IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Review On Molecular Mechanism Of Antibiotic Resistance

[1]Mr. Swaraj Ashok Rathod*, [2]Mrs.Ashwini A. Wakade ,[3]Dr. Megha T. Salve

[1]Shivajirao Pawar College of Pharmacy, Pachegaon, Tq. Newasa, Dist.Ahmednagar, Maharashtra,India.

[2]Department of Pharmacy, Pachegaon, Ahmednagar-413725

ABSTRACT:

Difficult-to-treat antibiotic-resistant infections are on the rise and are a global health problem. Molecular Mechanisms Antibiotic-resistant bacteria are essential to finding ways to avoid the conditions that promote persistent bacteria. The aim of this workshop is to examine the genetics of the molecular mechanisms of antibiotic resistance and to define the intrinsic, acquired, and environmental resistance to antibiotics that block different bacteria and the phenotypic response defined by the protocol that provides the antibiotic. This defense mechanism allows bacteria with this mechanism to survive and even actively grow in the presence of antibiotics. In addition, some different viruses have developed mechanisms to resist various drugs, making it difficult to target these viruses with treatments for common viruses, resulting in patient infection. Understanding the molecular mechanisms of the immune system is important for developing new strategies to overcome and prevent immune problems. Research on the development and prevention process must be understood in the early stages of drug development and ideas for developing antibiotics or improving access to antibiotics in the workplace.

Keywords:Antibiotics,Bacteria,Resistance,Biofilm

INTRODUCTION:

Antibiotics are the foundation of modern medicine; however, the number of diseases caused by multidrug-resistant bacteria is increasing worldwide and the prevalence of untreated diseases is becoming a reality. The latest World Economic Forum Global Risks Report lists antibiotic resistance as one of the biggest threats to human health[1-3]. The history of antibiotics parallels that of antibiotics. Ironically, penicillin was discovered before it was introduced into medicine. The first antibiotic reported in the literature was penicillinase produced by the bacterium Escherichia coli [2]. Bacteria can become resistant to antibiotics or be protected by mutations or acquired immune responses.

The use of selective antibiotics for different infections in populations that are less susceptible or resistant to the antibiotics used leads to situations where resistant bacteria exist in this selection [3]. In addition, selection for resistance to a single antibiotic often results in the emergence of different strains with multiple determinants [4]. This high selectivity is expected to occur in areas where antibiotics are widely used, such as human medicine [5], agriculture, and soil and water resources [6]. Antibiotic use therefore promotes the spread of bad bacteria and drug resistance in the population. Multidrug-resistant organisms can interfere with treatment by developing resistance to chemotherapy, which can lead to treatment failure of infectious diseases [7]

Concerns about the immune response diminished from the 1950s to the 1990s with the continued development of new vaccines that are now ineffective [8]. Gram-negative and other bacteria have genetic mechanisms to develop resistance and eliminate the effects of antibiotics. These include genes that enable the body to produce enzymes such as extended-spectrum beta-lactamases and various carbapenemases, efflux pump mechanisms, and plasmids carrying resistance genes. Recent reports of plasmid-mediated colistin resistance in Escherichia coli carrying the colistin resistance (mcr-1) gene have attracted considerable attention. Colistin is generally considered an antibiotic of last resort.The fact that many resistant bacterial infections were first reported in Asia and involved the use of antibiotics in animals illustrates the broad global impact of antiretroviral viruses (AMR)[9].

(AMR) poses a serious and growing threat to global health. Immune-mediated diseases are now estimated to kill at least 50,000 people a year in the United States and Europe alone, and hundreds of thousands more people elsewhere in the world. The consequences will be worse in the future if we do not slow the development of anti-inflammatory drugs.

The Centers for Immunology and Prevention predicts that 10 million people will die each year from vaccine-preventable diseases by 2050. 40% of the population dies prematurely from infectious diseases that we cannot treat [12].

