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AN INSIGHT INTO MULTIDRUG RESISTANT *MYCOBACTERIUM TUBERCULOSIS*

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ABSTRACT

One major barrier to efficient treatment and disease control is multi-drug resistance (MDR) in *Mycobacterium leprae* (ML) and *Mycobacterium tuberculosis* (MTB). An overview of the MDR mechanisms in these infections and the medications used to combat their resistance is given in this abstract. Mutations in the genes that code for the targets of drugs or the activation enzymes of drugs or metabolism are frequently the cause of MDR in *MTB*. Important first-line medications like rifampicin and isoniazid target essential cellular functions including RNA transcription and cell wall formation. Resistance mechanisms, such as changes in genes like rpoB and katG, impair the effectiveness of drugs. Gene alterations such as gyrA and rrs impair second-line medications, such as fluoroquinolones and injectable treatments, increasing treatment obstacles and resulting in extensively drug-resistant tuberculosis (XDR-TB). Similar to this, drug target genes, such as folP1 for dapsone and rpoB for rifampicin, as well as efflux pumps and metabolic pathways, are mutated in *M. Leprae* resistance mechanisms. Many different types of medications with different mechanisms of action are used to fight MDR in *MTB and M.Leprae*. Novel treatments targeting alternate routes are being developed in addition to traditional antibiotics. To reduce resistance and improve treatment effectiveness, combination medicines that are customized to each patient's unique resistance profile are crucial. Molecular assays and whole-genome sequencing are two examples of diagnostic breakthroughs that enable prompt therapeutic interventions by facilitating the quick identification of drug resistance mutations.

Keywords: Multi drug resistance, *M.tuberculosis, M.leprae,* Mechanism of drug resistance

INTRODUCTION

The frequency of microbial illnesses has sharply grown over the past few decades. As a result of the ongoing use of antimicrobial medications to treat infections, resistance has developed in different types of microbes. Multidrug resistance (MDR) is characterized by an organism's insensitivity or resistance to the antimicrobial medications that are provided to it **[1, 2]**.

Mycobacterium tuberculosis, the organism that causes tuberculosis (TB), spreads from person to person through the air. While mostly affecting the lungs, tuberculosis (TB) can also harm the brain, kidneys, or spine **[3]**. Of the 1.7 billion people infected globally, the number with active TB disease has significantly decreased (WHO 2018) **[4]**.

Mycobacterium leprae infection causes leprosy, also known as Hansen's disease [HD], Hanseniasis, and elephantiasis grecorum. It is a chronic but treatable disease that affects the skin, peripheral nerves, eyes, and upper respiratory tract mucosa **[5]**.

The World Health Organisation (WHO) reports that leprosy-specific MDT has been successful in lowering leprosy incidence and prevalence worldwide **[6]**. official data from 130 countries and territories state that there were '228,474', new cases of leprosy found in 2010 compared to the '192,246', cases of leprosy that were registered globally at the beginning of 2011 **[7]**.

Origins of resistance

It is not always the case that bacteria as a species or group are equally sensitive to or resistant to a given antimicrobial agent. Resistance levels might differ significantly even amongst related bacterial groupings **[8, 9]**.

Natural resistance: Natural resistance can be further classified as intrinsic or induced

Intrinsic resistance: may be characterized as an attribute that all members of the same bacterial species possess, that is unrelated to horizontal gene transfer, and that is unaffected by prior exposure to antibiotics **[10]**.

Table 1.1 Drug resistance and microorganisms

ORGANISM	INTRINSIC RESISTANCE
Bacteroides (anaerobes)	**Aminoglycosides, many ß-lactams, quinolones Aztreonam**
All gram positives	**Aminoglycosides, cephalosporins, lincosamides**
Enterococci	**Cephalosporins**
Listeria monocytogenes	**Glycopeptides, lipopeptides**
All gram negatives	**Macrolides**
Escherichia coli	**Ampicillin**
Klebsiella spp.	**Macrolides**
Serratia marcescens	**Sulfonamides ampicillin, 1st and 2nd generation**
Pseudomonas aeruginosa	**cephalosporins, chloramphenicol, tetracycline**
Stenotrophomonas maltophilia	**Aminoglycosides, ß-lactams, carbapenems, quinolones**
Acinetobacter spp	**Ampicillin, glycopeptides**

Extrinsic resistance: Genetic material that confers resistance may be acquired by bacteria by all of the fundamental processes of transposition, conjugation, and transformation. In addition, the bacteria may undergo alterations to its own chromosomal DNA. The acquisition could be long-term or short-term **[8, 11]**.

