inactivation by chemical alteration in M. tuberculosis to date is the process by which the enhanced intracellular survival protein (Eis) acetylates different aminoglycoside/cyclic peptide antibiotics used to treat MDR TB. Eis has been shown to acetylate and deactivate the cyclic peptide antibiotic capreomycin (Houghton et al. 2013) and the therapeutically useful second-line injectable aminoglycoside antibiotic kanamycin A (Zaunbrecher et al. 2009). Overexpression of Eis, which results in low-level resistance to kanamycin A but not amikacin, is caused by a number of promotor mutations seen in clinical M. tuberculosis isolates (Zaunbrecher et al. 2009; Kambli et al. 2016). Whether Eis overexpression alone results in clinically significant levels of capreomycin resistance is unclear (Kambli et al., 2016).Therefore, overexpression of Eis may be a precursor to the development of high-level resistance to aminoglycosides and cyclic peptides. M. tuberculosis has recently been found to have a unique drug inactivation mechanism. According to Warrier et al. (2015), the pyrido-benzimidazole compound "14" has strong bactericidal action against aerobically developing M. tuberculosis. A yet unidentified methyltransferase encoded by the gene Rv0560c may N-methylate compound 14. The target, decaprenylphosphoryl-β-D, cannot be inhibited by the methylated compound 14.

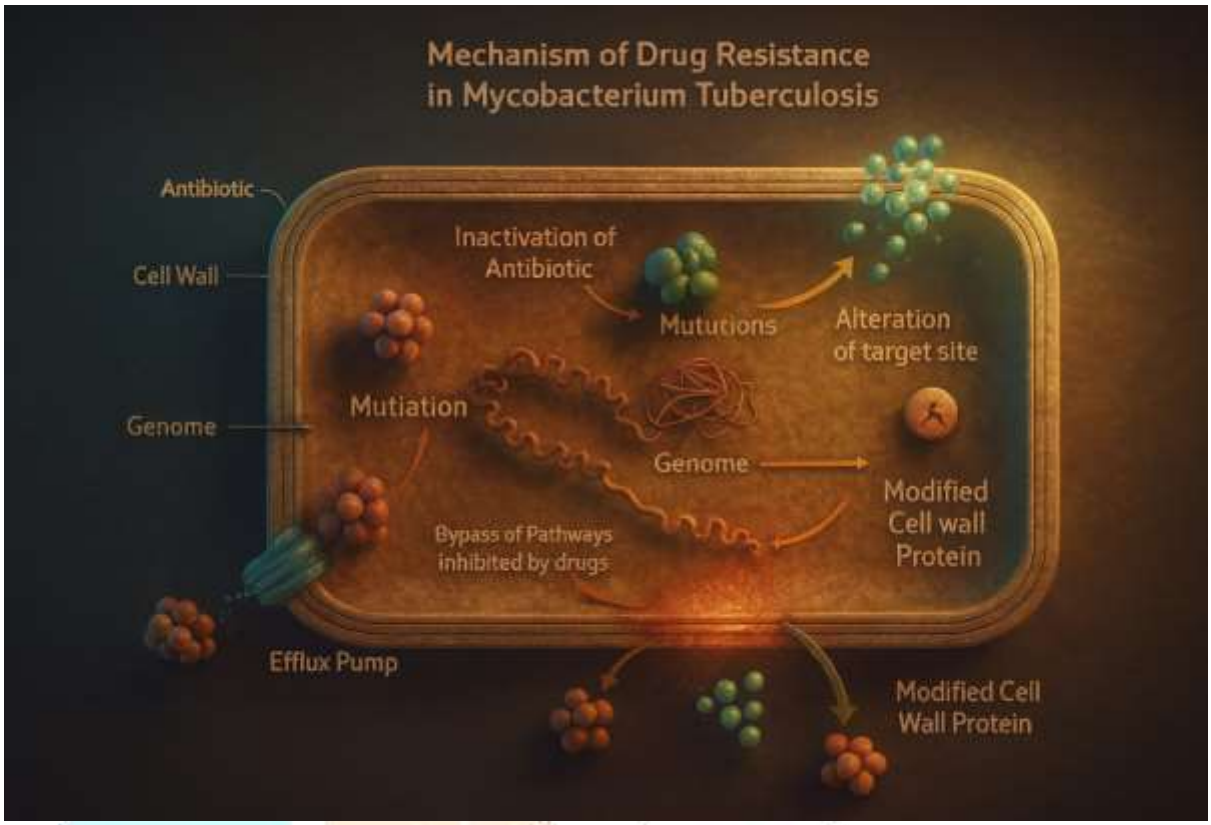

Fig2: Mechanism of Drug Resistance in Mycobacterium Tuberculosis [11]