Molecular mechanisms of bacterial resistance to antibiotics:

Understanding the molecular mechanisms of antibiotic resistance requires understanding the structure and function of bacteria [13]. The molecular mechanisms of resistance are genetically divided into two groups: intrinsic resistance and acquired resistance. The latter refers to the cases where bacteria are not affected by antibiotics due to their physical properties, such as Mycoplasma resistant to beta-lactams due to the absence of cell walls and Enterobacteriaceae resistant to vancomycin due to the coating process. The development of resistant strains of Gram-negative bacteria. Acquired resistance refers to the situation where bacteria that were previously sensitive to the antibiotic administered are not affected by the concentration (14). Vaccination studies (i.e., receiving vaccines) have important clinical consequences. This is because the outcome of the attack renders the previous treatment ineffective, causing more severe disease and death, especially during the transition period when there is not enough energy for change in empirical treatment. Gain protection can be divided into horizontal gain protection and gain of transfer resistance. Horizontally acquired resistance refers to the emergence of resistance due to horizontal gene transfer (HGT), which usually occurs during plasmid conjugation, phage transduction, or nonspecific DNA uptake. Instead, mutations occur when the organism's genome mutates to overcome these effects For all purposes, only the relative amount of antibodies (i.e. acquired immunity) is clinically important. This is because the outcome of the challenge is likely to override previous good treatments, leading to more severe disease and death, especially during the transition period when the resistance block is too small to warrant a change in empirical therapy. Gain protection can be divided into horizontal gain protection and gain of transfer resistance. Horizontally acquired resistance refers to the emergence of resistance due to horizontal gene transfer (HGT), which usually occurs during plasmid conjugation, phage transduction, or nonspecific DNA uptake. In contrast, acquired resistance mutations occur

when bacterial genomes change in a way that overcomes the effects of antibiotics and usually involve changes in one or a few nucleotides. It has been suggested that both horizontal and vertical resistance play an important role in clinical intervention [15].

1.Intrinsic Resistance:

It is the innate ability of an organism to prevent the action of specific antibodies through its active components. Intrinsic mechanisms are defined by genes on the host chromosome, such as β-lactamases and multidrug resistance (MDR) efflux systems of Gram-negative bacteria. Bacterial efflux in Gram-positive bacteria always has a polypeptide in the cytoplasmic membrane. The cell membrane of Gram-negative bacteria is the main barrier to antibiotics, and the molecular mechanism of antibiotics includes the plasma membrane, periplasm, and outer membrane (E. coli has innate resistance to vancomycin). The membrane is the main barrier to antibiotic entry by porins or passive diffusion across the membrane phospholipid bilayer. Lipopolysaccharide (LPS) provides a barrier to many antibiotics, but polycationic drugs such as gentamicin and colistin are transported across the membrane by interaction with LPS, a process called "self-induced" absorption. Efflux pumps of the resistant nodule compartment (RND) superfamily are important players in antibiotic resistance of Gram-negative bacteria [16].

It has been shown that physical attack is usually due to the impermeability of the cell membrane, the operation of multiple drug efflux pumps or the lack of a suitable target for the drug family. However, recent reports have shown that the characteristic phenotype of the immune system in bacteria derived from the combination of different elements is weak; the name is properly called intrinsic resistance. These decisions do not only involve classical genetics. Other elements, some of which are involved in the process of metabolic diseases, are related to the activity of the bacteria in the organism. The three most important causes of resistance are: lack of target, activity of chromosomally encoded antibiotic inactivating enzymes and decreased antibiotic resistance, including decreased permeability of the cell membrane and failure of the efflux pump [18].

2.Acquired resistance:

On the other hand, the modification of the organism's genome through mutation or horizontal gene acquisition will cause a change in the product of the protein expressed by the body. These changes can lead to changes in the structure and function of the affected bacteria, changes that can lead to resistance to specific antibiotics. This is called acquired immunity and is limited to the selective isolation of a species or microbiome. For example, we know that methicillin resistance in Staphylococcus aureus is mainly due to mutations in the penicillin-binding protein (PBP), which binds to beta-lactam antibiotics and inactivates them, thus preventing cell wall synthesis. This change is caused by the expression of specific genes in certain strains of these bacteria and it is suggested that this change is due to excessive penicillin use. Expression of this gene produces another PBP (PBP2a) that has no affinity for most β-lactam antibiotics, allowing this strain to grow in the presence of methicillin and other antibiotics. Some antiviral drugs are caused by various mutations in bacterial genomes [17].