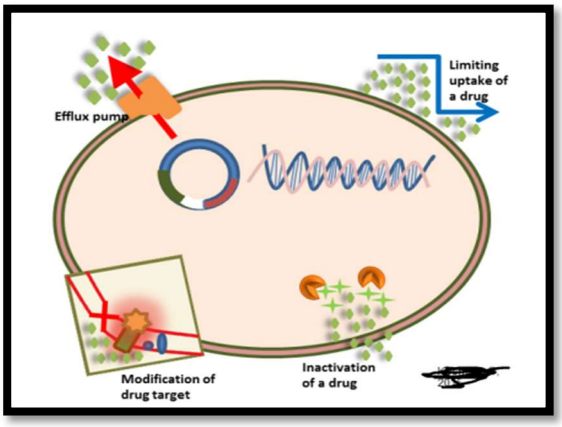


Figure 1: Drug resistant mechanism

MECHANISM OF RESISTANCE

Antimicrobial resistance mechanisms fall into four main categories:

(1) limiting uptake of a drug; **[12]**

(2) modifying a drug target; **[13]**

(3) inactivating a drug; **[14]**

(4) active drug efflux; **[15]**

Table 1.2 Drugs resistant to Micro organisms

Organisms (Bacteria)	Examples of drugs
Escherichia coli	Cephalosporins and fluoroquinolones
Klebsiella pneumoniae	Cephalosporins and carbapenems
Staphylococcus aureus	Methicillin
Streptococcus pneumoniae	Penicillin
Nontyphoidal Salmonella	Fluoroquinolones
Shigella species	Fluoroquinolones
Neisseria gonorrhoeae	Cephalosporins
Mycobacterium tuberculosis	Rifampicin, isoniazid, and fluoroquinolone
FUNGI	
Candida	Fluconazole and echinocandins
Cryptococcus neoformans	Fluconazole
Aspergillus	Azoles
Scopulariopsis species	Amphotericin B, flucytosine, and azoles
VIRUSES	
Cytomegalovirus (CMV)	Ganciclovir and foscarnet
Herpes simplex virus (HSV)	Acyclovir, famciclovir, and valacyclovir
Human immunodeficiency virus (HIV)	Antiretroviral drugs
Influenza virus	Adamantane derivatives
Varicella zoster virus	Acyclovir and valacyclovir
Hepatitis B virus (HBV)	Lamivudine.
PARASITES	
Plasmodia spp.	Chloroquine, artemisinin, and atovaquone Pentavalent
Leishmania spp.	antimonial, miltefosine, paromomycin, and amphotericin B
Schistosomes	Praziquantel and oxamniquine.
Entamoeba	Metronidazole
Trichomonas vaginalis	Nitroimidazoles

CAUSES OF MDR MUTATION

Most bacteria have the ability to split every few hours, which allows them to develop and adapt to changing environmental circumstances swiftly. Replication brings about changes, some of which may increase a single microorganism's resistance to an antibiotic's effects.

(1) gene transfer
(2) inappropriate use
(3) inadequate diagnostics
(4) hospital use **[16, 17]**

MULTI DRUG RESISTANCE IN MYCOBACTERIUM SPECIES-

MYCOBACTERIUM TUBERCULOSIS;

Mechanism

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 **[18]**. Among the processes that encourage the development of drug resistance in Mtb include drug degradation and modification, target mimicry, clonal interference, compensatory evolution, efflux pumps, cell envelope impermeability, and phenotypic drug tolerance. Both extrinsic and intrinsic antibiotic resistance may be the cause of treatment failure for tuberculosis **[19]**.

