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Multidrug-resistant pathogens and their plasmid curing by lactic acid bacteria

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Abstract

Antibiotics are used to treat and prevent infections, but the overuse of drugs makes the microorganisms drug resistant, and with the time they become resistant to more than one drug. These bacteria are known as multidrug-resistant bacteria. Resistivity of bacteria against the antibiotics makes them more hazardous for human beings and animals too and those bacterial infections become untreatable and lead to death of the person. The resistivity to bacteria is provided by the bacterial plasmids, which contains antibiotic resistant genes. This problem can be overcome by removing bacterial plasmids from the bacterial cells. This can be done by treatment with plasmid curing agents, but various plasmid curing agents such as acridine orange or SDS are toxic and mutagenic in nature. Various investigations have been undertaken to determine the antibacterial effect and plasmid curing ability of extracellular and intracellular extracts of lactic acid bacteria (LAB) to cure plasmids of antibiotic resistant bacterial isolates. The microtiter plate method was used to determine the minimum inhibitory concentration of LAB extracts. Plasmid curing mediated by LAB extracts resulted in the loss of antibiotics resistance encoded in plasmids, as well as the antibiotics resistance profile of cured strains. The extracellular extracts of LAB were considered a natural and harmless source to combat plasmid borne multidrug-resistant bacteria.

1. Introduction

Bacteria are the type of biological cells that constitutes a large domain of prokaryotic microorganisms. The earliest life on land may have been bacteria. They are living on land since 3.22 billion years ago (Homann, 2018). The vast majority of bacteria in the body are beneficial, particularly in the gut flora. However, several species of bacteria are pathogenic and cause infectious diseases, including cholera, syphilis, anthrax, leprosy, bubonic plague. Antibiotics play a vital role in fighting against the microorganisms and they are probably one of the most successful forms of chemotherapy in the history of medicine (Rustam *et al.*, 2010). Current antibiotics, some of them are heavily modified that target the same cellular processes as their natural or synthetic predecessors. The range of these targets is limited to the components of translational machinery, cell wall biosynthesis, DNA/RNA metabolism and some other cellular processes. After the genome sequencing, it becomes easy to implement the idea of a magic bullet in a more elaborate way, so that the targets defined much more precisely at the molecular level. This idea helps in the availability of chemically diverse compound collections to screen for the target/drug combination (Payne *et al.*, 2007). However, robust evidence has shown that exposure to antibiotics does offer benefits for patients but can also cause gastrointestinal symptoms, rash and increases the probability of selection for resistant commensal bacteria (Gloria, 2021). Drug resistance traits in bacteria are rapidly spreading by horizontal

gene transfer, especially through plasmids. Plasmid curing agents that are active both *in vitro* and *in vivo* will resensitize to reduce the burden of antibiotic resistance (Subhashree *et al.*, 2019).

2. Antibiotic resistant

With the vast use of antibiotic, resistance developed by microorganisms become more prevalent and their use is currently under threat (Junaid Ali *et al.*, 2018). As the antibiotic resistant increasing drastically, it is essential to examine the key socio-economic factors which contribute to the rise in the prevalence of antibiotic resistance in developing and developed nations. Although, it is difficult to get accurate estimates of drug resistance, it is predicted that antimicrobial-resistant infections will lead to nearly 10 million deaths per year by 2050 and a total GDP loss of \$100.2 trillion by 2050, if appropriate actions are not taken (O'Neill, 2014).

3. Causes of antibiotic resistant

Microbes undergo mutation; some of the mutations may help an individual microbe survive after the exposure to an antimicrobial agent. During conjugation, microbes get genes from each other, including genes that make the microbe drug resistant. Due to this, sensitive bacteria also become drug resistant. Antibiotics may influence this process by inducing the transmission of resistance elements; these antimicrobials may additionally exert a selective pressure to the emergence of resistance (Stokes and Gilling, 2011; Munita and Arais *et al.*, 2016). Antibiotic resistance among pathogenic bacteria, many also be due to include inadequate regulations and awareness deficiency in the use of antibiotics. Overuse of antibiotics in poultry and livestock promote the antibiotic resistant, rather than to control infection (Bartlett *et al.*, 2013; Spellberg and Gilbert, 2014).

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4. Multidrug resistance

Multidrug-resistance (MDR) is defined as insensitivity of a microorganism to the antimicrobial medicines (which are structurally unrelated and have different molecular targets) despite earlier sensitivity to it (Singh, 2013; Popêda *et al.*, 2014). According to WHO, these resistant microorganisms (like bacteria, fungi, viruses, and parasites) are able to conflict with antimicrobial drugs, which leads to ineffective treatment, resulting in persistence and spreading of infections. Although, the development of MDR is a natural phenomenon, vast increase in the number of immune-compromised diseases, like diabetic patients, HIV-infected individuals who have undergone organ transplantation, and severe burn patients, makes the body an easy target for hospital acquired infectious diseases, thereby contributing to further spread of MDR (Nikaido, 2009; WHO, 2014). Multidrug-resistance is considered as a major health problem, and the infections caused by MDR pathogens affect the effectiveness of antimicrobial drugs and are associated with a high death rate. Resistance among a variety of drugs has been increased all around the globe due to the extensive use of antibiotics (Pfaller *et al.*, 1997). Initially, these MDR species were restricted to the hospital environment, but now they can be found everywhere and became a prevalent cause of community-acquired infections (Lipsitch, 2001; Lipsitch and Samore, 2002). Nowadays, it has become difficult to treat infections due not only to the antimicrobial resistance but also the suppressed immune function, deprived drug bioavailability, or increased rate of drug metabolism. Persistence of

microbes after standard treatments points out different types of anti microbial drug resistance which is an expanding problem in medical world. MDR can be classified as primary or secondary resistance.

4.1 Primary resistance

It occurs when the organism has never encountered the drug of interest in a particular host.

4.2 Secondary resistance

Also known as “acquired resistance,” which only arises in an organism after an exposure to the drug (Loeffler, 2003; Khalilzadeh, 2006). Secondary resistant is further of two types: Intrinsic and acquired resistance.