2.1.Horizontal gene transfer:

The transfer of resistance genes from one disease to another is called horizontal transfer. The main mechanisms of disease transfer mutation are plasmid transfer,infection, and more. Antibiotics are carried on plasmids, transposons, or introns, which can serve as vectors to transfer genes to other members of the same species and to other genera or species of the organism. Horizontal transfer can occur through three main functions: transfer, transposition, or splicing. Mutations involve the addition of short sections of naked DNA from transgenic organisms. Transfection involves the transfer of DNA from one bacterium to another part of the

bacteriophage.Conjugation involves the transfer of DNA through the permeable pilus, which requires cell contact. DNA fragments containing the resistance gene acquired from the donor can cause the previously affected organism to express the resistance encoded by the newly acquired resistance gene [16].

Integrins are DNA elements that can capture genes from specific recombination sites, especially those encoding antibodies. A study on horizontal transfer - the formation of multiple antibodies in hospital bacteria suggests that the transfer of antibodies in the stomach can occur on Gram-positive or Gram-negative bacilli, usually through the acquisition of genetic consequences [21]. Multidrug resistance (MDR) is multiple drug resistance. Nucleotide sequence analysis of various anti-integrons showed that strains have significant differences in codon usage in bean genes, suggesting that the antiviral agents are different [22]. Many antibodies are carried on plasmids, transposons or integrons that can serve as vectors to transfer these genes to other members of the same species, as well as to organisms of other genera or species. Horizontal exchange can occur through three main processes: transfer, transposition, or incorporation. Mutations involve a short piece of naked DNA from a mutated organism. Transfection involves the transfer of DNA from one bacterium to another part of the bacteriophage. Conjugation involves the transfer of DNA through the permeable pilus and requires cell contact. DNA fragments containing resistins from donors can cause previously affected organisms to express the resistance encoded by these newly acquired genes [23].

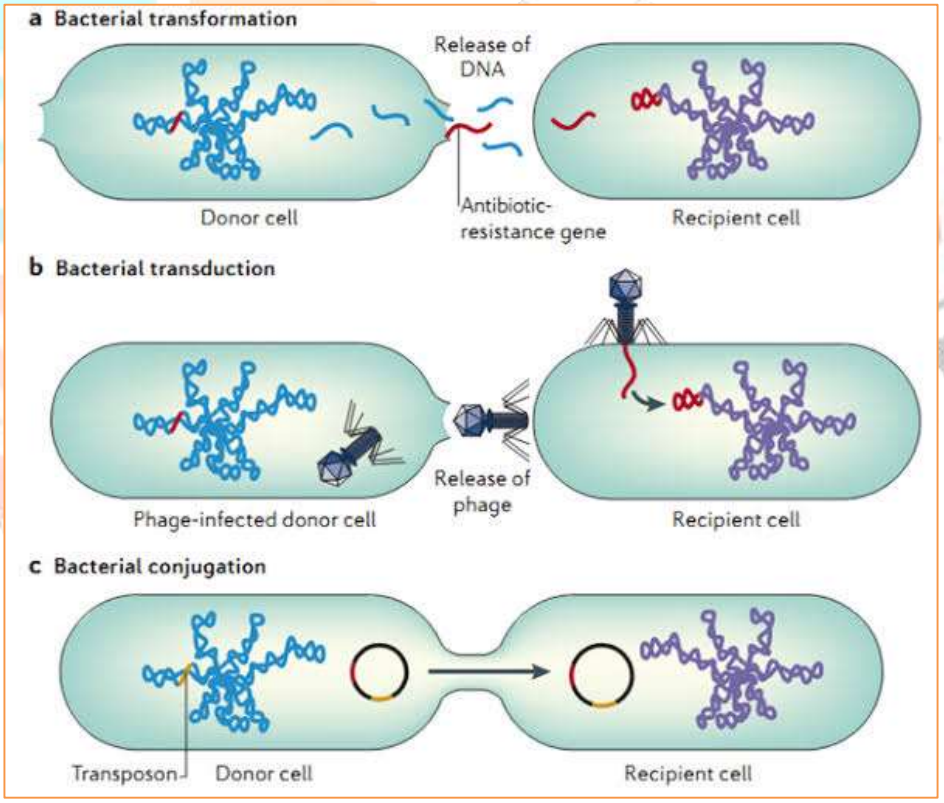

Fig.1. Horizontal gene transfer.