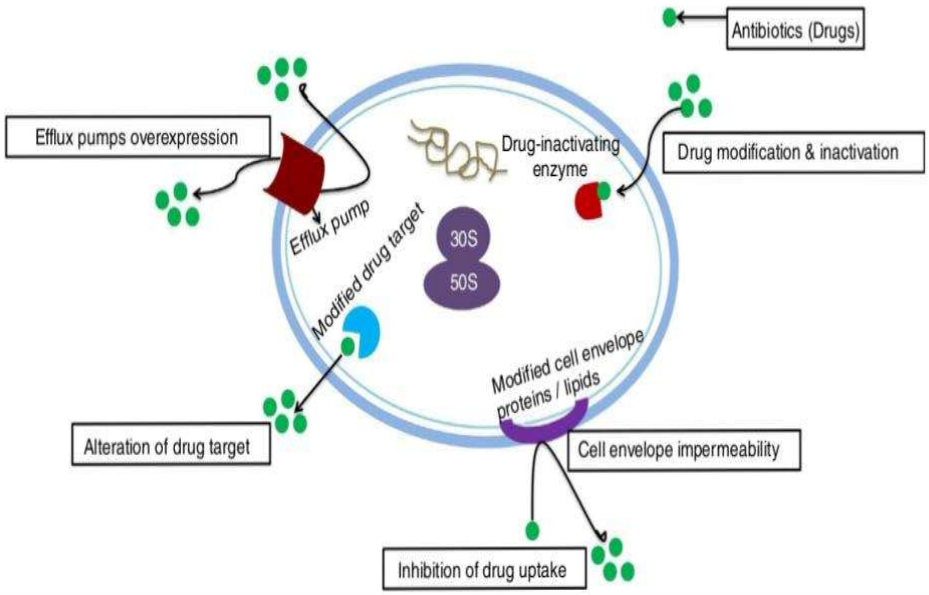


Figure 2: Mechanism of resistance in M.Tuberculosis

FIRST LINE ANTI T.B DRUGS:

Rifampicin

A rifamycin derivative called rifampicin was first used as an antituberculosis medication in 1972. It is one of the most potent anti-TB medicines and forms the cornerstone of the multidrug treatment regimen for tuberculosis, along with isoniazid. Both non-growing and growing (slow metabolising) Bacilli are susceptible to the effects of rifampicin **[20]**. Rifampicin works against *M. tuberculosis* by attaching itself to the β-subunit of RNA polymerase and preventing messenger RNA from elongating. Most of the rifampicin-resistant the β-subunit of RNA polymerase is coded by the *rpoB* gene, which is mutated in clinical isolates of tuberculosis **[21]**.

Isoniazid

Introduced in 1952 as an anti-tuberculosis drug isoniazid and rifampicin are the mainstays of the illness's therapy regimen. Unlike rifampicin, isoniazid is only effective against bacilli that multiply metabolically. Isonazid, also referred to as isonicotinic acid hydrazide, is a prodrug that, in order to work, needs to be activated by the catalase/peroxidase enzyme KatG, which is encoded by the *katG* gene **[22]**. Isoniazid works by preventing the production of mycolic acids via the NADH-dependent Enoyl-acyl carrier protein (ACP)-reductase, which is structurally encoded by the protein inhA simple. Genes such as *katG, inhA, ahpC, kasA*, and *NDH* have been implicated in resistance to this drug through mutation **[23]**.

Ethambutol

Since its introduction in 1966, ethambutol has been a part of the first-line therapy regimen for tuberculosis. Ethambutol inhibits the growth of bacteria by interfering with their ability to synthesise arabinogalactan within the cell wall **[24, 25]**. Ethambutol resistance mechanisms have been linked to mutations in the gene *embB*; in most of the investigations that were done, the most prevalent mutations were discovered at position *embB306* **[26, 27]**.

Pyrazinamide

Since its introduction to TB treatment in the early 1950s, pyrazinamide has been a conventional first-line regimen for the illness's management. The introduction of pyrazinamide, an analogue of nicotinamide, allowed for a six-month treatment duration reduction **[28]**. Pyrazinamide is also a prodrug; to convert pyrazinamide into its active form, pyrazionic acid, the pncA gene-coded enzyme pyrazinamidase/nicotinamidase is needed **[29, 30]**. Pyrazinamide works by converting to pyrazinoic acid which modifies the bacterial membrane's energetics and inhibits membrane transfer **[31]**. Passive diffusion allows pyrazinamide to enter the

bacterial cell, where it transforms into pyrazinoic acid, which is then eliminated by a weak efflux pump **[32]**.

