

GENETIC FACTORS ASSOCIATED WITH MUTATIONS OF MOLECULAR MECHANISM AND DRUG RESISTANCE IN *MYCOBACTERIUM TUBERCULOSIS*

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**Abstract:** *Mycobacterium tuberculosis* shows drug resistance patterns (drug-resistance tuberculosis DR-TB) for strains that are induced with high mortality rates. Because this acid-fast bacterium resists extensively against drugs and masks their effects to control the disease. However, these chromosomal mutations and genetic factors lead towards recent anti-TB drug discoveries. Anti-TB regimens are dearth to control this pandemic problem due to the high prevalence of this disease. These situations are remarkably given new ray to discover newer drugs that target such bacilli strains genetic factors and mutations. Also, it provides molecular updates to the resistance mechanism of mutations and genetic factors as a basic target then screened-out recent new anti-TB agents to limit the MDR-TB.

**Keywords:** *Mycobacterium tuberculosis*, drug, anti-TB agents, genetic factors, mutations

### Introduction

*Mycobacterium tuberculosis* (Mtb) exhibits multi-drug resistance against antibiotics. About one-third population of world seriously infected by very calamitous parasitic agent Mtb. World Health Organization WHO recorded that 8-10 million cases every year reported of new TB (Grobusch and Kapata, 2018; Takate et al., 2019). Mtb shows worldwide first-line drug resistant, second-line drug resistant, multi-drug resistant called (MDR), extensive drug-resistant called (XDR), extremely drug-resistant called (XXDR) and totally drug-resistant called (TDR) in sequence. **Mtb strains show drug resistance against**

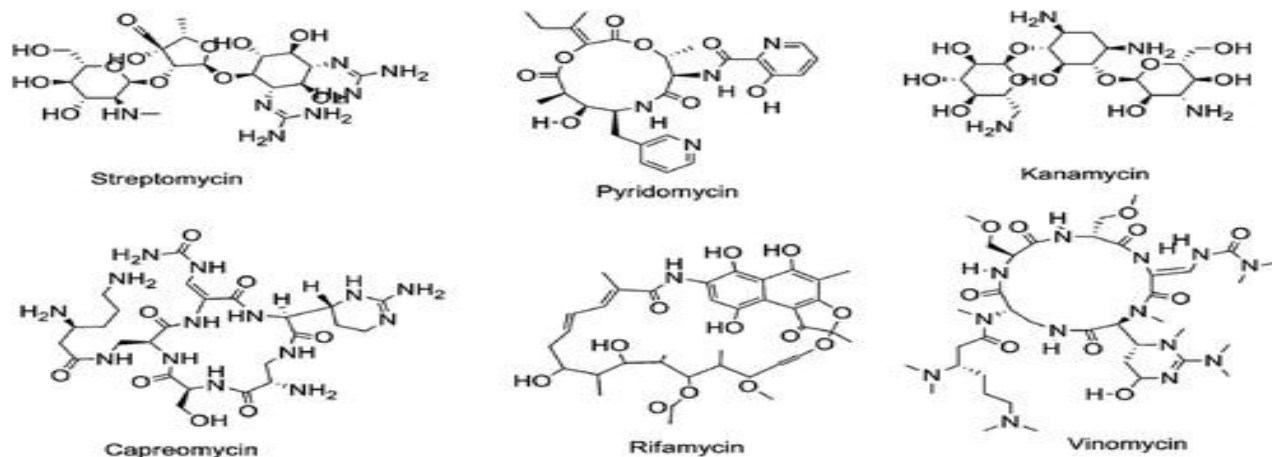
First-line drugs (Pyrazinadine/ Streptomycin/ Isoniazid/RIF)-3.9% cases per year of RIF resistant (Takate et al., 2019). Second-line drugs (ETHCAP/MXF/KAN) and Directly Observed Treatment Short (DOTS). First, second line drugs resistance and DOTS ineffectiveness significantly leads to arise the MDR (480,000 cases per year), XDR (9.5% cases from 17 countries per year)(Takate et al., 2019), XXDR and TDR. It induces the great challenge towards control treatment to disease (Zhang et al., 2015). In survey to Mtb in 2015 recorded 60% cases were from Pakistan, China, India, Nigeria, South Africa and Indonesia (Granich,