2.2.Reducing permeability or uptake by reducing cell membrane permeability:

The acquisition of antibodies requires significant structural changes in the membrane [16]. Gram-negative bacteria are naturally less permeable to many antibiotics than Gram-positive bacteria because their outer membrane forms a permeability barrier [16]. Lipopolysaccharide is a lipopolysaccharide (LPS) of the cell wall that contains a core containing lipid A, polysaccharides, and the O antigen. In Gram-negative bacteria such as Pseudomonas aeruginosa and Salmonella enterica species, which are particularly serious infections in immunocompromised patients, bacteria with the LPS portion are resistant to erythromycin, roxithromycin, clarithromycin, and azithromycin [25]. Other mechanisms that reduce permeability involve porin channels in

the membrane, allowing small molecular weight molecules (such as antimicrobial agents) to enter the cell. Antibiotics will alter the expression of the membrane sheet, preventing them from integrating into the membrane or malfunctioning, thus preventing the penetration of large growth inhibitory molecules [25]. Clinically important pathogens such as Serratia marcescens, Salmonella enterica, Klebsiella pneumoniae, and Pseudomonas spp. Pseudomonas aeruginosa use this drug to reduce resistance to important antibiotics such as beta-lactams, fluoroquinolones, aminoglycosides, and chloramphenicol[16].

3.Environmental resistance:

is the difference between the in vitro and in vivo effects of antibiotics. Agents that are active in the laboratory may not be effective in vivo because they cannot reach the site of infection, such as the failure of first-generation cephalosporins to cross the blood-brain barrier[26].

4.Genetics of antibiotic resistance mechanism:

4.1.Improve the exterior:

One of the most common resistance mechanisms is the active efflux of drugs from cells. These resistant bacteria have energy-driven drug efflux pumps that efflux the antibiotic, thus reducing its intracellular concentration to non-inhibitory or inhibitory levels. There are two main types of efflux pumps. The first type, called primary active transport, uses the hydrolysis of ATP to actively remove the drug from the cell; the second type, called secondary active transport, uses ionic gradients of active drugs to efflux from the cell. ATP-driven transporters are also called ABC (ATP-binding cassette) or P-glycoprotein transporters. The two transporters are commonly used by bacteria to counteract the effects of antibiotics and are often referred to as efflux pumps [27].

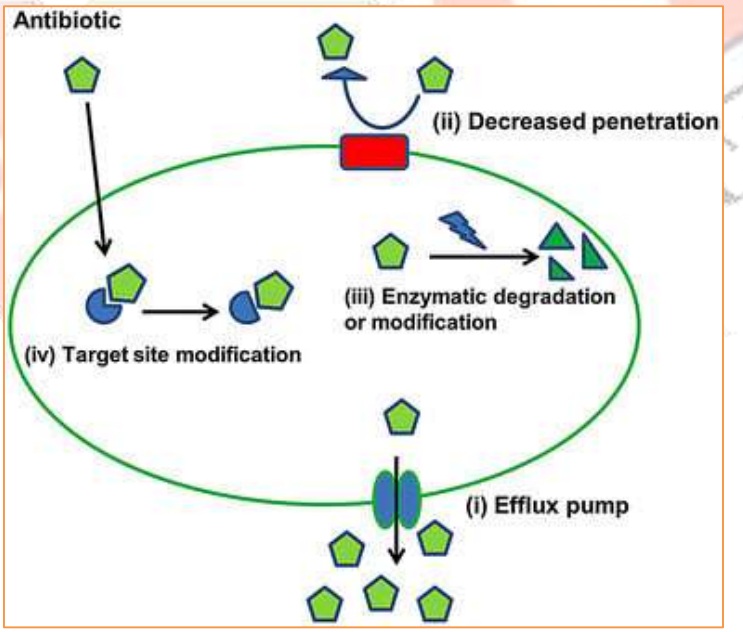

Fig.2.Mechanism of enhanced efflux drug resistance.

