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Antibiotic Resistances and Drug Delivery System Used To Combat Antibiotic Resistance

Shrestha Sharma[1], Vinod Kumar[2], Naved Khan[3*]

Abstract

The aim of this review is to explore and discuss the situational analysis of antibiotic resistance along with the various challenges with different strategies required to reduce this burden in developing countries. Researchers found that, this is an alarming condition, because diseases caused by bacteria/microbes become harder to treat. However, we the main reason of resistance are non-judicial use of antibiotics, withdrawal therapy, imbalance of antibiotic consumption etc. literature searched from various search engines like Google search, Medline and other authenticated sources were reviewed and analysed and suggested that we need to educate the patients and public regarding the antibiotic resistance.

Key words: *Bacteria, Antibiotics, Penicillin, Drug resistance*

I. Introduction

Sir Alexander Fleming discovered the penicillin in 1928 first time and treated a policeman of England suffered from *staphylococcus aureus* infection (Nabin *et al*, 2010 and Calvin *et al*., 1993).Antibiotics are the natural or synthetic preparation able to affect the survival of microorganism by inhibiting their growth or either kills them at very less concentration**(**Alain*et al*;2017**).** Antibiotics are most commonly used drugs and misuse of these drugs could harm the health, the issue of antibiotic resistance comes in the 1980s it is believed that in Europe and the US up to 50,000 people die each year due to antibiotic resistance(Carmen *et al*;2019).Antibiotics are also called as growth promoters as they have an impact on the growth rate because of thinning of the mucous membrane of the gut facilitating higher assimilation and generating beneficial conditions to the microbes in the gut of animal by inhibiting the harmful bacteria.However they areused as inappropriately and irrationally provide favourable conditions for the development of resistant microbes that can spread very easily**(**Dhama *et al*; 2013). Like most of the drugs, Antibiotics lose their efficacy over the time due to the development of resistant bacteria with the bacterial pathogens hence no classes of Antibiotic had escaped these unforgiving phenomena. The growth of resistance feature to different classes of antibiotics results in strains with multidrug resistance phenotype (MDR) has gradually reduced the available treatment options for some pathogens.

[1] *Assistant Professor, SMAS, K R Mangalam University, Gurugram, Sohna, 122103, India*
[2] *Assistant Professor, SMAS, K R Mangalam University, Gurugram, Sohna, 122103, India*
[3] *SMAS, K R Mangalam University, Gurugram, Sohna, 122103, India*

Resistance can be linked with decreased virulence; Most of the MDR strains retain an astonishing capability at cross infection and spreading in the clinical setting **(**Gian *et al*; 2014)**.**It is one of the greatest current challenges towards the effective treatment of infections Also there is every indication that antibiotic resistance will become an even greater challenge in the future**.** (James *et al*;2002).Antibiotic resistance happens when the bacteria or other microbes can oppose the impact of an antibiotic. These bacteria or microbes modifies and weakens the overall capability of drugs(Crouch *et al;* 2015**).** Resistance can also be developing because of mutation or direct transfer of genes encoding a resistance mechanism. Transfer of resistance genes can occur by a different mechanism such as conjugation (direct cell to cell contact with plasmid), transformation (uptake of DNA from the environment) or transduction (transfer of bacterial DNA from a bacteriophage - a bacterial virus which is replicated in a bacterial cell) table 1. The chances of resistance have become higher when the concentration required to kill or inhibit the microorganism exceeds(Sabtu *et al*;2015).Antibiotic resistance can spread from when the bacteria share or exchange the genetic material with other bacteria or where antibiotic resistance genes are passed from one gene to another with lack of ability(Christopher, 2017).The centre for disease control and Prevention had estimated that most of the prescriptions for antibiotics are written for outpatient every year areunnecessary. There are four types of resistance to antibiotics; Natural resistance, Acquired resistance, Cross-resistance and Multi-Drug Resistance.

- Natural resistance: Natural resistance is caused by the structural characteristics of bacteria and is not associated with the use of antibiotics.
- Acquired Resistance: It occurs due to changes in the genes of bacteria and is mainly due to the chromosomal and extra-chromosomal structures
- Cross Resistance: This type of resistance can be seen in antibiotics whose structures are the same.
- Multi-Drug Resistance: Multidrug resistance is the bacteria that become resistant to the antibiotics which have been used to treat them.It can be occurred by the two processes first the bacteria may accumulate multiple genes and each gene are coding for a single drug for resistance .second type of resistance can occur by enzymatic inactivation and change in the structure of the target. If the bacterial strains are resistant to 3 or more classes of antimicrobials then it is known as multidrug resistance**.**

