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MULTIDRUG RESISTANCE BY MICROORGANISMS: A REVIEW

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ABSTRACT
Multiple drug resistance (MDR) is the ability of some microorganisms to resist the actions of multiple antimicrobial agents. MDR include those resistant to multiple antibacterial, antifungal, antiviral, and anti-parasitic drugs. Similar activities of some microorganisms to certain chemical (drug) that would normally kill them or limit their growth is called antimicrobial resistance (AMR). Multi drug resistance can be classified as primary resistance, secondary resistance, intrinsic resistance, extensive resistance and clinical resistance. The classes of antibiotics that fall victim of resistance include beta-lactams, glycopeptide, aminoglycosides, sulphonamides, cephalosporins etc. The mode of action of antimicrobial drug includes cell wall synthesis inhibitors, protein synthesis inhibitor, blockage of key metabolic pathways, nucleic acid synthesis inhibitors etc. Bacteria often become resistant and this could be through one of several biochemical mechanisms such as mutation, destruction or inactivation and efflux or genetic transfer of materials between bacteria by several means such as conjugation, transformation and transduction. The mode of action of MDR protozoa occurs through decrease of drug uptake, the export of drugs from the parasite by P-glycoproteins and other traffic ATPases etc. The mode of action of MDR helminths occurs through genetic changes in the drug target, changes in drug transport, drug metabolism etc. The mode of action of antiviral drugs usually target viral DNA polymerase having the reverse transcriptase activity to inhibit the viral replication. The mode of action of MDR fungi occurs as they have learnt to modify the antifungal drug targets or most commonly increase the efflux of the incoming drugs There are various ways to reverse this resistance such as washing hands after seeing each patient, the public should wash raw fruit and vegetables thoroughly to clear off both resistant bacteria and possible antibiotic residues, avoid the misuse of antibiotics, etc.

Keywords: Microorganism, Multiple drug resistance (MDR)

INTRODUCTION

Multiple drug resistance (MDR) is an antimicrobial resistance exhibited by some microorganisms to multiple antimicrobial drugs. MDR microorganisms are mostly threatening to public health because they resist multiple antibiotics. Other MDR include those that are resistant to multiple antifungal, antiviral, and anti-parasitic drugs (Magiorakos, 2014; WHO, 2018).

A broad range of biochemical and physiological mechanism may be culpable for resistance (Liu and Pop, 2009; WHO, 2014). In the specific case of antimicrobial agents, the complexity of the processes that contribute to emergence and propagation of resistance cannot be overestimated, and due to the lack of elemental knowledge on these topics is one of the major reasons that there has been so limited significant fulfillment in the effective prevention and control of resistance development (Liu and Pop, 2009; WHO, 2014).

There are specific classes of compounds of antimicrobial that are capable of destroying or inhibiting microorganisms even in high dilutions. (Laxminarayan *et al.,* 2013). Antibiotics are substances that are produced by the natural metabolic processes of some microorganisms which can either inhibit or destroy other microorganisms (Talaro and Talaro, 2002; Nester *et al.,* 2004). The current root of antimicrobial drugs is diverse (Rudramurthy, 2016). The Synthetic antimicrobial drugs in the laboratory are derived from dyes or other organic compounds through chemical reactions (Laxminarayan *et al.,* 2013). For more than 60 years, antibiotics have been critical in the fight against infectious diseases which are caused by bacteria and other microorganism (Laxminarayan and Heymann, 2012). Nevertheless disease-causing microbes that have come to be resistant to antibiotic drug treatment such as pneumonia, septicemia, gonorrhea, tuberculosis, wound infections, and diseases that have become difficult to treat with antibiotics remains an increasing public health problem (WHO, 2013). One side of the issue is that bacteria and other microbes that cause infections are exceptionally volatile and have developed various ways to resist antibiotics and other form of antimicrobial drug (Boucher *et al.,* 2013). Another side of the issue is as a result of increasing use and misuse of current antibiotics in human, veterinary medicine and in agriculture (Todar, 2012). Microbes developing resistance, as well as due to economic reasons have arisen in the research and development in the search for novel antibiotics in order to provide a wide range of effective drugs at all times (WHO, 2014).