4.2.1 Intrinsic resistance

The inherent property of the microbes to resist the effect of a drug is classified as intrinsic resistance (Cox and Wright, 2013). Intrinsic resistance can also be termed as ‘insensitivity’ because of the insusceptible nature of the pathogen against particular drugs (Table 1). Intrinsic resistance is associated with the naturally occurring genes like AmpC or β -lactamase, which are found on the host chromosomes. Different mechanisms involved in the development of intrinsic resistance include modification of target sites, modification of antimicrobial agents, and presence of efflux pumps, low drug delivery, chemically induced adaptive changes, and stress response.

Table 1. Common bacteria with intrinsic resistance

Name of organisms	Intrinsic resistance
<i>E. coli</i>	Macrolides, tetracycline, penicillin, β -lactams
<i>Bacteroides</i>	Quinolones, penicillin, aminoglycosides, many β -lactams
<i>Acinetobacter</i> species	Glycopeptides, trimethoprim, chloramphenicol, ampicillin
<i>P. aeruginosa</i>	Cephalosporins, tetracyclines, trimethoprim-sulfamethoxazole, chloramphenicols, sulfonamides, ampicillin
<i>Klebsiella</i> spp.	Ampicillin, amoxicillin-clavulanate, ampicillin-sulbactam combination
<i>Enterococci</i>	Cephalosporins, trimethoprim, aminoglycosides, lincosamides, colistin
<i>Serratia marcescens</i>	Macrolides, ampicillin-sulbactam combination, ampicillin-clavulanate combination

4.2.2 Acquired resistance

In acquired resistance, genes targeted by antibiotics undergo mutations, and transfer the resistance determinants present on plasmids, transposons, and other transposable elements. The change in the genetic constitution of pathogens occurs due to gene transfer, gene alteration in stress regulating genes which in turn results in a change in protein expression and gene amplification methods (Flintoff, 1989). In general, the transfer of genes takes place by three processes involving: conjugation, transformation and transduction (Levy and Marshall, 2004). The most common method for the transmission of drug resistance requires conjugation, which is promoted by plasmids. During conjugation, “Pilus” is formed by plasmid between two adjacent bacteria to facilitate the transfer of genetic material. Transformation involves the uptake of exogenous DNA from surrounding or incorporation of DNA from the dying organism into the other recipient organism genetic cassette (Levy

and Marshall, 2004). Transduction is carried out by vectors (especially bacteriophages) that carry drug resistance genes and introduce them into the bacterial host. In a single bacterium, multiple plasmids carrying genes for resistance are present that have the ability to replicate independently to host chromosomes. These plasmids are differentiated by their origin of replication. Transposons are the transposable elements also termed as “jumping genes” present on a plasmid or can also integrate into other transposons or host chromosomes (Frost, 2005).

5. Multidrugresistant pathogens

Pathogens resistant to more than one antibiotic are termed multidrug-resistant pathogens. They are considered as one of the most important public health problems and major challenges to global drug discovery programmes (Vivas, 2019). Initially, MDR pathogens were restricted to hospital environments, but now they

can be found everywhere. In community acquired infections, MDR organisms are increasingly found. MDR infections have an impact on the effectiveness of antimicrobial agents and are associated with a high mortality rate. Such infections represent prolonged illness, an economic burden for the healthcare system and the immense risk of death (CDC, 2021). Due to resistance against many antibiotics, infections caused by MDR pathogens are mainly untreatable. MDR is a natural phenomenon; excessive use of antibiotics, poor sanitary conditions, inappropriate practices of infection prevention and control also lead to the spread of MDR. As per a report from the CDC (Centers for Disease Control and Prevention), more than 2 million infected and about 23,000 people die due to antibiotic resistant bacteria every year in the USA. Pathogens responsible for such an increase in the infection rates include methicillin-resistant *S. aureus* (MRSA), Vancomycin-resistant *E. coli* and fluoroquinolone-resistant *P. aeruginosa* (Solomon and Oliver, 2014). Due to the huge increase in multidrug-resistant pathogens, there is a decrease in antimicrobial agents which are used to treat infections caused by these pathogens (Cerceo, 2016). It was estimated that by 2050, if no new drugs are developed, there will be no antibiotics available to treat the infections effectively (Rolain, 2016). This leads to arise the need to search alternative methods for controlling antibiotic resistant pathogens. Almost all infectious agents like bacteria, fungi, viruses, and parasites show resistance toward multiple drugs and are able to resist attack by antimicrobial drugs, which results in ineffective treatment and spread of infections.

6. Mechanisms of MDR

Resistance is the insensitivity of a microbe to an antimicrobial drug when compared with other isolates of the same species. However, several new antimicrobial agents have been introduced commercially; this resistance development among infectious microorganisms is increasing especially in patients under prolonged drug exposure (Loeffler and Stevens, 2013). Antimicrobial agents generally act on the microbes either by prohibiting a metabolic pathway like synthesis of nucleotide which in turn leads to the inhibition of DNA/RNA synthesis and further protein synthesis and disruption of the cell membrane or by competing with the substrate of any enzyme involved in cell wall synthesis (Chethana *et al.*, 2013). Microorganisms have evolved many mechanisms to overcome the effectiveness of antimicrobial agents, therefore, they can survive under the exposure of antimicrobial agents.

Cell wall of bacteria and fungi plays an important role in their survival and most of the antimicrobial agents inhibit the cell wall synthesis by binding with the peptidoglycan layer in bacteria or affecting ergosterol synthesis (He *et al.*, 2013). This blocks the cell growth and division in bacteria and fungi. Microorganisms undergo certain chromosomal mutations (Aleksun *et al.*, 2007) or exchange of plasmid DNA through conjugation or transformation (WHO, 2014), which can cause changes in the cell membrane composition, resulting in decreased permeability and uptake of drugs into the cell (Singh, 2013; Loeffler *et al.*, 2003; Chethana *et al.*, 2013; Tenover, 2006). Altered membrane composition in microorganisms also lead to lack of active target sites for the drugs to bind (He *et al.*, 2013). Mutations in the genes that encode for the target, cause modifications at the molecular level and retain cellular function by reducing susceptibility to antimicrobial agents (Singh, 2013; Chethana *et al.*, 2013).