Enzymatic drug target modification:

Since many of the antibiotics now in use are naturally occurring substances made by bacteria, the bacteria that create them must be resistant to these substances; mycobacteria share some of these processes. Several kinds of antibiotics, such as macrolides, lincosamides, and streptogramins, are produced by Streptomyces species. By attaching to the 50S ribosomal subunit, these antibiotics block the bacterial ribosome. By producing methyltransferases that mono- or dimethylate the adenosine residue 2058 (Escherichia coli notation) of the 23S rRNA, Streptomyces species are resistant to various antibiotics. This prevents the medicines from attaching to the ribosome and halting translation.The methyltransferase Erm(37), a homologue of Erm methyltransferases seen in several actinomycetes, is encoded by the M. tuberculosis genome. Erm (37) may monomethylate residues 2057–2059 of the 23S rRNA rather than only residue 2058, which sets it apart from its homologues in terms of substrate selectivity. Resistance to several macrolide antibiotics is conferred by monomethylation of locations 2057–2059 (Buriankova et al. 2004; Madsen et al. 2005).

Drug efflux in Mycobacterium tuberculosis:

Efflux systems are crucial components of both eukaryotic and bacterial physiology. Efflux systems in M. tuberculosis have been the subject of several published reviews (Louwet al. 2009, 2011; da Silva et al. 2011; Warrell 2012; Anthony. Malinga and Stoltz 2016); the key ideas are outlined below. According to early comparative studies, M. tuberculosis's genome encodes a wide variety of putative efflux, including those that belong to the classes of ATP-binding cassette, major facilitator superfamily, small multidrug resistance, multidrug and toxic compound extrusion systems, and resistance-nodulation-cell division (Paulsen et al. 2001).Although debatable, the significance of drug efflux in producing clinically meaningful treatment resistance in M. tuberculosis has drawn increased attention recently.

Drug efflux may account for the finding that around 30% of clinical M. tuberculosis isolates resistant to isoniazid (Louw et al. 2009) and 3% of isolates resistant to rifampicin (Telenti et al. 1993) do not exhibit any known resistance mutations. However, the fact that not all medication resistance mutational targets are

identified may complicate this inexplicable resistance. Numerous resistance mechanisms are already known for several antibiotics, such as isoniazid (Vilcheze and Jacobs 2014). However, the role of efflux pumps to unexplained resistance phenotypes is more plausible since resistance to rifampicin is believed to be acquired exclusively by mutations in the gene encoding one ingredient of the drug target (more explored below). Efflux pumps may extrude a wide range of structurally unrelated molecules and show significant degrees of substrate promiscuity. Additionally, it has been demonstrated that M. tuberculosis requires efflux mechanisms for intracellular development in macrophages (Lamichhane, Tyagi, and Bishai 2005). Nearly all antituberculous medications, such as streptomycin, rifampicin, isoniazid, clofazimine, bedaquiline, fluoroquinolones, and ethambutol, can be extruded by mycobacterial efflux pumps (Anthony Malinga and Stoltz 2016).