Antimicrobial Resistance

This is the ability of microbes to grow in the presence of a chemical (drug) that would normally restrict their growth or destroy them (Huttner *et al.,* 2013).Microorganisms resistance to antimicrobial drug was basically effective for the treatment of infection caused by those microorganisms. Drug resistant microorganisms include (bacteria, fungi, viruses and parasite). These microorganisms are able to combat attack by antimicrobial drugs so that basic treatment becomes ineffective and infection prevails, raising the risk of spreading to others (Roca *et al.,* 2015). Antimicrobial resistance makes it harder to eradicate infections from the body as current drugs become less effective. Consequently, some infection diseases today are more difficult to treat than they were just a few decades ago (NIAID, 2009). As more microorganisms became resistant to antimicrobials, the protective value of these drugs is reduced due to the use and misuse of antimicrobial drugs and this is among the factors that have contributed to the development of drug resistant microbes (NIAID, 2009). Examples of these microbes include Drug resistant

Mycobacterium tuberculosis (TB), Methicillin-resistant *Staphylococcus aureus* (MRSA), Vacomycin- resistant *Enterococci* (VRE), and Multidrug- resistant *Neisseria gonorrhoeae* (Gonorrhea), Gram- negative bacteria (NIAID, 2009; Arumugam, 2016; Swamy and Sinniah, 2016).

Classification of Multi Drug Resistance

Administration of appropriate doses of drugs for a particular duration of time, survival of different microbial strains suggests the high levels of resistance developed in them (Tanwar *et al.,* 2014). This clinical failure is as a result of not only the antimicrobial resistance but also the suppressed immune function, deprived or poor drug bioavailability, or increased rate of drug metabolism. Multi drug resistance can be classified as primary or secondary resistance (Tanwar *et al.,* 2014).

Primary resistance: occurs when the organism has never confronted the drug of interest in a particular host i.e. it is a drug resistance in patient who has not received any previous anti-tubercular treatment (Mathur, *et al.,* 2000; Paramasivan *et al.,* 2000 Hemvani *et al.,* 2001). For example primary drug resistance tuberculosis, this occurs in patients who have not previously received tuberculosis treatment. Primary drug resistance is known to be caused by the dissemination of drug-resistant strains (Jassal and Bishai, 2009).

Secondary resistance: This is also known as "acquired resistance," this term is used to define the resistance that only occurs in an organism after an exposure to the drug (Loeffler and Stevens, 2003; Khalilzadeh *et al.,* 2006). This can also be define as resistance that evolve in a patient who has previously received chemotherapy (Mathur*, et al.,* 2000; Paramasivan *et al.,* 2000; Hemvani *et al.,* 2001). For example acquired drug resistance expressed tuberculosis isolated from patients who currently are getting or until that time have received anti-tuberculosis drug treatment for at least one month (Van Rie, *et al.,* 2000).

It can further be classified as follows;

Intrinsic resistance*:* Intrinsic resistance is the innate ability of a microorganism to resist activity of a particular antimicrobial agent through its inherent structural or functional characteristics, which allow tolerance of a particular drug or antimicrobial class (Chuanchuen *et al.,* 2003). This can also be called "insensitivity" since it occurs in organisms that have never been susceptible to that particular drug (Alekshun and Levy, 2007). Such natural insensitivity can be due to:

- Lack of affinity of the drug for the bacterial target
- Inaccessibility of the drug into the bacterial cell
- Extrusion of the drug by chromosomally encoded active exporters
- Innate production of enzymes that inactivate the drug (Alekshun and Levy, 2007).

For example, Gram-positive bacteria to aztreonam (a beta-lactam), Gram-negative bacteria to vancomycin, anaerobic bacteria to aminoglycosides, aerobic bacteria to metronidazole etc (Forbes and Sahm, 1998; Giguere *et al.,* 2006).

Extensive resistance*:*

It defines the ability of organisms to withstand the inhibitory effects of at least one or two most effective antimicrobial drugs (Loeffler and Stevens, 2003). Also termed as XDR, this seemed to arise in patients after they have undergone a treatment with first line drugs, for example, XDR-TB (extensive drug resistant tuberculosis) resistance against fluoroquinolone (Gandhi *et al.,* 2003; Loeffler and Stevens*,* 2003).