The MDR among microorganisms can also be by the over expression of drug target enzymes which lead to target bypass due to modification in certain metabolic pathways *e.g.*, azoles and allylamines in fungi (He *et al.*, 2013), or causes the production of alternate target molecules and interference in some protein synthesis. This can affect the entry of drugs to the target sites. Enzymatic degradation of drugs occurs by hydrolysis of ester or amide bonds (such as resistance to β -lactams due to β -lactamases) and hydroxylation of drug has also become increasingly apparent as causes of MDR (Singh, 2013; Chethana *et al.*, 2013; Aleksun and Levy, 2007). The resistant strains of clinical isolates also developed the ability to oxidize or reduce the drugs to prevent their interaction with the respective targets (Chethana *et al.*, 2013). MDR in parasites is also a global public health threat. These parasites also undergo certain point mutations resulting in altered drug targets, alter calcium homeostasis in endoplasmic reticulum and expel drugs out of the cells (McFadden *et al.*, 2000; Bloland, 2001).

Efflux pumps remain the predominant mechanism of MDR. The over expression of genes encoding for ATP-binding cassette transporter membrane proteins (*e.g.*, P-glycoprotein), also known as the multidrug efflux pumps are responsible for the export or expulsion of drugs out of the cell (Nikaido, 2009; Aleksun and Levy, 2007; Li, 2009) and usually generates MDR and continues cellular functions without any interference. Over expression of P-glycoprotein, in *Entamoeba* spp. and *Leishmania* spp. membrane or multidrug-resistant proteins (MRP), affects the fluidity and permeability, leading to an ATP-dependent efflux of the antimicrobials and decreasing their intracellular concentration (Bansal *et al.*, 2006; Orozco *et al.*, 2002; Ouellette *et al.*, 2001). Superbugs are bacteria-resistance to one or more antibiotics, and they make difficult to treat or cure infections that once were easily treated. The antibiotic has lost its ability to control or kill bacterial growth because they have developed genes for resistance and that gene protects them (Alain, 2017). Various mechanisms involved in MDR include extrinsic as well as intrinsic mechanisms (Figure 1).

6.1 Extrinsic mechanisms of MDR

6.1.1 Modification/absence of target site

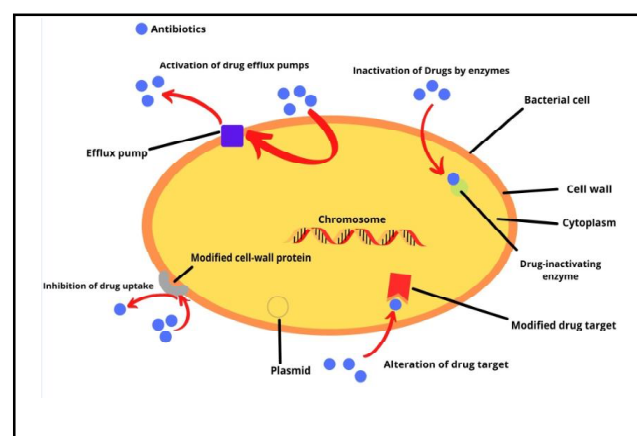


Figure 1: Various mechanisms of multidrug-resistance among bacteria (Bbosa *et al.*, 2014).

The uptake of antimicrobial drugs by microorganisms is essential for effective action of the drug against the specific target. In the outer membrane of Gram-negative bacteria, pore proteins called porins are present, which mediates the transfer of drugs to cross outer membranes of bacterial cells. In order to protect themselves from the action of drugs, some bacteria can modify the cell wall or membrane, as in the case of Gram-negative bacteria (Ray *et al.*, 2017). These bacteria modify the frequency and size of porin present on the outer membrane to decrease the uptake of certain bacteria, such as aminoglycosides. Similarly, modification in the penicillin-binding protein site results in resistance against many β -lactam antibiotics (Malouin and Bryan, 1986).

6.1.2 Limiting drug uptake and biofilm formation

The most common mechanism of intrinsic resistance is to reduce the permeability of the outer membrane within Gram-negative bacteria. The barrier to different types of drugs is provided by the lipid polysaccharide layer at the outer membrane, which confers innate resistance to various groups of antimicrobial agents (Blair *et al.*, 2014). The outer membrane of *Mycobacterium* has high lipid content, due to which drugs such as rifampicin, fluoroquinolones (hydrophobic drugs) have easier access to cells, whereas hydrophilic drugs have limited access (Pa, 2002; Kumar and Schweizer, 2005). The formation of biofilm by the bacterial community is the most common phenomenon of bacterial colonization. Biofilms are the clusters of bacteria that are firmly attached to the surface by means of tendrils, filaments and provide protection to bacteria from the attack by the host immune system, as well as from the antimicrobial drugs (Kanwar *et al.*, 2019).

These biofilms are surrounded by the thick, sticky coating of polysaccharides, proteins and DNA from resident bacteria that form the barrier, thus preventing antimicrobial drugs from reaching the bacteria. Therefore, to be effective, a much higher concentration of drugs is required. The complex three-dimensional structure of biofilm contains transport proteins, which helps in the uptake of nutrients, disposal of waste material, thereby helping in the pumping of drugs out of cells. Moreover, less oxygen and fewer nutrients are available for bacterial cells deep within the biofilm; therefore, these cells have slow cell division and metabolism. Hence, these are less susceptible to the action of antimicrobial drugs, which tends to target fast-growing and dividing bacterial cells. Bacteria that are capable of forming biofilm include *Salmonella* sp. on environmental surfaces, *Neisseria* sp. as dental plaque on teeth, *Staphylococcus* intermediates on orthopaedic implants and pacemakers (Kanwar *et al.*, 2018).

6.1.3 Inactivation of antimicrobial drugs via modification and degradation

Sometimes, microbes modify or destroy the active component of antimicrobial drugs in order to protect themselves from the harmful effect of a drug or to gain resistance against that particular drug. Many Gram-negative and Gram-positive bacteria possess this ability against various drugs such as chloramphenicol or aminoglycosides. The modification or deactivation of the β -lactam ring in case of penicillin and cephalosporins to produce inactive penicilloic acid, which is not able to bind to PBPs and; therefore, bacteria are able to maintain cell wall synthesis (Waxman and Strominger, 1983).