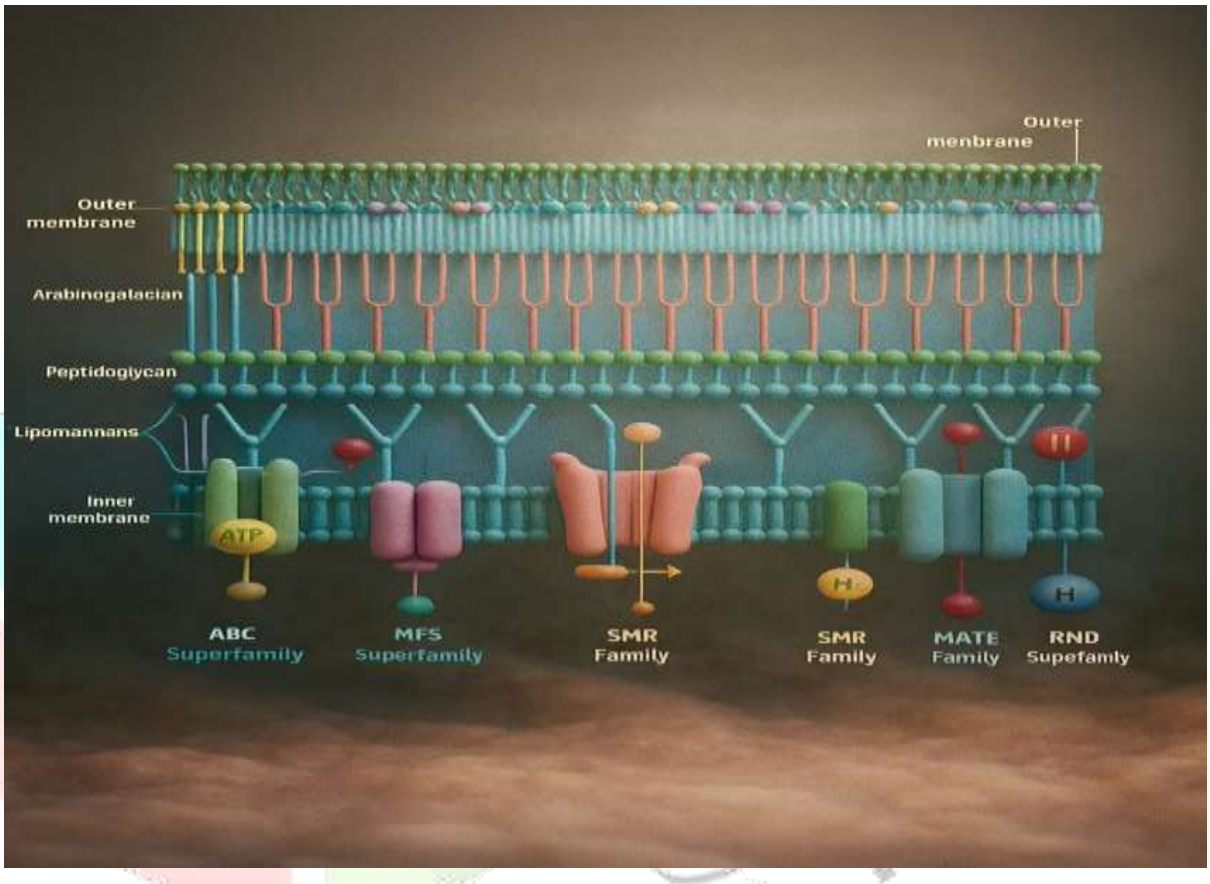

Fig3: Drug efflux in Mycobacterium tuberculosis [12]

Efflux pump expression may be thought of as a flexible attribute, which means that changes in the environment can alter expression levels through non-mutational mechanisms. Therefore, we may state that the presence of a certain environmental signal (such as antibiotics or the intracellular environment of a macrophage) induces or upregulates efflux pumps. Only mutants whose expression levels beyond the wild-type strains' response norm should be referred to as "overexpressing." The reaction norm of efflux pumps in M. tuberculosis has not, as far as we are aware, been thoroughly studied [6a].

4.Types of drug-resistant tuberculosis :-

Mono drug-resistant tuberculosis-

TB that is resistant to just one first-line anti-TB medication is known as mono drug-resistant TB. Rifampicin-resistant TB (RR-TB) and INH-resistant TB (INHr-TB) are two instances of monodrug-resistant TB. MTB bacteria that are resistant to R generate RR-TB, a form of tuberculosis. Because policy and research agendas are only focused on R resistance, which is thought to be a surrogate marker for MDR-TB, INHr-TB, a kind

of TB caused by MTB strains resistant to INH, is more prevalent than R resistance and is a developing worldwide public health concern.