Clinical resistance: Clinical resistance is described by the situation in which the infecting organism is inhibited by a concentration of an antimicrobial agent that is linked with a high likelihood of therapeutic failure or reappearance of infections within an organism as a result of impaired host immune function especially the pathogen is inhibited by an antimicrobial concentration that is higher than could be carefully attained with normal dosing (Loeffler and Stevens, 2003)

Common Drugs: Victim of Resistance

Table 1: Microorganisms and their resistance mechanism to various antibiotics

Organisms	Natural resistance against:	Mechanism
Anaerobic bacteria	Aminoglycosides	Lack of oxidative metabolism to drive uptake of aminoglycosides.
Aerobic bacteria	Metronidazole	Inability to anaerobically reduce drug to its active form.
Gram positive bacteria	Aztreonam (a beta lactam)	Lack of penicillin binding proteins (PBPs) that bind and are inhibited by this beta lactam antibiotic.
Gram negative bacteria	Vancomycin	Lack of uptake resulting from inability of vancomycin to penetrate outer membrane.
Klebsiella sp.	Ampicillin (a beta lactam)	Production of enzymes (beta lactamases) that destroy ampicillin before the drug can reach the PBP targets.
Stenotrophomonas maltophila	Imipenem (a beta-lactam)	Production of enzymes (beta lactamases) that destroy imipenem before the drug can reach the PBP targets.
Lactobacilli and *Leuconostoc*	Vancomycin	Lack of appropriate cell wall precursor target to allow vancomycin to bind and inhibit cell wall synthesis.
Pseudomonas aeruginosa	Sulfonamides, trimethoprim, tetracycline, or chloramphenicol	Lack of uptake resulting from inability of antibiotics to achieve effective intracellular concentrations.
Enterococci	All cephalosporins	Lack of PBPs that effectively bind and are inhibited by these beta lactam antibiotics

(Forbes and Sahm, 1998;Giguere *et al.,* 2006)

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Multidrug Resistance Bacteria and Mode of Action

Multi drug resistance (MDR) bacteria are bacteria that have become resistant to certain commonly used antibiotics. There are many different types of MDR bacteria that can easily be found throughout the environment including water and soil (Vaz-Moreira *et al.,* 2014). They cause the same type of infections as non-resistant bacteria (Tanwar *et al.,* 2014). The difference is that when an infection with multi-drug resistant bacteria is developed, the choice of suitable antibiotic to treat the infection may be considerably more limited, example include *Psuedomonas aeroginosa, Staphylococcus aureus* (MRSA), *Esherichia coli, Acinetobacter baumannii, Klebsiella pneumoniae, Mycobacterium tuberculosis, Neisseria gonorrhoeae* e.tc. (Arias and Murray, 2009; NHS, 2017). Antibiotic resistance could occur in bacteria through four types of mechanisms:

Drug inactivation or modification: for example, enzymatic deactivation as in penicillin G in some penicillin-resistant bacteria through the production of β-lactamases (Jacoby and Munoz-Price, 2005). Protecting enzymes manufactured by the bacterial cell will add an acetyl or phosphate group to a specific site on the antibiotic, which will diminish its capacity to bind to the bacterial ribosomes and disrupt protein synthesis (Giedraitien˙e *et al.,* 2011; Jose and Cesar, 2016).

Modification of target- or binding site: for example, alteration of PBP-the binding target site of penicillin's-in MRSA and other penicillin-resistant bacteria, or modification in structure of ribosomal protection proteins (Tang *et al.,* 2014). These proteins guard the bacterial cell from antibiotics through changes its conformational shape. Change of proteins conformational shape allows these proteins to loss their activity so, prevent inhibit protein synthesis, and this help in grow of bacteria and spread it (Jose and Cesar, 2016).

Alteration of metabolic pathway: for example, absence of paraaminobenzoic acid (PABA), this is precursor for the synthesis of folic acid and nucleic acids (Jose and Cesar, 2016).