6.1.4 High detoxication capacity

In order to escape the attack of predators and other competitors, many bacteria produce various toxic compounds. Such bacteria also possess the ability to escape the harmful effects of those toxic chemicals secreted by them (Ray *et al.*, 2017). These bacteria inactivate antibiotic products like streptomycin and neomycin secreted by them to develop resistance against drugs with the help of phosphotransferases and acetyltransferases. Moreover, in the case of higher organisms, protein expression that is associated with protection against various chemicals is highly tissue-specific. The mammalian lungs have developed the large number of resistance mechanisms, including glucose-6-phosphate, dehydrogenase, β -tocopherol, glutathione, catalase, superoxide dismutase, mainly due to their ability to resist the damage caused by oxygen-induced free radicals. Similarly, due to direct exposure to the environment, the bronchiolar epithelium contains a large number of detoxication enzymes.

6.1.5 Cell cycle effects

Rate of cell division in case of mammalian cells (solely tumor cells), is mainly responsible for the intrinsic drug resistance. The main dose-limiting factor is rapidly dividing normal cells in case of cancer chemotherapy and mostly, the antineoplastic drugs which are beneficial in treatment of cancerous disease are effective against quickly dividing malignant cells. Therefore, tumors in G0 resting state are slow growing and many anticancer drugs are not very effective on these slow growing cells.

6.1.6 Species specific structure of target

The species specificity has been observed in some cases due to the lack of affinity of drug to its binding site. Under a single genus of bacteria, by presenting various structural motifs for the same target, different species alter drug binding sites, therefore, developing resistance against these drugs (Aleksun and Levy, 2007). The crystal structure of large ribosomal subunits in *S.aureus* shows specific motifs and binding modes for different antibiotics of same functions and helps the bacterium to develop resistance against many antibiotics.

6.2 Extrinsic mechanisms of MDR

6.2.1 Resistance through chromosomal mutation

(a) Fluoroquinolones

Many bacteria develop fluoroquinolone resistance with the help of mutations, which in turn makes the target protein less susceptible to agent. However, fluoroquinolones resistance is mainly associated with the mutations within the target sites and drugs, such as DNA topoisomerase and DNA gyrase (Hooper, 2000; Drlica and Malik, 2003). These drug targets, when altered due to mutations, develop resistance against fluoroquinolones. These components are involved in the various ATP-dependent functions during the process of DNA replication. These multi-subunit complexes consist of two subunits, GyrA and GyrB for DNA gyrase and ParC/GrlA and ParE/GrlB for topoisomerase IV. Fluoroquinolones, mainly target subunit GyrA and ParC/GryA to perform DNA-binding functions, whereas subunit ParE/GrlB and GyrB help in ATP binding and breakdown are targeted by coumarin antibiotics. Mutations which are involved in fluoroquinolones occur first on DNA gyrase of Gram-negative

bacteria, whereas, in Gram-positive, mutations initially arise in topoisomerase IV. These mutations are mainly found in the quinolone-resistance-determining-region (QRDR) of GyrA and ParC/GrIa, and therefore, pathogens that are resistant to fluoroquinolones bear many QRDR mutations as well as other fluoroquinolone resistance mechanism such as drug efflux.

(b) Rifamycin

Rifamycin is the bactericidal drugs, which either alone or in combination with other drugs like isoniazid, streptomycin, pyrazinamide is the primary choice of therapeutic drug against *M. tuberculosis* infections. Rifamycin interacts with the RpoB, thereby, arresting the transcription. However, point mutations at the rifamycin binding site of RpoB at the frequency of about 1×10^{-8} prevent the binding affinity of the drug at the RNA polymerase subunit, thereby providing resistance against the drug (Mariam *et al.*, 2004). *M. tuberculosis* is resistant to these drugs and prevents efficient therapy among patients in different regions of the world (Sharma and Mohan, 2006).

(c) Sulfonamide and trimethoprim antibiotics

Sulfonamides were the first antimicrobials developed for large scale introduction into clinical practices, which targets dihydropteroate synthase. Mutation results in the alteration of dihydropteroate synthase, which in turn decreases the affinity of the enzyme for sulfonamides in *E. coli* and *S. pneumoniae* (Sköld, 2001). Trimethoprim causes inhibition of dihydrofolate reductase enzyme. Mutations in the gene specifying dihydrofolate reductase results in high level production of drug resistant enzymes with reduced drug affinity and therefore, provide resistance among *E. coli* and *H. influenzae* against trimethoprim (Sköld, 2001).

(d) Tetracycline, aminoglycoside and MLS antibiotics

Antibiotic resistance is also attained by point mutations at the ribosomes, which inhibit the protein translation. Components present in the tetracycline, aminoglycoside and MLS antibiotics target the ribosomes, as a result of which protein translation is inhibited. Tetracycline and aminoglycoside bind with 16SrRNA (rrs) whereas MLS antibiotics interact specifically with 23SrRNA (rrl). Resistance cannot be attained without mutation in all or majority of other operons therefore, resistance among tetracycline and MLS antibiotics is achieved by point mutation at 16SrRNA and 23SrRNA operons respectively (Ross, 1998).

(e) Oxazolidinones

Linezolid acts as an inhibitor of protein synthesis and was approved for treating the infections caused by methicillin-resistant *S. aureus* as well as vancomycin-resistant *Enterococci*. It is useful for treating both nosocomial and community-acquired infections because it is available in both intravenous as well as oral formulation. Point mutations in rrl results in linezolid resistance in *S. aureus* and *E. faecalis*. Moreover, linezolid resistance due to point mutation at rrl has also been documented in strains of *S. epidermidis*, *E. faecium*, *E. faecalis*, *S. aureus* and *Streptococcus oralis* (Eliopoulos *et al.*, 2004). The resistance in *S. aureus* increases with the increase of mutations in multiple rrl operons (Wilson, 2003).

6.2.2 Genomic duplication

Genome duplication or gene amplification is genomic doubling which results in the overexpression of drug targets and is the most common mechanism of drug resistance in eukaryotic cells (Albertson, 2006). In *E. coli* genomic doubling at acrAB locus in the presence of tetracycline results in the overexpression of AcrAB drug efflux pump, thereby, producing multidrug-resistance phenotype (Nikaido and Zgurskaya, 2001). Such type of amplification was observed in *S. aureus*, with respect to methicillin resistance (Matthews and Stewart, 1998). This type of mechanism is unstable because the microbes revert back to their normal phenotype in the absence of drug (Nicoloff *et al.*, 2007).