4.2.Enzyme inactivation:

Drug inactivation or modification: For example, penicillin G is inactivated by beta-lactamase production in some penicillin-resistant bacteria. The emergence of carbapenem-resistant Gram-negative pathogens poses a threat to public health worldwide. Klebsiella pneumoniae carbapenemase (KPC) and oxacillinase 48 (OXA-48) type carbapenemases have been reported worldwide. New Delhi Metallo-beta-lactamase (NDM)

Carbapenemase was first discovered in Sweden in 2008 and has spread worldwide [30]. Protective enzymes, generally produced by bacterial cells, add acetyl or phosphate groups to specific sites of the antibiotic, which reduces the ability of the antibiotic to bind to bacterial ribosomes and disrupts protein synthesis[30].

4.3.Modification or overexpression of the drug target:

Modification of the target or binding site: for example, modification of the penicillin-binding protein (PBP) The binding type target of penicillin in methicillin-resistant Staphylococcus aureus (MRSA) and other penicillin-resistant bacteria. Another defense system found in bacteria is the ribosome defense proteins. These proteins protect bacteria from antibiotics that target the cell's ribosomes and inhibit protein synthesis. This process involves the binding of ribosome protection proteins to the bacterial cell ribosomes, thereby altering their structure. Direct modification of the antibiotic's target at the DNA level is the process of target modification. This prevents antibiotics from entering the cell while allowing the ribosome to continue to produce important proteins of the cell. ribosome inhibits protein synthesis [30].

5.Phenotypic Resistance:

Phenotypic resistance is when bacteria stop multiplying and become less resistant to antibiotics. When the bacteria are then subcultured into new media and start growing again, they acquire antibiotic sensitivity. This complex process causes serious problems in biofilm and especially in the treatment of tuberculosis[31].

5.1.Biofilm Formation:

Pathogenic microbial biofilms are considered a global problem due to the presence of antibiotics in the body throughout their lifestyle [32]. In communities under medical conditions, bacterial infections are responsible for serious and dangerous diseases. Combating this cellular organization often requires long-term use of antibiotics, which often fails, resulting in continued disease [32]. In addition to limiting treatment, biofilms can also become a source of contamination when grown on medical devices. The problems caused by biofilms have motivated scientists worldwide to propose or develop other methods to control biofilms. The authors of this review suggest new areas that could be used to prevent or eliminate biofilms in clinical settings [32]. Membrane research has been conducted but remains a mystery. Previous pharmacokinetic (PK) and pharmacodynamic (PD) data on anti-inflammatory drugs provide valuable information that will help design optimal dosages and minimize the formation of antibiotics, at least in the presence of sex resistance and anti-biofilm formation [33].Most of the antibiotic PK/PD studies in the past have been conducted on planktonic cells. Extrapolation of results to biofilms is problematic because differences in bacterial biofilms from planktonic growth are related to cell differences in growth, gene expression and metabolism. . in vivo. It should be noted that not all controls in biofilms have been approved for clinical use or have been shown to be effective in antibiotic applications [33]. Mycobacterium tuberculosis is a global problem. At the core of the problem is that no treatment has been developed P. Pseudomonas aeruginosa biofilms are treated using standard antibiotics, including fluoroquinolones [34]. The authors address previously unexamined questions about the effects of the calcium channel blocker (CCB) diltiazem on biofilm growth. The overall growth and killing of Pseudomonas aeruginosa biofilms during fluoroquinolone treatment was monitored with and without diltiazem at the point of care. The authors found that the calcium channel blocker diltiazem, widely used for Pseudomonas aeruginosa biofilms, can lead to resistance to first-line fluoroquinolones [34]. Chemical simulation model- Macroscopic dynamics of antibiotic resistance of planktonic Pseudomonas aeruginosa. In this study, the authors proposed a new pharmacodynamic model of ofloxacin for the treatment of Pseudomonas aeruginosa biofilm activity [34]. and samples were taken from the central bioreactor (CCB) to evaluate its ability to remove biofilms and planktonic cells over 24 h. A bioassay method was used to measure the concentration of ofloxacin in each sample from the CCB [35]. The response to different doses of loxacin is not equal, which may explain the

discrepancy between the microbiological and clinical aspects of biofilm-associated diseases [35]. An unprecedented new dynamic model was developed to evaluate the microbiological outcomes of Pseudomonas aeruginosa biofilms and exfoliated planktonic cells in response to different dosage regimens of ofloxacin. As a result, Pseudomonas aeruginosa-associated diseases such as cystic fibrosis can be simulated. The use of different antibiotics for biofilm infections can be simulated using such a model [35].