SECOND LINE ANTI TB DRUGS

Fluoroquinolones

As of right now, fluoroquinolones are used as second-line medications to treat *MDR-TB*. The synthetic derivatives of nalidixic acid, which was found as a by-product of the antimalarial drug chloroquine, are ciprofloxacin and ofloxacin **[33]**. To reduce the duration of tuberculosis treatment, newer generation quinolones including gatifloxacin and moxifloxacin are being assessed in clinical studies and suggested as first-line antibiotics **[34, 35]**. Fluoroquinolones function by inhibiting topoisomerase II (DNA gyrase) and topoisomerase IV, two enzymes necessary for bacterial viability. The main mechanism behind the development of fluoroquinolone resistance in *M. tuberculosis* is chromosomal changes in the gyrA or gyrB region, which determines quinolone resistance **[36]**.

Ethionamide

Isonicotinic acid derivative ethionamide shares structural similarities with isoniazid. It is also a pro-drug that requires monooxygenase to be activated in order to function. By creating an adduct with NAD that inhibits the enoyl-ACP reductase enzyme, it obstructs the formation of mycolic acid. *EthA* is controlled by the transcriptional repressor EthR **[37]**. Resistance to ethionamide is caused by mutations in *etaA/ethA, ethR*, and *inhA*, which confer resistance to ethionamide as well as isoniazid **[38, 39]**.

Para amino salicylic acid

Although PAS was one of the first anti-tuberculosis drugs to be utilised in the treatment of the disease, it is now considered a second-line antibiotic for treating multidrug-resistant tuberculosis, along with isoniazid and streptomycin. Until recently, its precise manner of action was unknown **[40]**. It has been proposed that because of its resemblance to para-amino benzoic acid, it will compete with it for dihydropteroate synthase, preventing the synthesis of folate. The dihydrofolate synthase gene*, folC,* has several missense mutations that have been linked to resistance to PAS, according to a recent study. in *M. tuberculosis* isolates from laboratories. Five of the panel's eighty-five clinical MDR-TB isolates possessed *folC* mutations, rendering them PAS-resistant **[41, 42]**.

Cycloserine

Cycloserine is an oral bacteriostatic second-line anti-tuberculosis drug used in MDR-TB therapy regimens. It functions as a D-alanine analogue by stopping D-alanine from acting in

the same way. Inhibiting the formation of peptidoglycan is D-alanine ligase **[43]**. While the exact role of cycloserine in Mycobacterium TB is still unknown, previous studies in Mycobacterium Smegmatis showed that recombinant mutants resistant to cycloserine were produced by overexpressing *alrA* **[44]**. Additionally, it was shown more recently that M. The *cycA* gene, which codes for the D-alanine transporter, had a single mutation that contributed to the cycloserine resistance of Bovis BCG **[45]**.

Thioacetozone

Due to its excellent in vitro activity against *M. tuberculosis*, thioacetazone, an antiquated drug, was utilised to treat TB. TB and its incredibly cheap price. Nevertheless, there are toxicity concerns, especially in patients who also have HIV. It belongs to the WHO's group 5 of drugs and functions by inhibiting the production of mycolic acid **[46]**.

Macrolides

When treating other mycobacterial infections, the suggestion for macrolides is increasingly prevalent. owing to M. tuberculosis. Among these, clarithromycin is considered to be a drug in the WHO's category 5. Intrinsic resistance to macrolides has been associated with low cell wall permeability and expression of *emr37*, a gene that codes for a methylase at a specific position in the 23S rRNA and inhibits the antibiotic from binding **[47]**.

Clofazimine

Because there were more strong anti-TB drugs available at the time and there were a number of undesirable side effects, such as skin discoloration, its use was limited to treating leprosy **[48]**. It is currently regarded as one of the WHO's group 5 medications for the treatment of MDR-TB. The precise mechanism of action of this antibiotic was unclear until recently **[49]**.