6.2.3 Enzymatic drug modification or inactivation

Inactivation of drugs by means of enzymes is a common resistance mechanism, in which resistance genes encodes for enzymes that have ability to chemically modify the antimicrobial drugs, therefore, inactivating them through different processes like hydrolysis, phosphorylation, adenylation, acetylation. This mechanism is very common for the antibiotics of natural origin such as, aminoglycosides (amikacin, kanamycin), which are inactivated by enzymatic phosphorylation with the help of enzyme aminoglycoside phosphoryl transferase (APH), or by acetylation involving aminoglycoside acetyltransferase (ACC), or by adenylation catalyzed by aminoglycoside adenytransferase. β -lactam antibiotics such as penicillin, cephalosporins, and carbapenems are inactivated by the process of hydrolysis carried out by β -lactamases. Mechanism of enzymatic drug modification includes two types of enzymes; enzymes that are responsible for degradation of antibiotics/drugs such as β -lactamases, and other enzymes that result in chemical transformation including macrolide and aminoglycoside modifying enzymes (Kumar *et al.*, 2013; Blair, 2015).

(a) β -lactamases

β -lactamases are the enzymes that catalyze the enzymatic hydrolysis of the β -lactam bonds within the β -lactam ring of the drug molecule, causing the ring to open. The open ring drugs are not able to bind with target proteins as a result of which, the drug molecule loses its antimicrobial activity. This is the most common mechanism of β -lactam resistance, mediated by β -lactamases. Most of these resistances are associated with resistance genes present on plasmid or transposons, which encodes for β -lactamases and provide intrinsic resistance. On the basis of structure and functions, β -lactamases have been divided into two categories; one with serine at the active catalytic site and the other require metal ion cofactor (such as zinc-dependent metalloenzymes) (Jacoby and Munoz-Price, 2005). The β -lactamases with serine active site are classified into class A, C and D enzyme groups, whereas, β -lactamases with zinc-dependent metalloenzyme are classified in class B. Class A, C and D enzymes function as extended-spectrum- β -lactamases, whereas class B metalloenzymes function as carbapenemases that catalyze the hydrolysis of carbapenems. As class B enzymes are zinc-dependent, they are inhibited by EDTA. An inducible or plasmid-borne enzyme, AmpC is proteotypic class C enzyme, found in many strains of *Enterobacteriaceae* and *P. aeruginosa*, can be easily transfer to *E. coli*, *Klebsiella sp.* and *Salmonella sp.* (Jacoby, 2009).

(b) Aminoglycosides

Large number of enzymes that possess the ability to modify the aminoglycosides are present on mobile genetic units and integrons and are widely spread in clinically important organism (Davies and Wright, 1997). Resistance among aminoglycosides can be achieved by aminoglycoside modifying enzymes such as acetyltransferases, phosphotransferases and adenylates that reduce the net positive charges on these polycationic antibiotics. Aminoglycosides such as tobramycin, gentamicin, and amikacin are modified by acetyltransferases, whereas adenylates results in the modification of tobramycin activity and susceptibility of amikacin is affected by phosphotransferases. On integrons and transposable genetic elements, these modifying enzymes are further associated with other resistance determinants. In *P. aeruginosa*, three acetyltransferase genes were found on class 1 integrons, that also confer resistance to carbapenems and sulfonamides (Poirel, 2001).

(c) Modulated drug targets

Alteration, substitution or modification of the targets of antimicrobial drugs helps in developing resistance against them. In the 1940s, the first penicillin and methicillin resistant β -lactamase producing strain of *S. aureus* was identified. The gene encodes for β -lactamase helps in altering the penicillin binding protein (PBPs), thereby confers resistance against methicillin in *Staphylococcus* (Fuda *et al.*, 2005) as well as *Streptococcus* (Jacobs, 1999). The altered penicillin binding proteins (PBP2a) is encoded by the *mecA* gene present on the mobile genetic element called "Staphylococcal cassette chromosome" (SCCmec) of the methicillin resistant *S. aureus* (Wielders, 2001). The mobile genetic element contains regulatory loci (*mecR1-mecI*) and enzymes responsible for site-specific recombination.

In *S. aureus*, processes of cell wall synthesis require large number of PBPs. PBP2 enzyme is bifunctional and plays a double role in *S. aureus*, involving transpeptidase and transglycosylase activities, which switch their role on the basis of exposure to drug (Brown and Reynolds, 1980). PBP2 functions as transglycosylase while PBP2a functions as transpeptidase, thereby providing resistance to all β -lactam antibiotics. The plasmid borne *qnr* determinants which affect the sensitivity of fluoroquinolones have been found mainly in Gram-negative sp. of *E. coli*, *Shigella*, *Salmonella*, and provide the mechanism of decreased fluoroquinolone susceptibility (Piekarska, 2012). *Qnr* belongs to the pentapeptide repeat family of proteins, which regulates the resistance among fluoroquinolone by protecting DNA gyrase and topoisomerase IV, respectively, from the action of fluoroquinolones (Tran and Jacoby, 2002).

Moreover, another resistance mechanism of fluoroquinolone is MfpA, found in *Mycobacterium*, belongs to pentapeptide protein family, contain single type II topoisomerase with ability to mimic the structure of β -form DNA. Therefore, it acts as inhibitor of DNA gyrase of *M. tuberculosis*. Interaction of MfpA with *Qnr* has inhibitory effect on ciprofloxacin (Montero, 2001) and the organisms (bearing *Qnr* or MfpA), which can survive in the presence of low fluoroquinolone concentration favour the selection of fluoroquinolone resistance. Another major example of drug resistance is due to modification of drug targets of glycopeptides, found mainly in the Gram-positive spherical bacteria (Courvalin, 2006). These glycopeptides exert bactericidal activity by interacting with the

peptidoglycan precursors. In *Enterococci*, acquired glycopeptide resistance is associated with VanA, VanB, VanD, VanE and VanC phenotypes, where VanA and VanD confers resistance against both vancomycin and teicoplanin, whereas, VanC confers intrinsic resistance.