5.2.Salicylate-Induced Antibiotic Resistance:

Another form of phenotypic resistance is mediated by salicylic acid, a substance found in aspirin. Different strains have been found to have salicylate-mediated resistance. E. coli is the best example, but others include Klebsiella, Pseudomonas, Burkholderia, and Mycobacterium tuberculosis. Mycobacterium tuberculosis (TB) has been shown to be less resistant to isoniazid (INH), rifampicin, ethambutol (EMB) and p-aminosalicylic acid (PAS) in the presence of salicylates. Preliminary experiments in mouse models of the disease have shown that aspirin can counteract the action of INH, suggesting that it may also play a role in the body.Salicylic acid binds to MarR to derepress the MarAB operon. MarA encodes a transcription factor that activates transcription of the efflux pump acraAB as well as the membrane channel for the LC, which is essential for the pump's function. The first line of defense is therefore to increase efflux. In the second mechanism, MarA increases the transfer of an antisense RNA, micF, to ompF, a porin required for the entry of antibiotics. Thus, micF controls the expression of ompF in the antisense. When porin expression is reduced, drug uptake is also reduced [36].

5.3.Bacterial Persistence:

Persistence can be defined as the presence of phenotypic changes in survivors of lethal antibiotic treatment. Persistence is a variable that is tolerated for a period of time and allows the population to avoid antibiotic treatment. Immune responses are not genetic or inherited and are the result of a phenotypic transition from a normal, susceptible cell type to a tolerant, stable state. Persistents are now identified in nearly all bacterial species tested, usually at levels of magnitude between 0.001% and 1%. There is a wealth of information available about the risk of Gram-positive and Gram-negative bacteria. Persistence to antibiotic resistance has also been described in eukaryotes such as yeast. Although human cancer cells have the capacity to produce disease-like cells that can survive chemotherapy, it has been shown to contribute to treatment failure and to encourage hedging in drug development [37].

5.3.1.Toxin-Antitoxin (TA) Model :

Toxin-antitoxin (TA) systems are ubiquitous in organisms and play an important role in the transmission and evolution of antibodies, such as detecting various resistance plasmids and triggering the formation of persisters.In general, the activity of the venom is neutralized by the binding antitoxin. In contrast, antibodies are prone to degradation under certain conditions, such as stress, and free toxins can interfere with important cellular processes, including replication, translation, and cell wall synthesis. TA has also been shown to be responsible for plasmid maintenance, stress control, bacterial persistence, and biofilm formation [38].

5.3.2.PhoU:

Recently, a novel persistent gene PhoU was found in E. coli by transposon-based analysis. PhoU mutants are sensitive to many different antibiotics, including ampicillin, streptomycin, sulfonamides, and quinolones. They are also more sensitive to conditions such as heat, starvation, acidic pH, and weak acids. The PhoU mutant

phenotype can be obtained with the wild-type PhoU gene. An interesting feature of the PhoU mutant is that it is susceptible to ampicillin during the stationary phase. Many other antibiotics, especially penicillins, are only effective against growing bacteria, not against persistent bacteria. We also found from microarray experiments that PhoU mutants increase metabolism. Therefore, PhoU appears to be an inhibitory mechanism of cellular metabolism. It shuts down cellular metabolism when administered. Although the detailed mechanism is not clear, they believe that PhoU may be a chemical target to kill persistent bacteria. Therefore, we are now trying to attract the interest of some pharmaceutical companies in developing drugs targeting PhoU [38].

Conclusion:

In clinical practice, underuse and overuse of antibiotics make bacteria resistant to antibiotics. Organisms use different mechanisms to protect themselves. Acquired resistance occurs through mutations, alteration of genes by fusion or mutation, transposons and phages. Bacteria use the following resistance mechanisms: antibiotic inactivation, target mutations, permeability transitions and different phenotypic mechanisms for antibiotic resistance. It is necessary to determine the resistance of bacteria to each antibiotic class (phenotype) as well as the mutations that make bacteria resistant to drug diseases (genetic analysis). A better understanding of the immune system, the location of genes on chromosomes, and their expression will allow us to develop the screening and management strategies needed to reduce the spread of resistant bacteria and their evolution.