Linezolid

The oxazolidinone linezolid was first approved for use in clinical settings to treat skin infections and nosocomial pneumonia caused by Gram-positive bacteria. It works by inhibiting an early step in protein synthesis by binding to the 50S ribosomal subunit **[50]**. Although resistance to linezolid in *M. tuberculosis* is still uncommon, a study that examined 210 MDR strains discovered 1.9% of them to be resistant to the drug. Further analysis of in vitro selected linezolid-resistant mutants found that Strains with mutations in the 23S rRNA had MICs of 16–32 μg/mL, while strains with MICs of 4–8 μg/mL or susceptible strains showed no mutations. Prior research has also revealed indications that efflux pumps may play a role in *M. tuberculosis* resistance **[51]**.

MULTI DRUG RESISTANCE IN *MYCOBACTERIUM LEPRAE*:

The WHO Study Group on Chemotherapy of Leprosy for Control Programmes recommended the use of Multi-Drug Therapy (MDT) in 1982 because the widespread development of dapsone resistance constituted a serious danger to leprosy control. For patients with MB leprosy in WHO-MDT, rifampicin is paired with clofazimine and dapsone; for those with PB leprosy, it is mixed with dapsone **[52]**.

Drugs

Dapsone

Promin, a sodium glucosulfone (diamino-azobenzene 4'-sulfonamide) drug, was the first effective leprosy therapy and was originally introduced in 1943 **[53]**. Sulfone medications work by competitively inhibiting p amino benzoic acid (PABA), which targets the dihydropteroate synthase (DHPS), an essential enzyme in the bacterial folate production pathway **[54, 55]**. In *M. leprae,* the impact of dapsone on folate biosynthesis has been verified Dapsone competitively inhibits para-amino benzoic acid (PABA), the necessary substrate for the synthesis of folate. The key enzyme in this stage is dihydropteroate synthase (DHPS), which is encoded by the *folP* gene. Dapsone competitively inhibits this condensation, which ultimately leads to a reduction in tetrahydrofolate production—a crucial step in the manufacture of nucleic acids in *M. leprae* **[56, 57, 58]**.