Multiple proteins specified in the gene clusters contribute the resistance phenotype and result in the production of modified peptidoglycan. The activity of many enzymes specified by gene clusters is involved in developing glycopeptide resistance. Recemases and dehydrogenases produce serine and lactate from pyruvate and result in modification of peptidoglycan structure. These two component units regulate the mechanism of cellular biosynthesis. If an intact D-Ala is available, glycopeptides having low affinity for D-Ala-D-serine and D-Ala-D-lac substrates can still bind and inhibit cellular biosynthesis. To overcome this, dipeptidase and carboxypeptidase perform their functions of cleaving and removing terminal D-alanine. Dipeptidase cleaves C-terminal D-Ala-D-Ala whereas carboxypeptidase results in removal of terminal D-Ala. The VanA gene cluster, which is responsible for vancomycin resistance in *Enterococcus* has transferred its resistance determinants in methicillin resistant *S. aureus*, where these determinants reside on plasmid encodes Tn1546 transposon (Weigel, 2003). It was assumed that the plasmids from *E. faecalis* function as vehicles for the transfer of VanA into *S. aureus*.

(d) Efflux mechanism

The envelopes of Gram-negative bacteria affect the susceptibility of the drugs by inhibiting its penetration (Li and Nikaido, 2004). Because of the efflux mechanism, which ejects the drugs out of the cell, most of the antimicrobial drugs penetrate the Gram-negative organisms, but they are not able to reach intracellular targets (Levy, 1992). In this mechanism, five protein transporter families have been involved which include; ATP-binding cassette (ABC) transporters, major facilitator (MF) protein groups, small multidrug resistance (SMR) units, resistance-nodulation-cell-division (RND) family, and multidrug and toxic compound extrusion (MATE) protein super family, (Poole, 2005) (Figure 2).

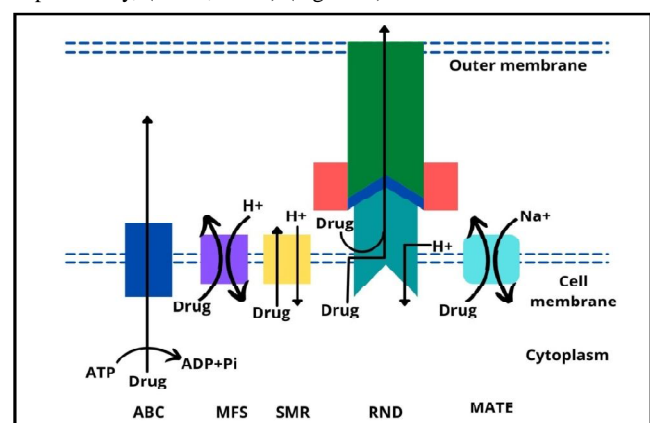


Figure 2: General structure of main efflux pump families.

Most of these efflux pumps transport drugs across cytoplasmic membranes (single-compound pumps), whereas, the RND family are multi-component pumps, which pumps out substrates across the entire cell envelope. These pumps function in association with periplasmic membrane fusion proteins (MFP) and outer membrane

protein (OMP-porin) (Kumar and Schweizer, 2005; Poole, 2007; Blair *et al.*, 2014). For efflux mechanism, ATP hydrolysis is performed by ABC group of primary transporters, while other transporter groups employ proton-motive gradient force to eject the drugs out of cells (Kobayashi *et al.*, 2001).

7. Approaches to combat the emergence of antimicrobial resistance or MDR

It has been suggested to use the appropriate antimicrobial agents (no antibiotics for viral infections) to limit the development of antimicrobial resistance. Identify the causative organism whenever possible, select an antimicrobial which target the specific organism rather than relying on broad spectrum antimicrobial. Although, overuse of antibiotics is mostly responsible for antibiotic resistant in bacteria, several studies have revealed that treatment indications, agent choice, and antibiotic therapy duration are inappropriate in 30% - 50% of the cases (Ventola, 2015; Lushniak, 2014). World population are now facing infections with a limited number of therapeutic options and alternative treatment must be developed. These options are either based on specific targets on the MDR bacteria or designed to improve the host response to the infectious injury (Anne-Sophie and Benoit, 2017).

7.1 Problems associated with MDR

The major problems associated with the MDR are, high mortality rates and high medical costs of treatment and these have significant impact on the effectiveness of antimicrobial agents (Figure 3). MDR cause problems in disease control by enhancing the possibility of spreading of resistant pathogens, and thus decline the efficacy of treatment and results in prolonged time of infection in patient. The cost of treatment of disease is increased due to MDR as the pathogens become more resistant to commercially available drugs, which has triggered the use of more expensive therapies. The resistance profile of bacterial and fungal as well as the quality of public hygiene also has a considerable impact on the effectiveness of antimicrobial agents especially in developing countries (WHO, 2014; Fishbain, 2010).

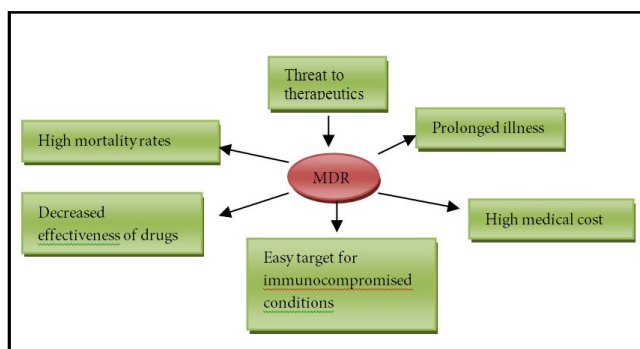


Figure 3: Problems associated with MDR (Tanwar *et al.*, 2014).

Plasmid is an extra chromosomal DNA molecule that carries the resistance property against drugs in bacteria. R-plasmids from resistant strains of pathogenic bacteria may transfer to sensitive bacteria that would show the same drug resistance as the donor strain (Datta, 1972). Plasmids can also be eliminated from bacteria by using curing agents. Different use of chemical agents such as intercalating dyes (acridine orange, ethidium bromide), treatment

with crystal violet, SDS, thymidine starvation and exposure to UV radiation, exposing the host strain to elevated temperatures helps in plasmid curing (Clowers, 1972).