(Multi-drug resistant tuberculosis)

Drug-resistant TB known as MDR-TB is brought on by MTB strains that are resistant to both R and INH. Two important first-line anti-TB medications are R and INH. Currently, the biggest obstacle to resolving the worldwide TB issue is the rise of drug-resistant MTB strains. Compared to Drug-Susceptible TB (DS-TB), MDR-TB is more difficult to treat. Patients with MDR-TB have a much higher death rate than those with DS-TB. The two biggest obstacles in the fight against drug-resistant tuberculosis have been improper treatment regimens and delayed diagnosis. The majority of underdeveloped nations have difficulties in promptly diagnosing drug-resistant tuberculosis and treating these patients empirically until they are deemed cured. Patients with poorly maintained MDR-TB/RR-TB disseminate drug-resistant MTB strains across their communities. Children have an extremely high risk of contracting drug-resistant MTB strains if they reside with patients who have these strains. There have been reports of nosocomial transmission of drug-resistant MTB strains to both HIV-positive patients and healthcare personnel in clinical settings.

Pre-extensively drug-resistant tuberculosis- Pre-extensively drug-resistant tuberculosis (Pre-XDR TB) is characterised by resistance to INR and R in addition to any one FLQ (ofloxacin, levofloxacin, gatifloxacin, or moxifloxacin) or any one of the second-line injectable medications/SLIDs (capreomycin, kanamycin, or amikacin). A high incidence of pre-XDR TB, which may eventually develop into XDR-TB, is caused by poor case management of MDR-TB[1]. When Pre-XDR TB is identified in MDR-TB patients, effective measures can be adopted to stop the development of Pre-XDR to XDR-TB and assist prevent treatment failure of MDR-TB [1,55,56].

Extensively drug-resistant tuberculosis-

The World Health Organisation has redefined XDR-TB as resistance to R and INH plus any FLQ plus any of the SLIDs (amikacin, capreomycin, or kanamycin) and at least one additional group A drug (linezolid or bedaquiline). Previously, XDR-TB was defined as a type of drug-resistant TB caused by MTB strains that are resistant to the first-line drugs, INH and R, plus any FLQ and at least one of the three SLIDs. When a patient has both HIV and XDR-TB, the disease worsens and advances more quickly than when the patient simply has XDR-TB.

Totally drug-resistant tuberculosis-

MTB strains that are resistant to all first- and second-line anti-TB medications create TDR-TB, a form of drug-resistant tuberculosis. There have been reports of TDR-TB in South Africa, Italy, Iran, and India. TDR-TB may exist in other nations even though it has only been documented in these four. However, it is difficult to identify instances with TDR-TB due to insufficient molecular diagnostic laboratory facilities, particularly in nations with minimal resources. TDR-TB develops from poorly treated XDR-TB [13].

5.Classification of anti TB drug.

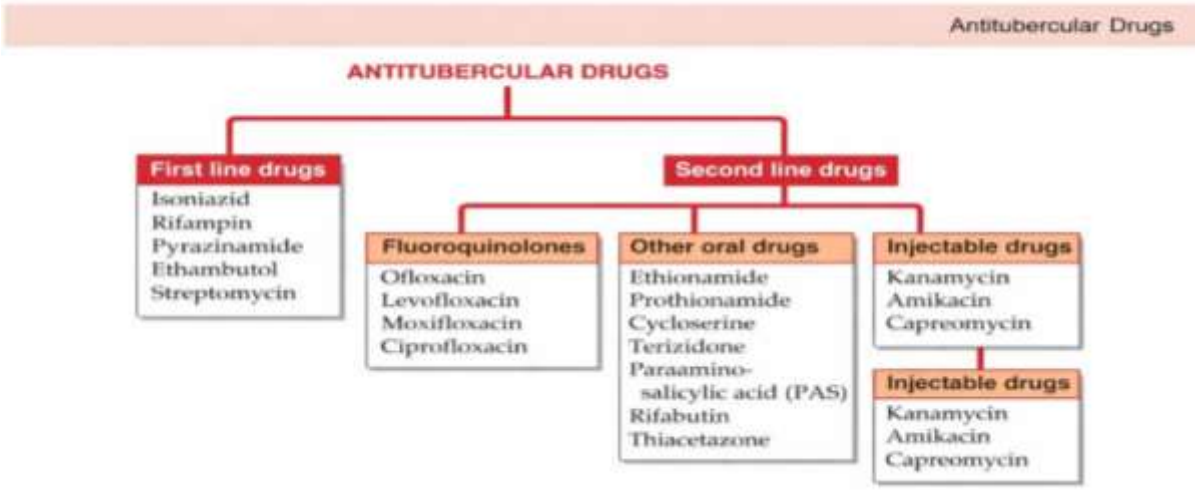

Fig4: Classification of anti TB drug [14].