Reduced drug accumulation: By decreasing drug permeability or increasing active pumping out of drugs through cell membrane (Jose and Cesar, 2016). The balance of antibiotic uptake and elimination determines the susceptibility of bacteria to a particular drug. Thus, reducing the amount of antibiotic able to pass through the bacterial cell membrane is one strategy used by bacteria to develop antibiotic resistance (Santajit and Indrawattana, 2016).

Multidrug Resistance Protozoa and Mode of Action

Parasitic protozoa are responsible for some of the most devastating and prevalent diseases of humans and domestic animals. Even though protozoa are eukaryotes and usually contain many of the organelles and metabolic pathways of their hosts, the differences in biochemistry between parasite and host are great enough to leave a large window for the development of parasite-specific drugs (Brianti *et al.,* 2016). For example Malaria (*Plasmodium* sp.), the various forms of (muco) cutaneous and visceral leishmaniasis (*Leishmania* sp.), African sleeping sickness (Trypanosoma brucei gambiense, T'ypanosoma brucei rhodesiense), *Toxoplasma gondii* etc (Doliwa *et al.,* 2013; Oliva *et al.,* 2014). Drug resistance mechanisms here in certain protozoans could be described as follows:

Decrease of drug uptake because of the loss of a transporter required for uptake. This decrease contributes to resistance to arsenicals and diamidines in African trypanosomes (Borst and Ouellette, 1995; Upcroft and Upcroft, 2001).

The export of drugs from the parasite by P-glycoproteins and other traffic ATPases. This export could potentially be an important mechanism of resistance, as these proteins are richly represented in the few protozoa. There are indications that such transmembrane transporters can be involved in resistance to emetine in *Entamoeba* sp., to mefloquine in *Plasmodium* sp., and to antimonials in *Leishmania* sp (Borst and Ouellette, 1995; Upcroft and Upcroft, 2001).

The involvement of the PgpA P-glycoprotein of *Leishmania* sp. in low level resistance to arsenite and antimonials. This raise the possibility that this protein transports glutathione conjugates of arsenite and antimonials rather than the compounds themselves (Borst and Ouellette, 1995; Upcroft and Upcroft, 2001).

Loss of drug activation as the main mechanism of metronidazole resistance in *Trichomonas* and *Giardia* sp. Recent evidence indicates that a decrease of the proximal cellular electron donor for metronidazole activation, ferredoxin, is the main cause of resistance in *Trichomonas* (Borst and Ouellette, 1995; Upcroft and Upcroft, 2001).

Resistance arising through alteration of drug targets. The amino acid substitutions in the dihydrofolate reductase-thymidylate synthase of *Plasmodium* sp. are good examples of this mechanism (Borst and Ouellette, 1995; Upcroft and Upcroft, 2001).

Multidrug Resistance Helminths and Mode of Action

Helminths are a diverse group of parasitic worms, encompassing nematodes, cestodes and trematodes are a major health problem for human and animals in many part of the world (Kaplan, 2004; Hotez *et al.,* 2008).

Genetic changes in the drug target

Most efforts to identify drug resistance in helminths have concentrated on alteration of the drug's cellular target, identified by changes in the genome sequence. Several single-nucleotide polymorphisms (SNPs) have been associated with resistance (Gilleard, 2006). SNPs are unique genetic differences between individuals and are the basis of genetic differences in a population. SNPs can also arise by gene mutation after drug treatment (Voisey and Morris, 2008).

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Changes in drug transport

Although genetic selection contributes to anthelmintic resistance, other mechanisms also contribute. Early studies in cancer cells showed that some tissues were inherently resistant to treatment, whereas other tumours acquired resistance after treatment (Zhou, 2008).This resistance was to a variety of drugs and was mediated by the expression of a membrane protein known as P-glycoprotein (Zhou, 2008). The transport of several anthelmintics (including ivermectin, benzimidazoles and imidazothiazole derivatives) by human P-glycoprotein in cells expressing the transport protein has been reported (Nare *et al.,* 1994; Brayden and Griffin, 2008). This suggests that drug efflux mechanisms might function in drug resistance in Helminths that contain functionally related transport proteins.

Drug metabolism

There is also evidence for increased drug metabolism as a mechanism for drug resistance in parasites, but this is mainly substantiated for protozoa. However, many anthelmintics currently in use cause increased free radical production as part of their cytotoxic activity – for example, praziquantel and artemisinin used to treat *Schistosoma* sp (El-Bassiouni *et al.,* 2007).