2018). There is not only problem about TB but also it leads the induction of co-infection (in immune-compromised persons) such as TB-HIV means that a person faces both bacterial and viral infections. It creates very serious condition to MDR-TB control, hence in 2005 WHO reported approximately 0.4 million people mortality ratio due to co-infection of TB-HIV (Padayatchi et al., 2017). It has been reported that stepwise drugs discoveries happened such as after 1944, STR or streptomycin (called a first-line of drug) discovered for TB treatment which is anti-TB drug. In drug development there were many drugs sequentially introduced but recently showed that all single called mono and cumulative therapies (which includes DOTS and DOTS plus) are not efficiently working against MDR-TB patients (Koul et al., 2011; Zhang et al., 2015). Hence now it is reported that TB become one of the challenging infectious disease globally. Genetic mutations are vigorously strong enough to induce MDR-TB in new combinatorial therapies, it is proved by that 50-70% cases by these combinatorial therapies but now they become ineffective. TB is bacterial disease it become very worst because anti-TB treatment vastly adopt to resistance against any new recent therapeutic agent, although it is slow expensive and time taking treatment of anti-TB agent (Koul et al., 2011). Resistant anti-TB agents show that there's need to

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emerging advanced competitive anti-TB agents to control the disease prevalence globally. Anti-TB drugs are unable to show effectiveness against intracellular and dormant states of Mtb strains.



**Figure 1. Anti-TB drugs that are extract from natural sources (Swain et al., 2020d)**

To built the advancement in anti-TB agents which can tackle the mutational effects and stop causing the MDR. Many ways are introduced to snippet the potential compounds and chemicals of anti-mycobacterium agents from natural intrinsic sources. RIF and STR are included in natural drug discoveries (Figure 1)(Liu et al., 2012b; Santhosh and Suriyanarayanan, 2014; Swain et al., 2017). Natural sources are considered as parental sources for semi-synthetic (RIF from rifamycin) drugs. For this challenging situation many molecular discoveries happened by drug candidates by giving chemical assays in comparison to, previous discoveries(J Sloan et al., 2013). WHO considered critical situation for this pandemic and create the slogan “Stop TB to End TB”(Mitchison and Davies, 2008b).

#### ***Mycobacterium tuberculosis* mechanisms of drug resistance**

Through evolutionary theory it is stated that mutations are adapted to environmental forces. Environmental conditions and long-term therapies of various combinations cause evolution in drugs to become gradually resistant strains against new emerging drugs (Figure 2). Epigenetics effects includes environmental factors that are significant cause of genetic mutations they leads to induce both ineffectiveness of new drugs as well as provide potent fit environment to Mtb strain survival also in harsh conditions (Palomino and Martin, 2014). Hence

it is very dangerous situation in which epigenetic change induce such type of survival conditions for Mtb strain. It promotes MDR phenotypes and bactericidal antibiotics mutagenesis (Mitchison and Davies, 2008a; Palomino and Martin, 2014).

Immune system cells dendrite cells or alveolar macrophages (in lungs) engulf the bacterium then TB infection takes place in most cases, here bacilli consistent to reproduce by destroy the killing mechanism of host (phagocytosis, phagolysosome). Granuloma is specific site which contains complementary macrophages and other immune cells (Burian et al., 2012; Siroy et al., 2008). Mtb bacilli strains are rapidly growing in granuloma with dormant state that confer with environmental situations and create dangerous conditions of nitric oxide production, hypoxia, anorexia and nutrient deprivation (Kashyap et al., 2018).