Classification of Anti-Tuberculosis Drugs:

1. First-line drugs:

a) Bactericidal: Isonicotinic acid hydrazide (H), rifampicin (R) and pyrazinamide b) Bacteriostatic: Ethambutol (F)

2.Second-line drugs:

a)Bactericidal: Fluoroquinolones (FQ-Levofloxacin Lfs and moxifloxacin: Mix); Injectables eg amikacin (Am), streptomycin (S), capreomycin (Cm) and kanamycin (K);

b)Bacteriostatic: Ethionamide (Et), cycloser ine (C), terizidone (Trd), clofazimine (Cfz linezolid (Lzd),

3.Third-line drugs: Bedaquiline (Bdq), delamanid (Dlm), umipenem plus cilastatin (Ipm-Cln), meropenem (Mpm), thiacetazone (T), paraminosalicylic acid (PAS)The second and third-line drugs are used for multidrug resistant (MDR) and extensively drug resistant (XDR) TB.

[A single drug should never be used to treat TB, as this leads to the rapid development of drug-resistant tubercle bacilli [15].

First-Line Anti-TB Drugs:

Isoniazid: The primary antibiotic used to treat TB is isoniazid. Usually found in its inactive state, isoniazid is metabolized by the body to become active. The two primary underlying mechanisms of isoniazid resistance are associated with gene mutations in the katG&inhA or its regulatory domain. In fact, several studies have found that changes exist in the two genes most commonly associated with isoniazid susceptibility. It has been discovered that most of them contain the katG gene mutation S315T, which stops isoniazid products from forming the isoniazid-NAD combination required to exhibit their antibacterial properties. High susceptibility to isoniazid has been frequently linked to this variation, which is more prevalent in strains resistant to several drugs. The active site of InhA is impacted by the second most common mutation, which lowers the sensitivity of InhA to the isoniazid-NAD combination. InhA is overexpressed as a result of these two mutations. The most common mutation found is at position 15C/T, and it is often associated with mild isoniazid tolerance.

Mode of action: MTB-resistant strain with mutations in katG and inhA. The katG 315T mutation is seen in MTB isolates from individuals in the Republic of Moldova who have (MDR) and (XTR) tuberculosis. A recent interesting finding revealed that the 4R isomer of the isoniazid-NADP crosslinking inhibits the dihydrofolatereductase (DfrA) in M. tuberculosis, indicating that dfrA mutations may be a factor in isoniazid resistance. Furthermore, proteome analysis of isoniazid attacks in M. tuberculosis discovered sixteen other proteins that were cross-linked with higher affinity in addition to InhA and DfrA, indicating that the medication may have additional, as yet unknown, impacts on the bacterium. Despite this, two subsequent investigations have not discovered a dfrA mutation associated with isoniazid tolerance Since ahpC transcripts an alkyl hydro peroxidase reductase connected to resistance to reactive oxygen intermediates, it was initially suggested that mutations in the promoter of ahpC may be used as representational indications for isoniazid-resistant M. tuberculosis. Isoniazid-resistant strains of M. tuberculosis have been shown to contain genetic variations in other genes, including kasA and the oxyR-ahpC and furA-katGintragenicarea

Second-Line Anti-TB Drugs:

Fluoroquinolones: Currently, MDR-TB is treated with fluoroquinolones as a second medicine. Both ofloxacin and ciprofloxacin are synthetic forms of the parent compound nalidixic acid, which was discovered to be a byproduct of the parasite chloroquine. Newer generation quinolones, such as moxifloxacin and gemifloxacin, are now being investigated in clinical trials and recommended as the first medicines to shorten the duration of TB therapy. A chemotherapeutic drug called fluoroquinolone, mostly ciprofloxacin, is used to treat TB. Gyrase and topoisomerase IV, two enzymes involved in bacterial DNA synthesis, are inhibited by fluoroquinolones. gyrA or gyrB mutation resistance. There are two primary ways that fluoroquinolone resistance arises: changes in the drug target enzymes, such as gyrase and topoisomerase IV, and changes in how the drug target enzymes are accessed. Fluoroquinolone resistance in Mycobacterium tuberculosis is also influenced by the bacterial cell wall.