Multidrug Resistance Viruses and Mode of Action

Viruses have developed numerous resistance mechanisms that enable them to evade the effect of antimicrobials and antivirals. As a result, many have become resistant to almost every available means of treatment (McKeegan *et al.,* 2002).This problem, although not new, is becoming increasingly acute and it is now clear that a fundamental understanding of the mechanisms that microbes and viruses deploy in the development of resistance is essential if we are to gain new insights into ways to combat this problem (McKeegan *et al.,* 2002). Antiviral drugs usually target viral DNA polymerase having the reverse transcriptase activity to inhibit the viral replication. Drug resistant mutant strains undergo mutations in the reverse transcriptase domains of the polymerase gene which affects the interaction between the drug and the enzyme. Resistance to the inhibitory effects of drug on the enzyme can also emerge due to any conformational changes or altered binding of substrate to the viral polymerase (Strasfeld and Chou, 2010).

Multidrug Resistance Fungi and Mode of Action

Fungal cells have developed several strategies to deal with the antifungal. They have learnt to modify the antifungal drug targets or most commonly increase the efflux of the incoming drugs. Cell wall, in fungi plays a crucial role in their survival. Drugs affecting ergosterol synthesis (e.g polyenes) in fungi, thus, blocking the cell to grow then (He *et al.,* 2013). Such as reduction in the ergosterol content in fungal plasma membrane) resulting in decreased permeability and uptake of drugs into the cell (Loeffler and Stevens, 2003; Singh, 2013). Altered membrane composition (such as β-1, 3-glucan and lipid content in fungal cell membrane) also leads to lack of active target sites for the drugs (e.g., echinocandins in fungi to bind (He *et al.,* 2013). Mutations in the genes encoding for the target cause modifications at the molecular level and retain cellular function by reducing susceptibility to inhibition (Loeffler and Stevens, 2003; Singh, 2013). Another mechanism of MDR was found to be an over expression of drug target enzymes leading to target by pass due to modification in certain metabolic pathways (e.g., azoles and allylamines in fungi), which causes production of alternate target molecules and interference in some protein synthesis (He *et al.,* 2013). Examples include yeast such as *Candida* species can become resistant under long time treatment with azoles preparations requiring treatment with a different drug class. *Scedosporium proflificans* infections are almost uniformly fatal because of their resistance to multiple antifungal agents (Howden *et al.,* 2003).

Mechanisms and the Emergence of Antibiotic Resistance

The long awaited "superbug" arrived in the summer of 2002 *Staphylococcus aureus,* a common but sometimes deadly bacterium, had acquired a new antibiotic resistance gene. This new strain was isolated from foot ulcers as diabetic patients in Detroit, Michigan, methicillin resistant (formally methicillin-resistant*) S. aureus* (MRSA) had been well known as the bane of hospitals (Deurenberg *et al.,* 2007; Willey *et al.,* 2008; Paterson *et al.,* 2014). The newer strain had developed resistance to vancomycin, one of the few antibiotics that were still able to control *S. aureus.* This new vancomycin resistant *S. aureus* (VRSA) strain also resisted most other antibiotics including ciprofloxacin, methicillan and penicillin. Isolated from the same patient was dread of hospitals vancomycin-resistant *Enterococc*i (VRE) (CDC, 2004). Genetics analysis reveal that the patient's own vancomycin sensitive S. *aureus* had acquired the vancomycin resistance gene VanA, from VRE through conjugation, so was born a new threat to the health of the human race (Willey *et al.,* 2008; Paterson *et al.,* 2014).