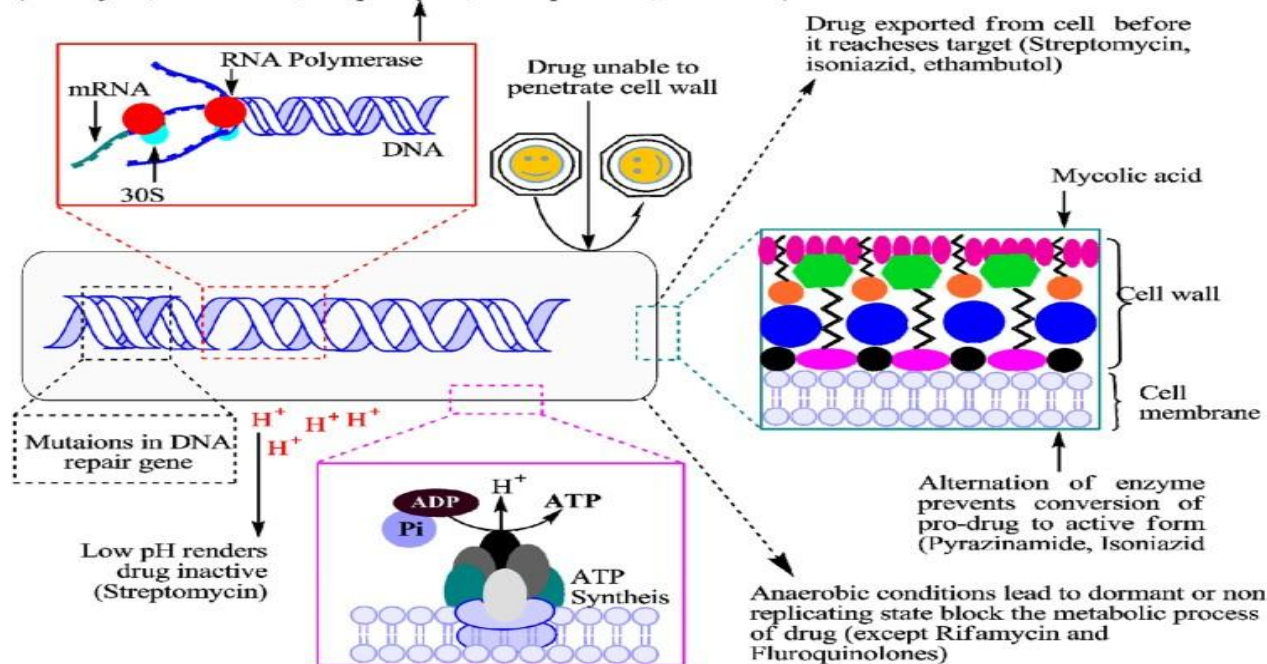
#### ***Mycobacterium tuberculosis* intrinsic resistance mechanism**

Mtb strain is naturally become resistant to wide range of drugs from first-line drugs to XXDR pattern. It is very drastic situation in which natural Mtb intrinsic mechanism not confined to previously drugs that identified but also to new emerging medicines. It is divided into two types one is intrinsic and second is acquired passive neutralizing anti-TB drug regimens (Palomino and Martin, 2014).

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### Genetic factors which induces the mutations and regulate intrinsic drug resistance

Alteration of target protein structure prevent drug recognition (Rifamycin, Ethambutol, Streptomycin, Fluroquinilone, Macrolide)



**Figure 2. Mtb drug resistance mechanism by schematic view (Swain et al., 2020c)**

The *emr37* gene (is genetic factor which organizes binding site for 23rRNA by methylation) is attributed to cause low cell wall permeability in macrolide class of antibiotics. *Mtb* shows natural resistance mechanism by *emr37* gene (Kashyap et al., 2018; Palomino and Martin, 2014). Clarithromycin shows eight to four fold decreased minimum inhibitory concentration (MIC) for natural mechanism of resistance in *Mtb*. *Mtb* has low permeability cell wall structure to anti-TB chemotherapy (Palomino and Martin, 2014; Viveiros et al., 2012). *MspA* is genetic factor in *Mtb* which lower drug permeability of cell wall. *Mtb-Rv1698* is also gene which is related to intrinsic resistance with antimicrobial hydrophilic activities due to *MspA* gene (Viveiros et al., 2012). *WhiB7* is called minor protein structure that contain sulfur group with 122 amino acids that are also related to redox reagents like *emr37* (Burian et al., 2012). *WhiB7* is auto-regulator called transcriptional activator which can manage the control of intrinsic drug resistance. It confers with *tap*, which is mycobacterial efflux transporter when binds to somatic sigma factor *SigA* against tetracycline, STR

and PAS (Siroy et al., 2008; Viveiros et al., 2012). *PknG* is eukaryotic like protein kinase G is followed redox-homeostasis and a virulence factor which can allow to *Mtb* survive in host macrophage easily. *Lsr2* which is transcription factor related to nucleoid, that regulate the level of oxygen for *Mtb* in macrophage by *iniBAC* and *EfpA* (efflux transport protein)(Burian et al., 2012). A significant genetic protein *MarA* which controls the MDR efflux pump also it lower the susceptibility of TET. Antibiotic sensitivity and redox reaction manage by NADH (Figure 3)(Bartek et al., 2014; Burian et al., 2012; Kashyap et al., 2018).