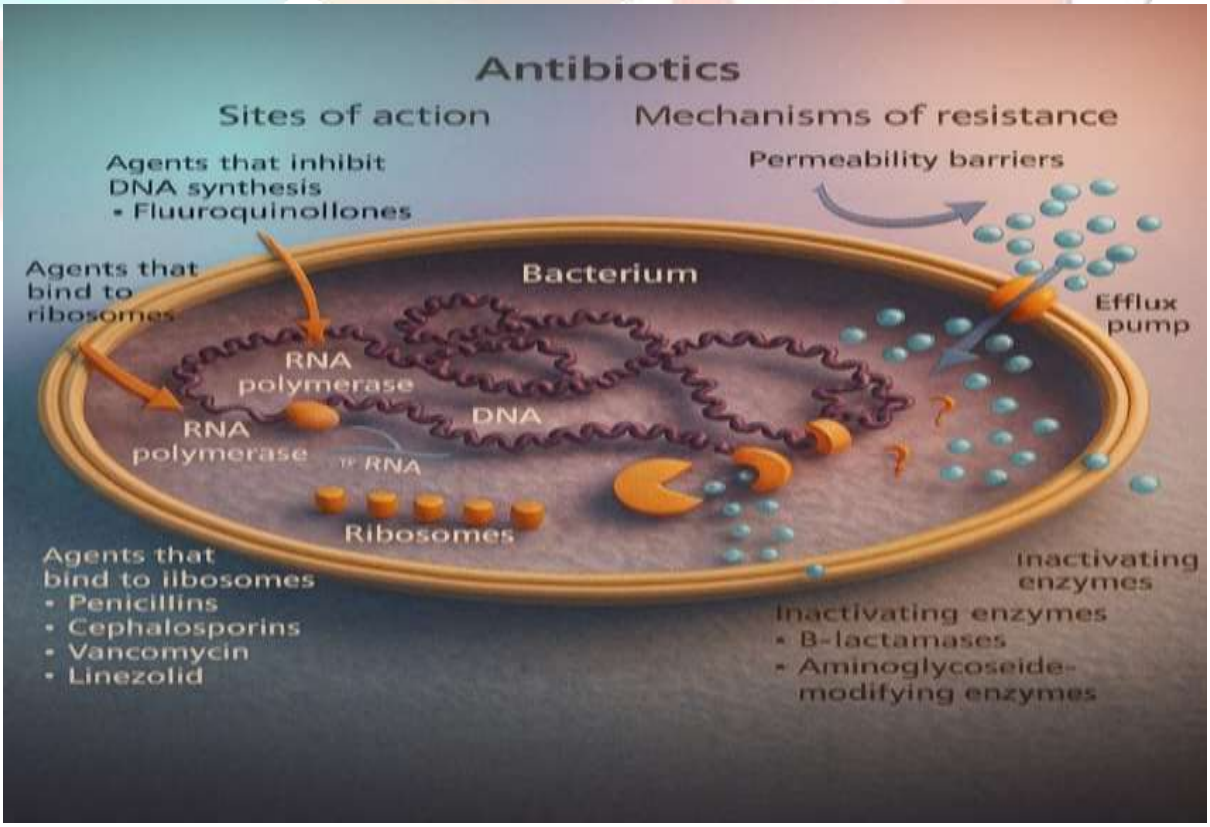

Fig5: Sites of action / Mechanisms of resistance [16]

Mode of action: Gyrase and topoisomerase IV, two enzymes involved in bacterial DNA synthesis, are inhibited by fluoroquinolones. gyrA or gyrB mutation resistance. There are two primary ways that fluoroquinolone resistance arises: changes in the drug target enzymes, such as gyrase and topoisomerase IV, and changes in how the drug target enzymes are accessed. Fluoroquinolone resistance in Mycobacterium tuberculosis is also influenced by the bacterial cell wall.

Linezolid: Because it is an oxazolidinone, it is utilised in clinical settings to treat skin conditions and nosocomial pneumonia. Linezolid functions by preventing the 50S ribosomal subunit from binding, which is the initial stage of protein assembly. A more recent study using next-generation sequencing has identified in vitro chosen mutants, clinical isolates of Mycobacterium TB resistant to linezolid, and the mutation T460C in response, encoding the 50S ribosomal L3 protein [17].