Recommendations:

Drug resistance testing should be mandatory in the early stages of drug development; regional treatment strategies should be designed to target drugs rather than all drug-induced virivities; and public health education on their use is required.

Acknowledgement:

The author would like to thank Prof. Babasaheb Chopade sir, Prof. Ashwini Wakade mam, Dr. Megha Salve mam, Dr. Abhijeet Shete sir,Mr. Sagar Aute and all persons directly or indirectly involved in the preparation of this article.

REFERENCES:

1. Walker, D. & Fowler, T. Annual Report of the Chief Medical Officer: Volume Two, 2011: Infections and the Rise of Antimicrobial Resistance (Department of Health, 2011).

2. World Economic Forum. Global Risks 2013 — Eighth Edition http://www.weforum.org/reports/global-risks- 2013-eighth-edition (2013).

3. World Economic Forum. Global Risks 2014 Report http://www.weforum.org/reports/global-risks-2014-report (2014).

4. Abraham, E.P. and E.B. Chain, 1940. An enzyme from 17: 171-176. bacteria able to destroy penicillin. Nature, 46: 837. 19. Roberts, M.C., 2005. Update on acquired

5. Levy, S.B., 1998. The challenge of antibiotic Tetracycline resistance genes, FEMS Microbiol. resistance. Scient. Americ, 278: 46-53. Lett., 245: 195-203.

6. Summers, A.O., 2002. Generally overlooked 20. Ploy, M.C., T. Lambert, J.P. Couty and F. Denis, 2000. fundamentals of bacterial genetics and ecology. Clin. Integrons: An antibiotic resistance gene capture Infect. Dis, 34: 85-92. and expression system, Clin. Chem. Lab. Med.,

7. Beovic, B., 2006. The issue of antimicrobial resistance 38: 483-487. in human medicine. Intern. J. Food Microbio., 21. Dzidic, S. and V. Bedekovic, 2003. Horizontal gene 112: 280-287. transfer-emerging multidrug resistance in hospital

8. Aminov, R.I., 2011. Horizontal gene exchange in bacteria. Acta. Pharmacol., 24: 519-226. environmental micro biota. Frontiers in Microbio, 22. Nirdnoy, W., C.J. Mason and P. Guerry, 2005. Mosaic 2: 158. structure of a multiple-drug-resistant, conjugative

9. Neu, H.C., 1992. The crisis in antibiotic resistance. plasmid from Campylobacter jejuni. Antimicrob. Science (New York, NY), 257: 1064-1073.

[10] World Health Organization (2016). Race against time to develop new antibiotics.

[11] Liu, Y.Y, Wang, Y., and Walsh, TR. (2016). Emergence of plasmid mediated colistin resistance mechanism MCR-1inanimalsandhumanbeings in China. Lancet Infect Dis.16: 161–68.

[12] O'Neill Review in to AntibioticResistance, March.2017.

13. Kahne, D., C. Leimkuhler, W. Lu and C. Walsh, 2005. 27. Floyd, J.L., K.P. Smith, S.H. Kumar, J.T. Floyd and Chemical Reviews, 105: 425-448. M.F. Varela, 2010. Multidrug efflux pumps of the

14. Walsh, C., 2000. Molecular Mechanisms That Confer major facilitator superfamily from Staphylococcus Antibacterial Drug Resistance Nature, 406: 775-781. aureus. Antimicrob.Chemothe, 54: 5406-5412.

15. Wright, G.D., Q. Wright and A. Wright 2010. 28. Giamarellou, H. and G. Poulakou, 2009. Multidrug-Antibiotic Resistance: where does it come from and resistant Gram-negative infections: What are the what can we do about it? BMC Biol., 8: 123.

[16] EngidawAbebe, BetelihemTegegne and Solomon Tibebu (2016). A Review on Molecular Mechanisms of Bacterial

Resistance to Antibiotic. European Journal of Applied Sciences 8 (5): 301-310.