Many intrinsic factors of genetics which are *SigA* and *SigF* (stress responsive sigma factors) and their *MarA*, *SoxR* and *Rob* (transport proteins) induce resistance of anti-TB drugs (Morris et al., 2005). It is essential thing which is evaluated by bioinformatics that *Mtb* outer membrane proteins act with intrinsic resistance genetic factors it happens at proteomic level. Permeability barriers also related to intrinsic drug resistance by physiological adaptations (Nguyen and Pieters, 2009). By *Mtb* drug development a new

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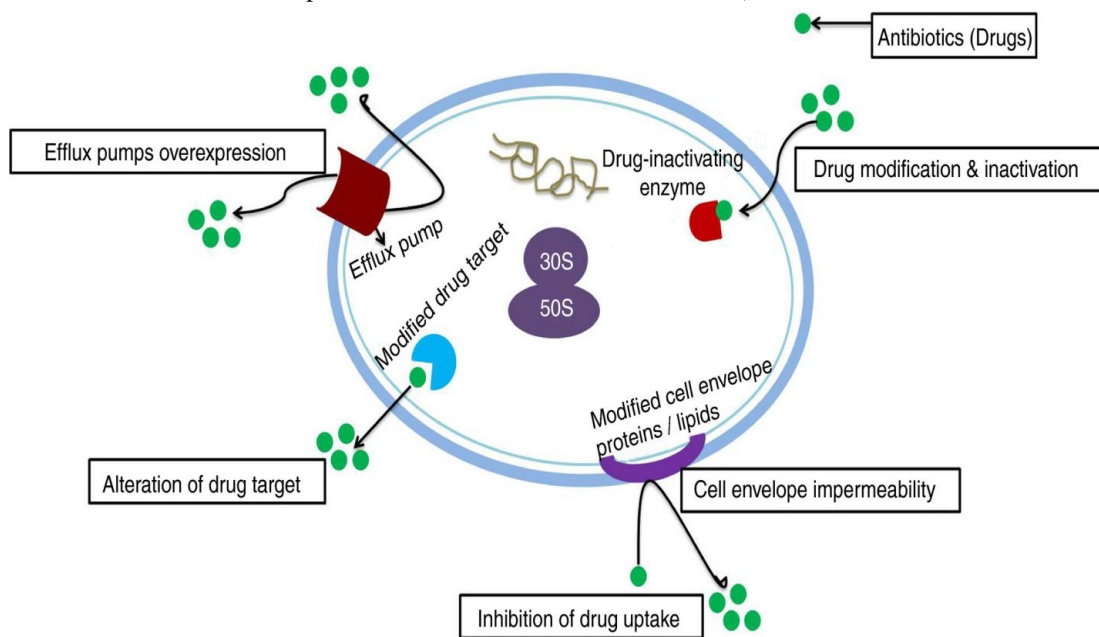
drugs discovered with iron containing gruesome Mtb strain which specifically targeting the intrinsic genetic factors (Lomovskaya and Bostian, 2006; Swain et al., 2020c).

**Mycobacterium tuberculosis acquired resistance mechanisms**

Unlike matters in different microorganism wherever non-inheritable drug resistance is usually mediate that plasmid and transposons are mobile genetic elements that are horizontally transfer by acquired drug resistance. it occurs in two different ways; 1) Chromosomal or gene mutation, 2) Extra chromosomal or gene transfer mechanism

Drug resistance is caused by impulsive mutations in body genes, manufacturing choice of resistance shear throughout the sub-optimal drug medical care. Whereas, no single pleiotropic mutation it was found that to cause associate MDR compositions in mycobacterium infectious disease, potential advanced

association between serious mutation related to resistance drug may well as associated with the starting steps within the resistance to different medications (Siroy et al., 2008). In prokaryotes, therefore the rate of mutation per replication in base pair is inversely equal to 0.0033 but in Mtb case anti-TB regimens appears at 10-9 Mutations per cell division. That's why the reason anti-TB medication area unit given as mix, because the risk of mutant factor contain 2 resistance mutations is less than 10-18.23 (Figure4) (Morris et al., 2005). RIF resistance in Mtb clinical isolation managed by Mutations on rpoB gene. Yet in some cases isolates have different fitness cost. i.e: less cost of fitness in vitro. Hence it depend upon Mutations that are associated with some major or minor cost of fitness strain. As a result cost of fitness depend upon genetic circumstances of the strain and specific resistance Mutation(Palomino and Martin, 2014).