2.Characterization of Mycobacterium tuberculosis:

M. tuberculosis is one of the pathogenic bacteria in the Mycobacteriaceae family. 2019 saw the discovery of the combination of M. tuberculosis sensu stricto, M. africanum, M. Canetti, M. bovis, M. caprae, M. microtia, M. pinniped, M. fungus, & M. origins. It is non-motile, requires oxygen to thrive, and it's debatable if it produces spores. Every 18 to 24 hours, M. tuberculosis divides. This is extremely sluggish in comparison to other bacteria, whose division times are usually measured in minutes. It is a little bacillus that may survive for weeks in a dry environment and withstand inadequate disinfectants. Its resistance to desiccation is likely due to its distinct cell wall, which is rich in lipids like mycolic acid and a key component of its pathogenicity. Microscopy: The fixed smear was colored with auramine fluorochrome stain. The acid fastness feature was assessed using Ziehl-Neelsen staining, which is essential for M. tuberculosis infection screening. Culture: M. tuberculosis is selectively cultivated using solid agar and egg-based culture medium, such as Middle Brook 7H11 & Lowenstein Jensen (LJ). Recently, the diagnostic lab adopted matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) as a precise and straightforward method of detecting yeasts and bacteria. Genome: The genome of the H37Rv strain was made public in 1998. In addition of utilising the lipid cholesterol as a carbon source, M. tuberculosis may also thrive on it.

At various stages of the infectious disease lifecycle of M. tuberculosis, genes implicated in the cholesterol consumption pathways have been shown to be essential, especially during the persistent phase of the illness when alternative nutrients are most likely unavailable. History: The recipient was Robert Koch. The discovery of M. tuberculosis, often known as the "tubercle bacillus," on March 24, 1882, earned him the Nobel Prize in Physiology or Medicine (1905). Thus, "Koch's bacillus" is another name for the M. tuberculosis bacterium. Sneezing, coughing, or even talking can easily transmit M. tuberculosis via the air. Anybody can get M. tuberculosis by reacting to a contaminated droplet. An estimated 1.8 billion people worldwide develop the aforementioned illness each year [17a].

6.Conclusion:

Tuberculosis remains a serious global health problem, mainly because Mycobacterium tuberculosis is becoming resistant to many anti-TB drugs. This resistance develops mostly due to mutations in the bacterium’s own genes rather than by acquiring resistance from other bacteria. These mutations change drug targets, block drug activation, or increase drug removal through efflux pumps, which reduces the effectiveness of treatment.

Resistance to first-line drugs like isoniazid and rifampicin is especially important because it leads to multidrug-resistant tuberculosis. When resistance extends to second-line drugs, treatment becomes longer, more expensive, and less successful. The emergence of pre-XDR, XDR, and totally drug-resistant TB shows how serious the situation has become, particularly in low-resource settings where diagnosis and proper treatment are often delayed.

This review highlights that drug resistance in TB is not caused by a single mechanism but by a combination of genetic mutations, drug-inactivating enzymes, altered drug targets, efflux pumps, and bacterial survival strategies such as per sister cell formation. Understanding these mechanisms is essential for early detection of resistance, choosing the right treatment combinations, and preventing further spread of resistant strains.

References:-

1.Getachew Seid,Ayinalem Alemu,Getu Diriba1,Betselot Zerihun,Gemechu Tadesse,Solomon H. Mariam and Balako Gumi (Drug resistance profile of Mycobacterium tuberculosis complex isolated from pulmonary tuberculosis patients and their household contacts in central Ethiopia) BMC Infectious Diseases, 2025, Page 2.

2. Jean-Pierre Flandrois1, Gérard Lina and Oana Dumitrescu2 (MUBII-TB-DB: a database of mutations associated with antibiotic resistance in Mycobacterium tuberculosis) Flandrois et al. BMC Bioinformatics 2014, Page 1 http://www.biomedcentral.com/1471

3.Deepak Vishwakarma , Abhay Gaidhane , Sweta Sahu , Ashwini S. Rathod, (Multi-Drug Resistance Tuberculosis (MDR-TB)Challenges in India: A Review) Open Access Review Article, Published via DMIHER School of Epidemiology and Public Health,2023.