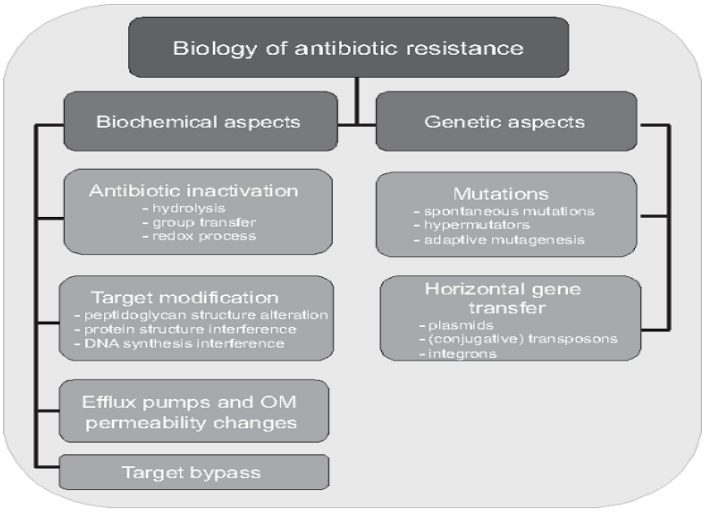

Fig. 2: Biochemical and genetic aspects of antibiotic resistance mechanisms in bacteria (Dzidic *et al.,* 2008).

Bacteria often become resistant in several ways. Unfortunately, a particular type of resistance mechanism is not confined to a single class of drugs. Two bacteria may use different resistant mechanisms to withstand the same chemotherapeutic agent (Willey *et al.,* 2008). Susceptible bacteria can acquire resistance to antimicrobials by either genetic mutation or by accepting antimicrobial resistant genes from other bacteria (Martinez *et al.,* 2009). This could be through one of several biochemical mechanisms such as mutation, destruction or inactivation, efflux or genetic transfer of

materials between bacteria by several means such as conjugation, transformation and transduction (Wiley *et al.,* 2008; Munita and Arias, 2016).

Mutation

This is a change in the DNA that can sometimes cause a change in the gene product, which is the target of the antimicrobial. When a susceptible bacterium comes in contact with a therapeutic concentration of antimicrobials, like fluroquinolones, the antimicrobial can bind to the specific enzymes, in this case, DNA gyrase (Cattoir *et al.,* 2007). The DNA gyrase is an essential bacterial enzyme required for DNA replication. The end result is that fluroquninolones blocks bacterial DNA replication leading to cell death (FDA, 2004; Cattoir *et al.,* 2007). However, when spontaneous mutations occur in specific areas of the genes encoding these enzymes, antimicrobials no longer bind efficiently. This allows the bacterium to continue DNA replication. Pathogens often become resistant simply by preventing entrance of the drug. Many gram negative bacteria are unaffected by penicillin G because it cannot penetrate the envelops outer membrane (Delcour, 2009). Genetic mutations that lead to changes in penicillin binding proteins also render a cell resistant. A decrease in permeability can lead to sulfonamide resistance (FDA, 2004).

Destruction or Inactivation

Many bacteria possess genes which produce enzymes that chemically degrade or deactivate the antimicrobial rendering them ineffective against bacterium. Here the antimicrobial is either degraded or modified by enzymatic activity before it can reach the target site and damage the bacterial cell (Bush, 2013).The best known example is the hydrolysis of the β - lactam ring of penicillin's by the enzymes penicillinase drugs are also inactive by the addition of chemical group (FDA, 2004). For example, chioramphenicol contains two hydroxyl groups that can be acetylated in a reaction catalyzed by the enzyme chioramphenicol acyltransferase with actyl CoA as the donor. Aminoglycosides can be modified and inactivated in several ways. Acetyltransferases catalyze the acetylation of amino groups. Some aminoglycoside modifying enzymes catalyze the addition of hydroxyl groups of either phosphates (phosphotransferasses) or adenyl groups (addenyltransferases) (FDA, 2004; Bush, 2013).