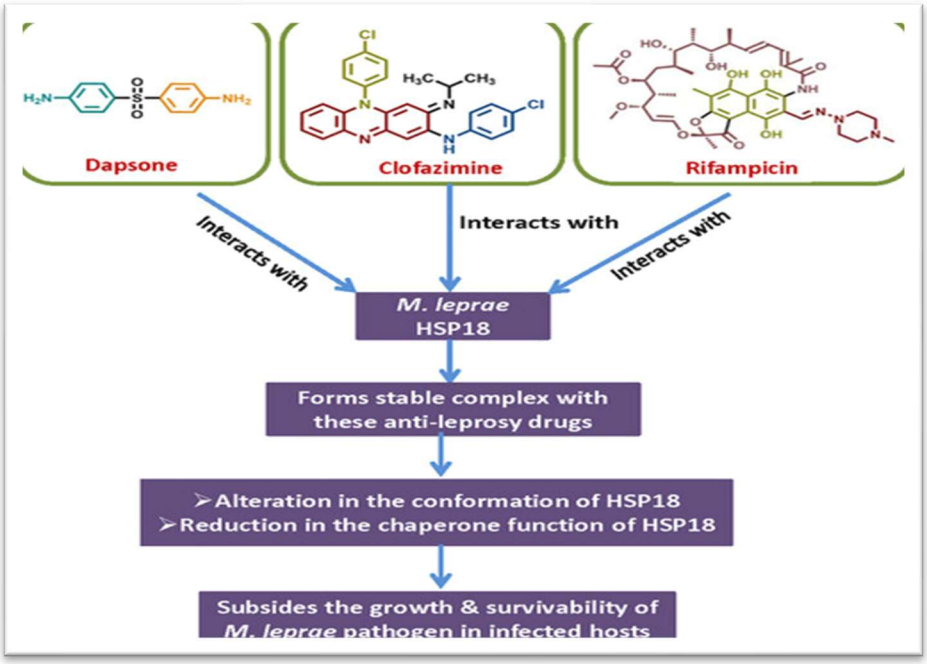


Figure 3: Drug acting towards *M. Leprae*

Drug resistance mechanism

Studies aiming at defining the mechanism of dapsone resistance in *M. leprae* have employed direct sequencing of the two genes that encode *DHPS1 and DHPS2* (folP1 and folP2, respectively) from isolates of *M. leprae* that are both dapsone-susceptible and -resistant **[59, 60]**. Since the resistant mutant's *DHPS2* genes showed no changes, *FolP2* was ruled out as a functional component of dapsone resistance **[61]**. Mutations observed in the dapsone-resistant mutant resulted in a DHPS1 enzyme with decreased dapsone binding **[59]**.

Rifampin

Rifampin, also known as 3-(4-methyl-1-piperazinyl)-imino-methylrifamycin is a derivative of rifamycin and is the primary bactericidal agent in the WHO-recommended multidrug therapy for leprosy **[62]**. The β-subunit of the DNA-dependent RNA polymerase, which is made up of an α-subunit dimer, a β-subunit, a β′-subunit, and an ω-subunit, is the target of rifampin in bacteria **[63]**.

Drug resistance mechanism

M. tuberculosis resistance to rifampin is connected with changes in the β-subunit of RNA polymerase structure. These modifications resulting from missense mutations are mostly caused by the *"rpoB DRDR*," a highly conserved region of the *rpoB* gene. Missense mutations in the *rpoB DRDR* are also correlated with rifampin resistance in *M. leprae* **[64, 65]**.

Clofazimine

Due to its high lipophilicity, clofazimine seems to bind to mycobacterial DNA quite firmly. Treatment of multibacillary leprosy with clofazimine, dapsone, and rifampin has proven effective **[66]**.

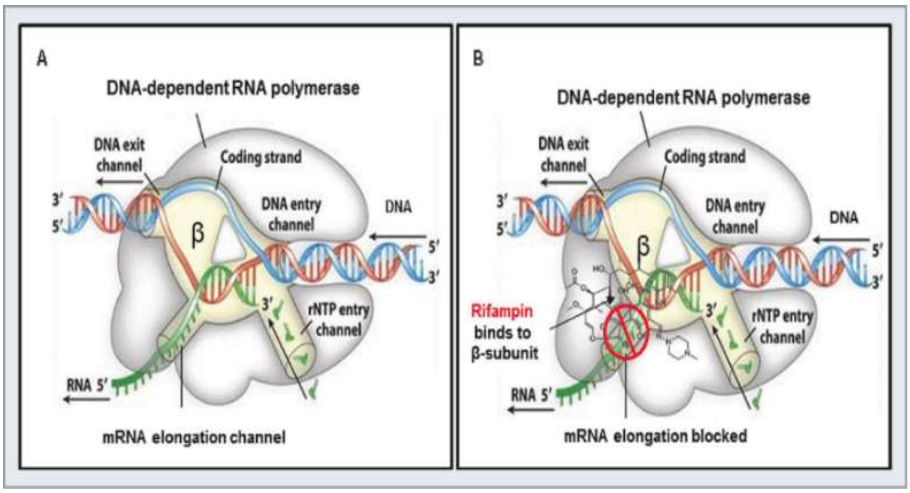


Figure 4: Drugs resistant mechanism of clofamizine

Drug resistance mechanism

More recently the efflux pump MmpS5-MmpL5 was found to be overexpressed as a result of mutations in the *Rv0678* gene **[67]**.