4. Rahul Pal, Zeeshan Fatima and Saif Hameed, (Efflux pumps in drug resistance of Mycobacterium tuberculosis: A panoramic view),Int.J.Curr.Microbiol.App.Sci (2014 (tp://www.ijcmas.com), Page no: 528-546

5.Qiyao Chai,Yong Zhang and Cui Hua Liu(Mycobacterium tuberculosis: An Adaptable Pathogen Associated With Multiple Human Diseases) frontiers in Cellular and Infection Microbiology,15 May 2018 | Volume 8 | Article 158, Page 1.

6.Sebastian M. Gygli, Sonia Borrell, Andrej Trauner and Sebastien Gagneux, (Antimicrobial resistance in Mycobacterium tuberculosis: mechanistic and evolutionary perspectives) oxford FEMS journals investing in science 25 March 2025,354-355.

7. Jae Jin Lee, Daniel H. Swanson, Sun-Kyung Lee,Stephanie Dihardjo,Gi Yong Lee, Sree Gelle, Hoon Je Seong, Emily R. M. Bravo,Zachary E. Taylor, Michael S. Van Nieuwenhze, Abhyudai Singh,Jong-Seok Lee, Seokyong Eum, SangNae Cho ,Benjamin M. Swarts2 & Hyungjin Eoh(Trehalose catalytic shift inherently enhances phenotypic heterogeneity and multidrug resistance in Mycobacterium tuberculosis) Nature Communications 11 july 2025, https://doi.org/10.1038/s41467-025-61703-3

8. Sander N. Goossens, Samantha L. Sampson, Annelies Van Riea (Mechanisms of Drug-Induced Tolerance in Mycobacterium Tuberculosis Sander N. Goossens, Samanth) 14 octomber 2020 Volume 34 Issue 1,page2.

9. Pallavi Chandra,Steven J. Grigsby and Jennifer A. Philips (Immune evasion and provocation by Mycobacterium tuberculosis) 752 |December 2022 | volume 20 https://www.nature.com/articles/s41579-022-00763-4

10.Debasu Damtie, Desalegn Woldeyohannes and Biniam Mathewos (Review on Molecular mechanism of first line antibiotic resistance in Mycobacterium tuberculosis), Mycobact Dis ISSN:2161-1068 MDTL, an open access journal, Volume 4 • Issue 6 • 1000174, November 18, 2014 (3-4).

11. Aarav Sinha,Dr. Rajagopal Appavu and Jothsna Kethar(Prevention of Drug-resistant Tuberculosis) Journal of Student Research, Volume 12 Issue 3 (2023) Page 1.

12. Gautam Kumar, Priya Mondal, Amit Kadam, Isha Dhamija, Ravindra Pal Singh, Deepak Nathiya and Sandeep Kumar, (Combating Multi-drug Resistant Mycobacterium Species by Efflux Pump Inhibitors: Contemporary Trends), Bio Integration, https://bio-integration.org Volume 6, June 2 2025 Page no: 1

13. David Kajoba Mumena, Geoff rey Kwenda, Caroline Wangari Ngugi and Andrew Kimang'a Nyerere, (Drug-Resistant Tuberculosis Types and Their Treatment Regimens Using First-Line, Second-Line Injectable,Third-Line, Fluoroquinolones,Aminoglycosides, Cyclic Polypeptides, Novel and Repurposed AntiTuberculosis Drugs), Journal of Biomedical Research & Environmental Sciences,7-14 days, volume: 3 issue: 8 – 30 august, 2022 Page no: 989-990.

14.Dr.K.D.Tripathi, 8th Edition, (Essentials of medical pharmacology) book, ISBN: 9789352704996,23 september 2018, Page no: 145.

15.R.S.santoskar, Nirmala N. Rege, Raakhi K. Tripathi, Sandhya k. Kamat, (pharmacology and pharmacotherapeutics) ISBN: 9788131256954, 26th Edition, section 12 Page no: 658.

16. Rana H. Raheema and Zahraa Eisaa Sadeq, (Antibiotic resistance: A literature review), World Journal of Biology Pharmacy and Health Sciences, 2024, 19(02), 536–544 https://wjbphs.com/

17.Mansi Vaghela, Dr. Murtaza Hajoori (Acquired resistance of Mycobacterium tuberculosis against antibiotics – A review), International Journal of Pharmaceutical Research and Applications Volume 7, Issue 4 July-Aug 2022, pp: 611-623, www.ijprajournal.com ISSN: 2456-4494.