**Figure 3. Efflux pumps (Swain et al., 2020c)**

**Anti-TB medicines' drug-resistance pathways**

Due to the advent of MDR-TB as well as XDRTB strains, certain newly introduced drugs were reported to really be unreliable. In contrast to STR, the new regimens of anti-TB that are operated strains for this bacteria can never lasted on a long-term foundation (Gygli et al., 2017; Zhang and Yew, 2015). In the emergence of drug-resistant Mtb strains, environmental influences, antibiotic pressure, and

chromosomal mutations all play a large part and then there's the transfer of such strains to new hosts (Morris et al., 2005).

**Drugs that target cell wall, mycolic acid, and folic acid synthesis have established resistance mechanisms**

Cell wall of this bacteria is made up of three covalently bound macromolecules called mycolyl-

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arabinogalactan-peptidoglycan” or mAGP complex and have peptidoglycan, arabinogalactan, and mycolic acid. Mycolic acid's importance in biosynthesis appreciably established, and many drugs are produced by potentially pointing it with associated enzymes called isoniazid and EMB that were stimulate as a prodrug to inhibit biosynthesis of mycolic acid by targeting encoded enzymes inhA and katG(Almeida Da Silva and Palomino, 2011).Resistance to EMB and INH can be gained by genetic changes in the enzymes inhA and katG. Many genetic factors associated to cell wall synthesis (kasA, ndh, niA, AhpC FadE24, and FabG1) were investigated in relation to drugs of anti-TB resistance using modern molecular techniques(Timmins and Deretic, 2006). Hence same with genetic mutations in

embB and embC, which are also engaged in mycobacterium cell wall synthesis, cause resistance via Robinson transfers(Xu et al., 2015). Mutations in embB, and also mutational changes in the gene (ubiA) of decaprenyl-phosphoryl-5-phosphoribose (DPPR) synthesis, have recently been related to an increased degree of EMB resistance (Table 1-3). Resistance showing in single genetic factors pointing to cell wall drugs of anti-TB including imipenem, DCS, clofazimine, meropenem, amoxicillin and thioacetazone have been associated with poor outcomes. Folic acid biosynthesis-associated enzyme dihydropteroate synthase stimulated by the PAS and prevents regulation of iron , which is one of the most potential anti-drugs against multidrug-resistant tuberculosis since 1994 (Zhao et al., 2014).