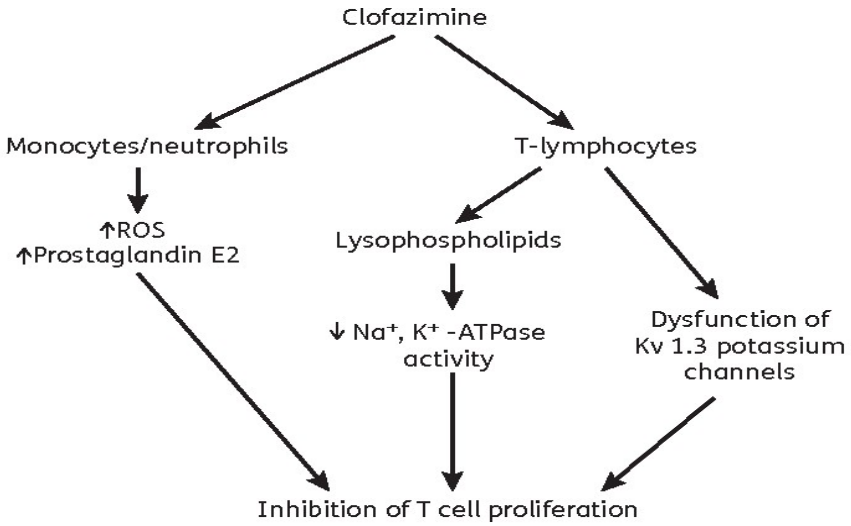
Fluoroquinolones

Fluoroquinolones were investigated against *M. leprae*. By inhibiting type II topoisomerases,

they prevent replication and cause double strand breaks in DNA **[68, 69]**. While DNA gyrase and topoisomerase IV are the two type-II topoisomerases found in most bacteria, *M. TB* and *M. leprae* do not seem to have the latter. Therefore, the target of fluoroquinolones in M. leprae and M. tuberculosis is the DNA gyrase, a tetramer made up of two A-subunits (GyrA) and two B-subunits (GyrB). It has been demonstrated that fluoroquinolones inhibit the *M. leprae*. Inhibition of DNA Gyrase by Ofloxacin (GyrB), converts positive-coiled DNA into negative-coiled DNA to allow replication to continue **[70]**.

Drug resistance mechanism

The majority of mutations in a highly conserved region of gyrA (gyrA DRDR) have resulted in the development of ofloxacin resistance in resistant strains of M. tuberculosis **[71]**. Ofloxacin-resistant strains of *M. leprae* have been shown to exhibit missense mutations within codon 89and 91 **[64]**.



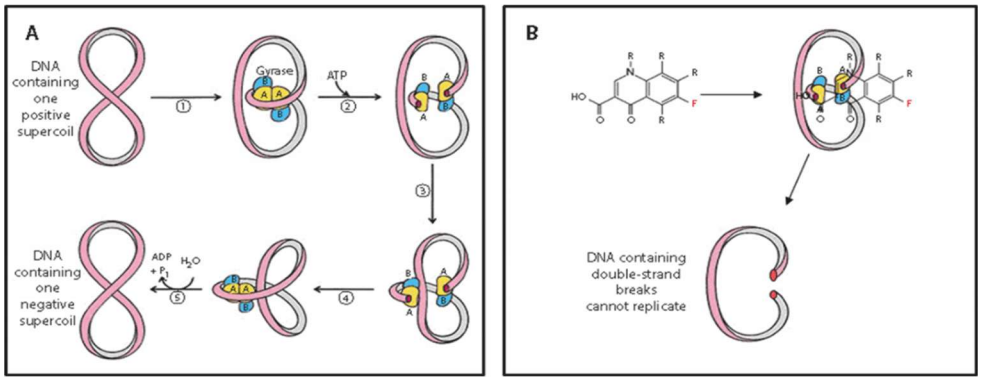


Figure 5: Inhibition of DNA gyrase

CONCLUSION OF MDR:

There is no denying the sharp rise in serious systemic infections and the dissemination of resistant microbes. The inadequate availability of antimicrobial medications forces ongoing research and development of novel therapeutics (6 Interdisciplinary Perspectives on Infectious Diseases). Furthermore, it is necessary to put in place a number of awareness campaigns that should make it easier to use them appropriately to regain control over illnesses. MDR is a huge worldwide hazard to human health and is an unavoidable natural occurrence. Action and global collaboration are required to address the MDR. Pathogens frequently employ a range of resistance mechanisms to survive in unfavorable conditions. A better understanding of the molecular mechanisms governing MDR will aid in the creation of novel treatments to fight these resistant infections and advance our knowledge of the pathobiology of microorganisms **[72]**.

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