7.2 Plasmid curing

Plasmid curing is the elimination of plasmid DNA from bacterial isolates in order to determine the relationship of multidrug resistance with plasmid DNA (Raj, 2012). This is an attractive approach to combat antimicrobial resistance, the plasmid curing agents have the potential to remove antimicrobial resistant genes from a population while leaving the bacterial community intact. This means, the gastrointestinal microbiome of a chicken treated with a plasmid curing agent might remain largely unchanged, but potentially pathogenic bacteria which may unfortunately be transmitted into the food chain would be susceptible to antibiotics. Alternatively, a plasmid curing agent could be given to a patient prior to surgery, to reduce the resistant hospital acquired infection. Plasmid curing agents could also be taken by international travelers to reduce the global spread of antimicrobial resistance, but the plasmid curing agents should be safer for the human beings; they should not show any impact on the microbiome. Furthermore, removing drug-resistance plasmids is a strategy for all sectors to reduce the overall burden of antimicrobial resistance. For example, plasmid curing agents could be used to remove antimicrobial resistant genes from bacteria in sewage before release into the environment. Human and animal waste is often recycled and used to fertilize agricultural land; this can contain high concentrations and varieties of antimicrobial resistant genes which can be passed on to people (Meek *et al.*, 2015; Rahube *et al.* 2016). Abundance of antimicrobial resistant genes have been detected in plasmid metagenome libraries constructed from the activated sludge and digested sludge from two waste water treatment plants, demonstrating that these were important reservoirs of antimicrobial resistant genes. Treatment of sewage with plasmid curing agents will help in reducing the antimicrobial resistant genes (Li and Zhang 2015).

7.3 Plasmid curing compounds

In bacteria, resistance occurs with the accumulation of genes coding for resistance to specific agents on the plasmids, most commonly on R-plasmids (Schelz *et al.*, 2006). Plasmids are independent, circular, extrachromosomal DNA elements capable of replicating independently of the host cell. Plasmid encodes different types of properties, including resistance to antimicrobial drugs, heavy metals and degradation of hydrocarbons. Many compounds have shown some plasmid curing activity which include detergents, biocides, DNA intercalating agents, antibiotics (aminocoumarins, quinolones, rifampicin), ascorbic acid, plant-derived compounds and lactic acid bacteria. The effectiveness of these compounds varies and depends on bacterial strain, plasmid and growth conditions. Plasmid curing compounds act through different mechanisms, in many cases, they disrupt plasmid replication by integrating into the DNA (intercalating agents and chlorpromazine), cause breaks in DNA (ascorbic acid) or influence plasmid supercoiling (amino coumarins and quinolones). Each of these can result in reduced plasmid prevalence within the population over time (Michelle *et al.*, 2018). Unfortunately, at the moment no such treatment options are in use. In fact, there are very few curing mechanisms that have been tested *in vivo*, even in experimental models. Therefore, research in this area is urgently needed. It was shown that 24% of non-antibacterial drugs impact

the growth of members of the human microbiome (Maier *et al.*, 2018). LAB extracts also showed antibacterial and anti-plasmid effect against multidrug resistant bacterial strains and are also safer for human beings (Nehal *et al.*, 2015).

However, no single antimicrobial agent has the ability to cure all the plasmids from different hosts. Some of these curing agents such as acridine orange, ethidium bromide, and SDS are very toxic and mutagenic in nature; therefore, not suitable for therapeutic applications. Thus, the development of new non-toxic agents with high efficiency and safety are necessary to reduce the development of MDR. On the basis of various studies, LABs come under the category of generally recognized as safe (GRAS). Moreover, extracellular and intracellular fractions purified from LAB extract have various antimicrobial and anti-plasmid activities against MDR bacterial strains.

7.3.1 Detergents

Detergents, bile and sodium dodecyl sulfate (SDS) an anionic surface-activating agent, are powerful agent for curing of plasmids (Tomoeda *et al.*, 1968; Inuzuka *et al.*, 1969). SDS known to eliminate certain plasmids determining constitutive synthesis of F pili, had no effect on cultures with wild-type (repressed) R factors (Vyvyan *et al.*, 1972). SDS was effective in eliminating F-lac and the R factor R100dr (Tomoeda *et al.*, 1969). Both these plasmids produce F-like pili constitutively (Nishimura *et al.*, 1967). SDS also had other effects on bacteria, which include changes in the peptidoglycan layer, bacterial cell size, septation and loss of outer membrane components (Rosas *et al.*, 1983).

7.3.2 DNA intercalating agents

Intercalating agents such as acridine orange and ethidium bromide have played an important role in curing bacterial plasmids. The modes of action of intercalating agents are through preferential inhibition of plasmid replication (Vengadesh, 2015). Acriflavine cured some resistance plasmids from *Salmonella oranienburg*, *S. Panama* and *E. coli* K12 *in vitro* and in murine *in vivo* model (Bouanchaud and Chabbert 1971). Acriflavine, acridine orange and ethidium bromide cured resistance to antimicrobials from both donor and transconjugants *B. fragilis* and *B. thetaiotaomicron* (Rotimiet *et al.*, 1981).

7.3.3 Antibiotics

The plasmid-mediated resistance to the compound emerges and subsequently spreads after the introduction of a new antibiotic into medical practice. Bacterial resistance of this type is likely to precede the clinical use of the new molecule, but use of the antibiotic favors selection, dissemination, and hence detection of resistance. The availability of the drug is a prerequisite for screening and finding, by medical microbiologists, of the new resistance phenotype. As usual, there are a few exceptions to the rule; nitrofurans, novobiocin, polypeptides, quinolones, and rifampin have no known plasmid-mediated resistance (San, 1990). It is noteworthy that novobiocin (coumermycin), which also inhibits DNA gyrase, belongs to this group. There has been a single report of plasmid-mediated resistance to nalidixic acid in bacteria (Munshi, 1987).

7.3.4 Ascorbic acid

Ascorbic acid (vitamin C) is a readily available compound which is a non-hazardous curing agent and safe to handle and have demonstrated the physical loss of a plasmid from a strain of *Pediococcus acidilactici* CFR K7 which was previously shown to be a pediocin producer (Ramesh *et al.*, 2000). The effect of ascorbic acid was also noticed in curing of *Serratia marcescens* plasmid. In *S. aureus*, 1 mM ascorbic acid resulted in loss of penicillin and aminoglycoside resistance encoding plasmids (Amañile Cuevas, 1988; Amañile-Cuevas *et al.*, 1991). Two plasmids, pI258 (penicillin resistance) and pT181 (tetracycline resistance), were not cured by ascorbic acid. However, there was a significant decrease in the MIC of tetracycline, which might be due to reduction in plasmid copy number (Amañile-Cuevas *et al.*, 1991).