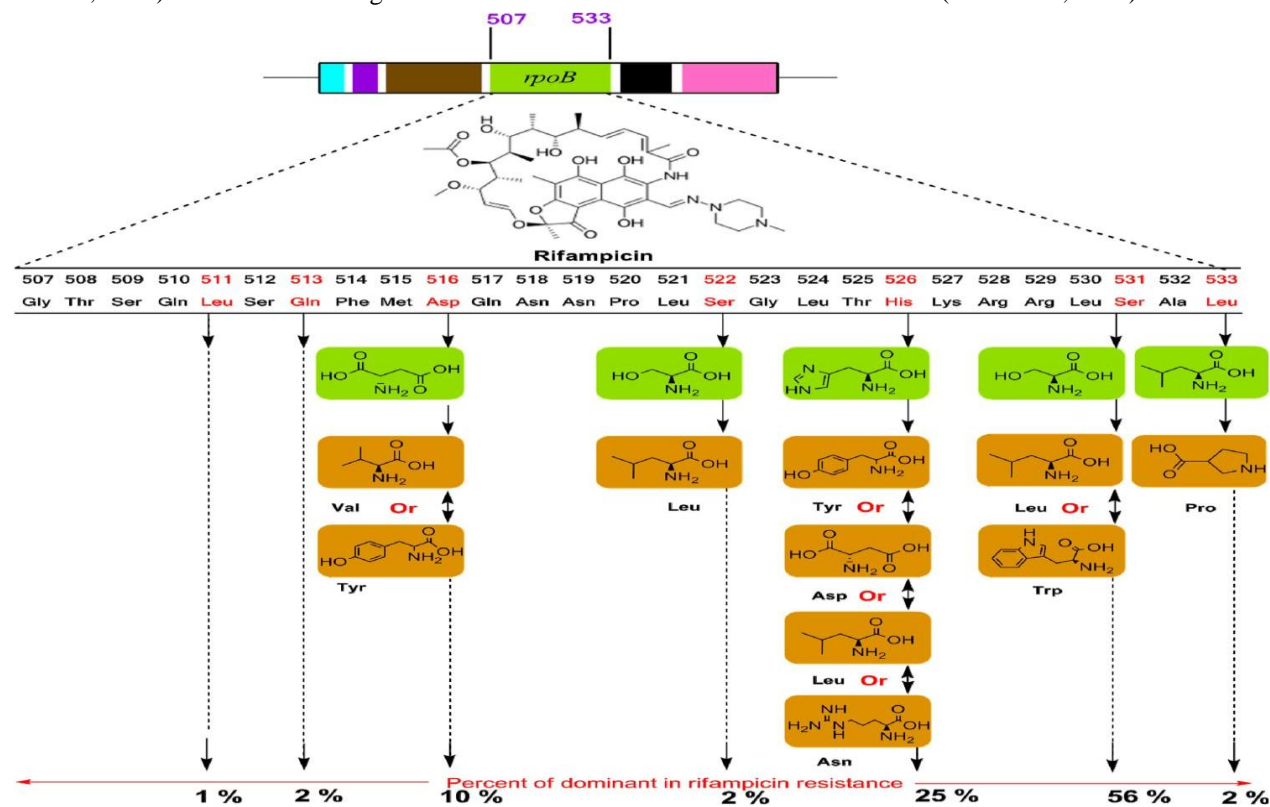


Figure 4. Genetic mutations of rifampicin target drug-resistance mechanism(Swain et al., 2020c)

For illustration, a mutation at thyA gene of Thr202Ala is found in about thirty seven percent of PAS-resistant strains of bacteria. Since from the last few years, two newly designed drugs have been more effective in suppressing Mtb cell wall synthesis ,hence resistance to these two drugs (delamanid and pretomanid) newly identified globally drugs (Mathys

et al., 2009). A range of chemicals that are pointed to aminoacyl-tRNA synthetases called (AARS)-associated enzymes, which are crucial for protein synthesis of bacteria (Palencia et al., 2016). Furthermore, the Mtb cell envelope comprises certain specific lipids they are the blockers of drugs to anti-TB. Hence, the lipid fence is vital to the improvement

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of Mtb drug resistance (Nguyen and Pieters, 2009). The acyl-CoA carboxylases (ACC) subunits that are originated from malonyl coenzyme A (AccD1 with AccD6, AccA1 with AccA3, and AccE5) assemble different structural mycobacterium lipids. Furthermore, ACC (biotin vitamin H or B7 and called

cofactor in the posttranslational procedure) is required for the preparation of mycolates, fatty acids and lipids by Mtb. As a result, inhibition of denovo biotin biosynthesis or biotin-ACC ligation acted as innovative inhibition for Mtb (Oh et al., 2006; Swain et al., 2020c; Tiwari et al., 2018).

**Table 1.** First-line Genetic factors related to drugs of anti TB resistance (Swain et al., 2020c)

DRUG (year)	Chemical class	Genetic factor	Resistance of medicines	Reference
(1952) INH	Isonicotinic acid	KatG, AhpC, nihA	Modification over-expression of drug target	(Timmins and Deretic, 2006)
(1961) Ethambutol	Ethylenediamine	Emb A, embR	Change and over-expression of drug target	(Pourakbari et al., 2016)
(1963) Rifampicin	Rifamycin	RpoB, FabG1	Modification in drug target	(Campbell et al., 2001)
(1944) Streptomycin	Aminoglycoside	RpsL, gidB, gpsl	Variation in drug target	(Dookie et al., 2018)
(1952) Pyrazinamide	Pyrazine	RpsA, rmLD, iniA	Abolition of pro-drug conversion	(Zhang et al., 2013)

**Table 2.** Second-line Genetic factors of anti TB drug resistance (Swain et al., 2020c)

DRUG (year)	Chemical class	Genetic factor	Drug resistance	Reference
(1996) Moxifloxacin	Quinolones/8-methoxyfluroquinolone	gyrA, gyrB	Alternation of drug	(Rustomjee et al., 2008)
(1955) Cycloserine	Serine derivative	ddl, Aid	Over-expression of resistance gene	(Cáceres et al., 1997)
(1956) Ethionamide	Isoconitic acid derivative	ethA, ethR	Alternation and over-expression drug	(Lin et al., 2014)
(1963) Capreomycin	Cyclic polypeptide	rrs, thyA	Mutation alternation drug	(Lin et al., 2014)
(1957) Kanamycin	Amino-glycosides	Rrs, eis, whiB7	Mutation on 16S rRNA	(Dookie et al., 2018)
(1972) Amikacin				