Efflux

One of the most common drug resistance mechanisms is active efflux of drugs from, the inside of the bacterial cells. Such drug resistant bacteria habour energy-driven drug efflux pumps which extrude antimicrobial agents thus reducing their intracellular concentration to sub or non-inhibitory levels (Piddock, 2006). Efflux pump is essentially a channel that actively exports antimicrobial and other compounds out of the cell. The antimicrobial enters the bacterium through a channel termed as porin and then is pumped back out of the bacterium by the efflux pump (FDA, 2004). Because they are relatively non-specific and can pump many different drugs, these transport proteins often are called multidrug resistant pumps. There are two main types of active efflux pumps; the first type called primary active transport uses the hydrolysis of ATP to actively efflux drugs from cells, while the second type, called secondary active transport, uses an iron gradient for actively efflux drugs from cells (Poole, 2005).The ATP driven transporters are also known as ABC (for ATP Binding Cassette) or P-glycoprotein transporters. Both active transport systems are used by bacteria to resistant the inhibitory effects of antimicrobial agents and are often referred to as efflux pumps (Sanath and Manuel, 2013). Many are drug/proton antiporters that are proton enters the cell that the drug leaves. Such systems are present in *E. coil, P. aeruginosa* and *S. aureus* etc (Willey *et al.,* 2008).

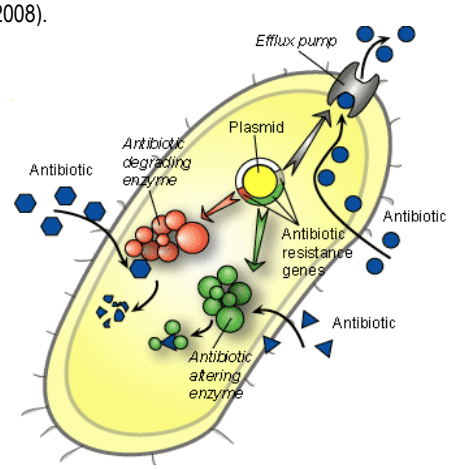

Fig 3: Showing Efflux and Enzymatic degradation (Todar, 2012).

Measures to Reverse Resistance

In main genetic processes, horizontal gene transfers, the resistant microbe is affected not only in its ability to withstand the antibiotic, but due to the fact that its interaction with the host and its ability to be transmitted between hosts. Usually, it is observed that most resistance mechanisms will confer a reduction in bacterial fitness, which might be expressed as reduced growth and survival inside and outside a host, and reduced virulence or transmission rate from environment to host or between hosts (Todar, 2002; Laxminarayan, 2003; Dromigny and Perrier-Gros-Claude, 2003).

Washing hands after seeing each patient is a major and obvious, but too often overlooked precaution (Okeke *et al.,* 2001). Two epidemiological studies, of erythromycin resistance in *Streptococcus pyogenes* and penicillin resistance in *Streptococcus pneumonia*, have been suggested as providing support for their versatility of resistance in community settings (Masters *et al.,* 2003; Szczepannowski *et al.,* 2009).

Several laboratory and epidemiological studies indicate that various processes are predicted to cause long-term persistence of resistant bacteria. One process is compensatory evolution, where the costs of resistance are ameliorated by additional genetic changes, resulting in the stabilization of resistant bacteria in the population. Even though most resistance is associated with fitness cost, some resistance mutations appear to be gratuitous. The occurrence of such cost-free resistances will also cause irreversibility since the driving force for reversibility is absent (Woodhead and Blasi, 2005).

The public should wash raw fruit and vegetables thoroughly to clear off both resistant bacteria and possible antibiotic residues. When they receive prescriptions for antibiotics, they should complete the full course of therapy (to ensure that all the pathogenic bacteria die) and should not "save" any pills for later use (Stephen and Kennedy, 2011).

Consumers also should refrain from demanding antibiotics for colds and other viral infections and might consider seeking non antibiotic therapies for minor conditions, such as certain cases of acne. They can continue to put antibiotic ointments on small cuts,

but they should think twice about routinely using hand lotions and a proliferation of other products now imbued with antibacterial agents. New laboratory findings indicate that certain of the bacteria-fighting chemicals being incorporated into consumer products can select for bacteria resistant both to the antibacterial preparations and to antibiotic drugs (Stephen and Kennedy, 2011).

Conclusion

Inadequacy of available antimicrobial drugs compels continuous development of newer drugs. MDR is an unavoidable natural phenomenon, posing a serious worldwide menace to public health. A cooperative action at global level is a must to combat the MDR. Pathogens tend to adopt various resistance mechanisms to survive the unfavourable conditions. Improved knowledge of molecular mechanisms controlling MDR should facilitate the development of novel therapies to combat these intransigent infections and will help cultivate a deeper understanding of the pathobiology of microbial organisms.

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