17. Giguère, S., 2006. Antimicrobial Drug Action and Interaction: An Introduction. Antimicrobial therapy in Veterinary Medicine 4th edn. Ames Iowa, USA

18. Fernandez, L. and R.E. Hancock, 2012. Adaptive and mutational resistance: role of porins and efflux pumps in drug resistance. Clin. Microbiol. Rev., 25: 661-681.

19. Roberts, M.C., 2005. Update on acquired Tetracycline resistance genes, FEMS Microbiol. Lett., 245: 195-203.

20. https://images.app.goo.gl/JQAT3dZtSqQVQUvZ9

21. Dzidic, S. and V. Bedekovic, 2003. Horizontal gene transfer-emerging multidrug resistance in hospital bacteria. Acta. Pharmacol., 24: 519-226.

22. Nirdnoy, W., C.J. Mason and P. Guerry, 2005. Mosaic structure of a multiple-drug-resistant, conjugative plasmid from Campylobacter jejuni. Antimicrob. Chemother, 49: 2454-2464.

23. Nordmann, P. and L. Poirel, 2005. Emergence of Plasmid-Mediated Resistance to Quinolones in Enterobacteriaceae. J. Antimicrob. Chemother, 56: 463-469.

24] Rodríguez-Rojas, A.; Rodríguez-Beltrán, J.; Couce, A.; Blázquez, J.(2013). Antibiotics and antibiotic resistance:A

bitter fight against evolution. Int. J. Med. Microbiol303: 293– 297.

[25] Monack, D.M. (2012). Salmonella persistence and transmission strategies. Curr. Opin. Microbio. 15: 100-107.

[26] Olowe O Adekunle (2012). Mechanisms of Antimicrobial Resistance In Bacteria, General Approach. International journal pharma medicine and biological science 1(2): 2278–5221.

[27] Sanath Kumar and Manuel F.Varela (2013). Molecular Mechanisms of Bacterial Resistance to Anti-Microbial Agents. Science, technology and education.

28. Blair JM, Webber MA, Baylay AJ, Ogbolu DO, Piddock LJ (2015) Molecular mechanisms of antibiotic resistance. Nat Rev Microbiol 13(1):42–51

29. Lambert P (2002) Mechanisms of antibiotic resistance in Pseudomonas aeruginosa. J R Soc Med 95(Suppl 41):22–26

[30] Lee, C.R., Lee, J.H., Park,K.S., Kim,Y.B., Jeong,B.C., Lee,S.H. (2016). Global dissemination of carbapenemase producing Klebssiella pneumonia. Microbial 7:895.

[31] Tarek M. Mahfouz and Michael J. Young (2017). New Bacterial Targets and Computational Methods against Bacterial Resistance. Medical Research Archives 5: 4.

[32] Ribeiro SM, Felício MR, Boas EV, Gonc¸alves S, Costa FF, Samy RP, et al. New frontiers for anti-biofilm drug development. Pharmacol Ther 2016;160(April):133—44.

[33] Hengzhuang W, Høiby N, Ciofu O. Pharmacokinetics and pharmacodynamics of antibiotics in biofilm infections of Pseudomonas aeruginosa in vitro and in vivo. Methods Mol Biol 2014;1147:239—54.

[34] Elkhatib WF, Haynes VL, Noreddin AM. Unexpected induction of resistant Pseudomonas aeruginosa biofilm to fluoroquinolones by diltiazem: a new perspective of microbiological drug-drug interaction. J Infect Public Health 2008;1(2):105—12.

[35] Noreddin AM, Elkhatib WF. Novel in vitro pharmacodynamic model simulating ofloxacin pharmacokinetics in the treatment of Pseudomonas aeruginosa biofilm-associated infections. J Infect Public Health 2009;2(3):120—8.

[36] Ying Zhang (2007). Mechanisms of Antibiotic Resistance in the Microbial World. Clin. Pharmacol. 82:595-600.

[37] Bram Van den Bergh, Maarten Fauvart and Jan Michiels (2017). Formation, physiology, ecology, evolution and clinical importance of bacterial persisters. FEMS Microbiology Reviews 41: 219–251.

[38] Qiu E. yang, Timothy R. Walsh (2017). Toxin–antitoxin systems and their role in disseminating and maintaining antimicrobial resistance. FEMS Microbiology Reviews41: 343–353.