**Table 3.** Third-line Genetic factors of anti TB drug resistance (Swain et al., 2020c)

Drug (Year)	Chemical class	Genetic factor	Drug resistance	References
(1954) Clofazimine	Iminophenazine derivative (bacteriostatic)	rv0678, rv1979c, rv2535c, ndh	Up-regulation of efflux pump, MmpL5 because of mutations	(Yano et al., 2011)
(2012) Bedaquiline	Quinoline (bactericidal/bacteriostatic)	rv0678, atpE, pepQ	Mutational changes to co-infection and binding site	(Palomino and Martin, 2013)
(2014) Delamanid	Nitroimidazole (bactericidal)	fgd1, fbiC, fbiA, fbiB, ddn	Mutations on reductive activating gene	(Feuerriegel et al., 2011)
(2020) Pretomanid				
(2000) Linezolid	Oxazolidinone (bactericidal)	rp1C, rr1	Mutation in 50S ribosomal L3 protein	(Richter et al., 2007)

**Drug targeting ATP, DNA, RNA and protein synthesis resistance mechanism**

MTB resistance trait in the pandemic that have arisen as a result of evolution, antibiotic strain, and other factors indicate that this mutant function is necessary for his or her survival in a completely new environment. Because of a degree mutation, the used

drug is unable to bind to the correct target sites, lowering its efficacy (Dookie et al., 2018; Morris et al., 2005). The pathways of central dogma for example Nodal enzymes, DNA, polymer and super molecule synthesis, that have been encoded associate degreed forerunner attained the specified combination for extant within a setting or even a

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number body. As a result, several anti-TB drugs have been produced that target ATP, DNA and super molecule synthesis, all of which are important for Mtb survival. Antibiotics/drugs in the imidazopyridine and dirylquinoline organic compound categories target Mtb's adenosine triphosphate synthesis, while PAS inhibits Mtb's DNA synthesis precursor, and antibiotics in the fluoroquinolone class inhibit Mtb's DNA gyrase (Morris et al., 2005). Polymer synthesis is inhibited by RIF, whereas macrolides, cyclic peptides, oxazolidinones (linezolid) and aminoglycosides inhibit super molecule synthesis. Linezolid, for example, is a potential orally available drug that targets Mtb super molecule synthesis. Mutated rpoB causes a conformational change in RIF's binding affinity at the subunit of the polymer enzyme, rendering the drug inactive and preventing it from binding to the specific pointing website (Kashyap et al., 2018; Morris et al., 2005). Newly introduced two medication, pretomanid and delamanid are simpler in the direction of Mtb inhibition plasma membrane arrange within the few year, Recently, drug resistance to these two medications has been recorded all over the world (Palomino and Martin, 2014).

#### **Drug Resistance and Drug Development upcoming future prospective**

Among microbes and human individuals there is a battle for persistence since long time. For this survival evolution of antibiotics helps a lot from many centuries. But contemporarily the bacteria (*Mycobacterium tuberculosis*) creates some specific genetic factors and produce competence and bio-film formation through colony wide coordination for the purpose of retribution opposing to novel anti-TB drug (Nguyen and Pieters, 2009; Viveiros et al., 2012). From pre-existing variants strains, contemporary variants or mutants can retrieve proficiency for intensify transmission of virulence through adopting resistance mechanism with a worthy environmental pressure (Gygli et al., 2017; Lynch, 2011). In past it was suggested many MDR (multi-drug resistance) epidemics involved in the development of regulation systems through an antibiotics enhancement of phenotypic drug tolerant ability of latent TB and also convert Mtb into active growth from dormant state. According to nowadays

examination TB which is drug resistant mostly compared on basis of Mtb target enzymes which lie on genetic mutations (Almeida et al., 2016; Mathys et al., 2009; Zhang et al., 2013). Variations led to resistance factors which are mostly divided into two types:

Cellular mechanism is a type in which mismatch renovations takes place like DNA polymorphisms error or like translational inaccuracy. Second type is External mechanism which is mainly interlinked to stress factors, pollutions or quality of diagnosis (Lomovskaya and Bostian, 2006). There are also some social and economic factors which are mainly involved in drug resistance of TB: Insufficient hospital facilities, Ill-suited guidance, Long lasting expenses, National antibiotic policy has lack of strictness, Lack of awareness, Illiteracy rate and Indigence (Bhatt et al., 2019).