8. Plasmid curing by LAB

Lactic acid bacteria (LAB) are a group of Gram-positive, non-sporulating, anaerobic or facultative aerobic *cocci* or rod shape bacteria (Hayek and Ibrahim, 2013). They play an important role in food production and health maintenance (Emiliano *et al.*, 2014). They are of particular interest to the food industry (Nettles and Barefoot, 1993), since these bacteria have generally been regarded as safe (GRAS status). Their growth lowers, the carbohydrate content of the food they ferment as well as the pH due to lactic acid production. LAB secretes antimicrobial compounds of low molecular weight, cationic proteins, and bactericidal to other Gram-positive bacteria (Klaenhammer, 1988). These antimicrobial compounds have long been used in fermentations to preserve the nutritive qualities of various foods. This bioactive compound may be proteinaceous bacteriocin (Tagg *et al.*, 1976). Most of these LAB live in harmless and beneficial association with humans and generally found on decaying plant materials, milk and milk products. In human and animal, they are part of normal flora and natural inhabitants of intestinal tract, oral cavity and the vagina, where they play beneficial roles (Ayivi *et al.*, 2020). Moreover, various members of the LAB are used commercially as a starter culture in the manufacture of dairy products such as yoghurt, butter-milk and hard and soft cheese (Hati *et al.*, 2013). Fermentations of LAB results in the production of high quality nutritious and healthy food products which include meat, alcoholic beverages, vegetables, legumes, cereals and milk products. LAB also have many therapeutic properties which are beneficial for the improvement of human health (Carr *et al.*, 2002).

8.1 Bacteriocins produced by LAB

Bacteria are developing resistant against antibiotics and this cause significant public health problem (Lipsitch, 2001; Lipsitch and Samore, 2002). MDR pathogens can transfer genes horizontally and this transfer of genes can take place by three ways, through plasmids, phages, or uptake of naked DNA (Thomas and Nielsen, 2005). Some microbial pathogens have acquired resistant against antibiotics due to their frequent uptake and bacteriocins have the advantage over conventional antibiotics. Bacteriocins are ribosomally synthesized peptides that have antibacterial activity towards closely related strains (De-Vuyst and Leroy, 2007; Cleveland *et al.*, 2001). Bacteriocins can be produced by both Gram-positive as well as Gram-negative bacteria, but bacteriocins produced by LAB are inherently tolerant to high thermal stress and

are known for their activity over a wide pH range. Bacteriocin shows their antimicrobial mechanism by forming pores in the membrane of target bacteria, even at low concentrations. They can be easily degraded by proteolytic enzymes due to their proteinaceous nature and due to this, the fragments of bacteriocins do not live long in the human body or in the environment (U.S. Federal Register, 1988).

Bacteriocins obtained from *L. fermentum* were found to possess antimicrobial potential against methicillin resistant *S. aureus* (Nawaz *et al.*, 2009). Bacteriocins produced by *Lactobacilli* strains isolated from yogurt was found to possess antimicrobial potential against cephalosporin resistant *E. coli* (Riaz *et al.*, 2010). LAB produced antimicrobials might play a serious role during the *in vivo* interactions occurring in the human gastrointestinal tract and contribute to gut health (De-Vuyst and Leroy, 2007). This live biotherapeutic agent has been tried as alternative innovative approaches to antibiotics in treating gastrointestinal diseases (Daly and Davis, 1998; Soomro *et al.*, 2002; Oyetayo *et al.*, 2003).

8.2 Reutericyclin produced by LAB

Reutericyclin is a low molecular weight antibiotic produced by LAB (*Lactobacillus reuteri*). It is hydrophobic in nature and structurally related to naturally occurring tetramic acids. It shows its antimicrobial effect on Gram-positive and Gram-negative bacteria, several fungi and yeasts (Ganzle and Vogel, 2003; Ganzle, 2004).

8.3 Lactic acid produced by lactic acid bacteria

The primary antimicrobial effect exert by LAB is the production of lactic acid (Mobolaji and Wuraola, 2011). Lactic acid shows antimicrobial activity by causing acidification of cytoplasm and failure of proton motive force. It increases the pH gradient within the cell and decreases the amount of energy required for cell growth and microbes failed to grow in the presence of lactic acid (Wee *et al.*, 2006). It can inhibit the growth of both Gram-positive and Gram-negative bacteria as well as yeast and mold (Rathanachahaikunsopon and Phumkhachorn, 2010). Different microorganisms vary in their sensitivity to lactic acid. The lactic acid was found to be inhibitory towards spore forming bacteria at pH 5.0 whereas ineffective for yeast and mold (Yang, 2000).

8.4 Hydrogen peroxide (H₂O₂) produced by LAB

Hydrogen peroxide produced by LAB can be used in food, pharmaceutical, dental products and textile industries (Abbas *et al.*, 2010). H₂O₂ produced by LAB inhibit the growth of pathogenic bacteria at refrigeration temperature (Abriouel *et al.*, 2004). H₂O₂ shows its antimicrobial effect by the oxidation of sulfhydryl groups, which cause denaturation of number of enzymes as well as peroxidation of membrane lipids to increase the membrane permeability. The H₂O₂ acts as precursor for the production of bactericidal free radicals such as superoxide and hydroxyl, which can damage DNA (Ammor *et al.*, 2006).

9. Conclusion

Majority of pathogenic bacteria developed resistant against antibiotics and this resistance is mainly due to plasmids. Many plasmid curing agents have been used for the elimination of plasmid

from the bacteria, but these are not safer for human beings. The *in vivo* plasmid curing studies will be crucial in developing methods to make bacteria sensitive to existing antibiotics. The interest in bacteriocins produced by LAB has increased dramatically and there are many bacteriocins that inhibit the growth of pathogenic bacteria. However, there are different kinds of pathogens in nature and bacteriocin alone can not eliminate all bacterial pathogenicity. Subsequent studies are needed to evaluate the health-promoting activity of bacteriocins. The development of new generation of antimicrobial agents is necessary in order to reduce the burden of antibiotic resistant. Biotechnological methods have to be applied to create new or multifunctional bacteriocins, so they could be widely used in medicine.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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