Apart from these factors when TB patients do not cooperate and show carelessness about their disease then it's become impossible to achieve complete cure. Costs of drugs are also directly effect on cure rate. From other infectious diseases like malaria HIV and hepatitis TB is the primary disease which cause mortality rate high among adults or youngsters in Asian populations (Sizemore et al., 2012; Sotgiu et al., 2019). Co-infection is actually a type of infection which cause due to multiple pathogen species and when TB which is mostly co-infect with HIV developed than it's led to enhance strains of XDR-TB and MDR-TB strains. Because when both disease cause at the same time than its latent or active TB disease and its cause resistance against TB drugs (Kaplan et al., 2018).

Due to this co-infection of HIV and TB rate of TB infections gets high triplet times in Africa. Rate of TB infections in Africa were round about 39%. Due to this record it seems to more difficult to treat co-infected TB. There is some anti-TB drugs which include bed aquiline pretomanid and delamanid are approved continuously and in small time period they provide best drug development performance. Still we have to be compelled to produce or develop more drugs to control TB infection through which globally millions of people died (Palomino and Martin, 2013). In medical research round about 265 billion dollars deposit for research and development of new

techniques of medication and diagnosis but from all this input only 0.25% output provided (Beena and Rawat, 2013). According to WHO (World Health Organization) report or documentary there are many agents which acts against to TB located in drugs pipeline and WHO has hope for to discover them in future. In some reports and articles, there are some agents of tubercular which contain heterocyclic nitrogen which contain pyridine and pyrazine derivatives which are similar to previously present anti-TB drugs which are pyrazinamide and Isoniazid. The presence of nucleus in nitrogen heterocyclic is beneficial for future anti-TB drug because it is a necessary chemical scaffold in which some metabolic, physiochemical and pharmacokinetic properties are present. In recent future for development of productive anti-TB (mycobacterium tuberculosis) drugs the outstanding progress carry out through screening with some techniques in molecular and mechanism of medicine. Secondary plant metabolites involved natural phyto-metabolites and cyanobacterium compound include phyco chemical are under search for to achievement of drugs of anti TB because both of compounds have special potential towards health and health problems and disease rate (J. Sloan et al., 2013; Kumar et al., 2011).

One of the classes of phyto-chemicals is terpenoid: From well Indian medicinal plant mono-O-methyl curcumin isoxazole 00019 mg/MI is MIC value of *Curcuma longa*, 0.00039 mg/MI is MIC value of *Plectanthus granadidentatus*, MIC values 0.0015-0.0033 mg/ mL of Plumbagin from *Disopyros anisandra*, from South African medicinal bosket 7 methyljuglone has its MIC value 00057mg per mL, from Malaysian sub-species which is organic heterocyclic compound is MIC value 0.0031-0.016mg per mL of *Calophyllum lanigerum* and *Celastrus vulcanicola* is group of alkaloid components with its MIC value 0.0062mg/ml (Changtam et al., 2010; Lall et al., 2005; Uc-Cachón et al., 2014; Xu et al., 2004). When their talks about host-toxicity then plant chemicals are consider being ideal drugs candidates in contrast to marine chemicals but drug progress rates are high in aquatic drug products than to plants drug outcomes (Liu et al., 2012a). In purpose to be an ideal participant in drug effectiveness then participant must maintain

cumulatively process of toxicity and activity with pharmacokinetic characteristics. Many medicinal chemistry procedures and synthesis of nano-particle take place in order to establish anti-TB drug development (Nasiruddin et al., 2017; Swain et al., 2020a; Swain et al., 2020b). Many factors play important role in order to sustainable TB-free society like scientific Endeavour geographical support administrative commitment and long-term investment.

### Conclusion

Drug resistance of *mycobacterium tuberculosis* now has become serious issue globally in medical concerns. All lines of drug resistances become stronger due to lack of heavy potential drug awareness. Potential molecular mechanism of this bacterial drug resistance required rapid latest regimens of anti-TB drugs .New modified genetic sciences that are combat to this critical situation should develop these mutational modifications. Mtb gives us innovative ways to study how can certain bacteria resist all the drugs by modifying its genetics and its enable us to discover more and more potential drugs.

### Conflict of interest

The authors showed absence of conflict of interest.

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