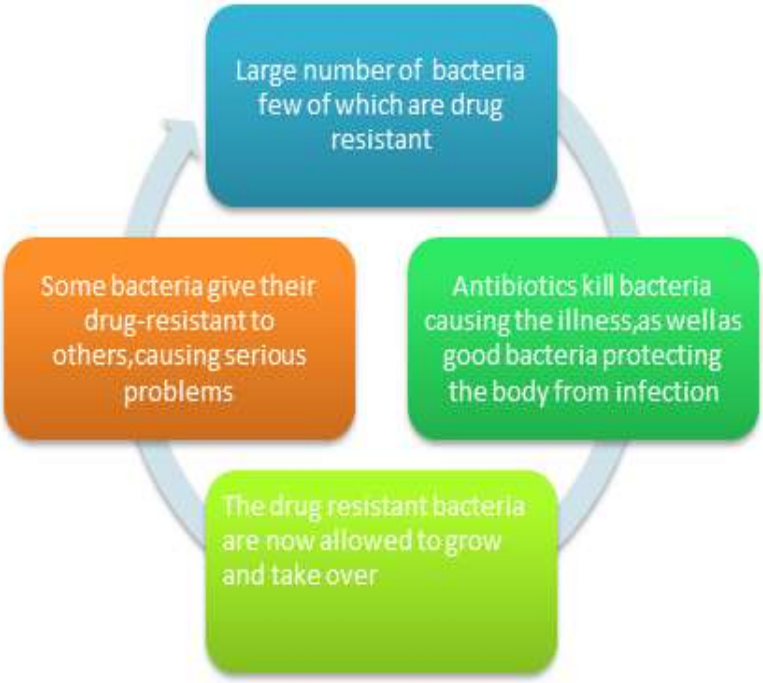

Figure 1: Cycle of Antibiotic resistance

History of Antibiotics

In the 20th century, Selman Waksman defined the term antibiotics as a chemical compound derived from a microorganism that inhibits the growth of microbes(Julian, 2010). Most antibiotics which have been used today are derived from Actinobacteria class from the genus *Streptomyces* (Bakra*et al*; 2015). In 1928 Alexander Flemming discovered the first natural antibiotic commonly known as Penicillin which inhibits cell wall synthesis of bacteria and found to be very useful against the gram-positive bacteria (Kumar *et al*., 2010).After the discovery of Penicillin other scientists including Rene Dubos and Selman Waksman start working on antibacterial agents among soil microorganism including bacteria and fungi, later on they realized that antibacterial activity was present in actinomycete culture other than bacteria or fungi. During this period many antibiotics were discovered by these scientists but few of them proven to be effective in clinical use. In 1943 Streptomycin was discovered produced by *streptomyces griseus*. Streptomycin inhibits the protein synthesis by binding to the 30s subunit of the ribosome and was found to be effective against the gram-negative and the tubercle bacillus.The period of 1940 – 1960 is known as the "The Golden Era of Antibiotics" during this period most of the antibiotics which we use today were discovered in that Period. Today there are fewer antibiotics under development and at the same time, antibiotic-resistant bacteria that survive antibiotic treatment are becoming more and more ineffective(Elizabeth, 2018).

The Rise of Antibiotic Resistance

Since after the discovery of Antibiotics these drugs have become an essential and crucial part of health care system however the Antibiotic resistance possess a worldwide health threat that involves all major microbial pathogens the Antibiotic Crises occur due to the lack of new antibiotics and misuse of these medicines have contributed to the antibiotic resistance(Lee*et al*; 2014).Microorganism develops antibiotics resistance due

to genetic changes and by the non genetic mechanism. Non-Genetic resistance caused when the bacteria strain changes into the L forms which lack the cell wall due to lack of cell wallthese bacteria become resistant to the antibiotics due to the natural selection of the genes(Perovic, 2018).The WHO has listed various pathogens that have established resistance to many bacteria that leads to common infections out of these are the "ESKAPE" pathogens which include (*Enterococcus faecium,Staphylococus aureus,Klebsiella pneumonia, Acinetobacter baumanni and Pseudomonas aeruginousa)*as they are responsible for most of the infections caused in humans like lung and urinary tract infections (Kumari *et al*; 2018). After the discovery of sulphonamides in 1935 the rise of distinct mechanism of resistance had to increase their therapeutic use.Sulphonamide resistance was first reported in the 1950s which tells us the same mechanism of resistance that still promote now figure 2 and 3. The Methicillin-resistant *staphylococcus aureus* (MSRA) poses a serious threat.Strains of *Klebsiella* pneumonia carbapenem-resistant produce the enzyme which is responsible for damaging the antibiotics: The gene which codes for this enzyme is inserted into a plasmid, a DNA fragment which can easily move from one to other bacteria, which allows the rapid spread of this resistance mechanism to different species. Currently, there are two drugs which are available for the treatment for infections caused by CRE carbapenem-resistant *Enterobacteriaceae*(Giancarlo,2016).Inmore economically Developed countries Antibiotics were given to animals in their food, water or sometimes by injection which may be responsible for carrying microbes' resistance to those antibiotic, coordinated efforts are required to manage such crisis.

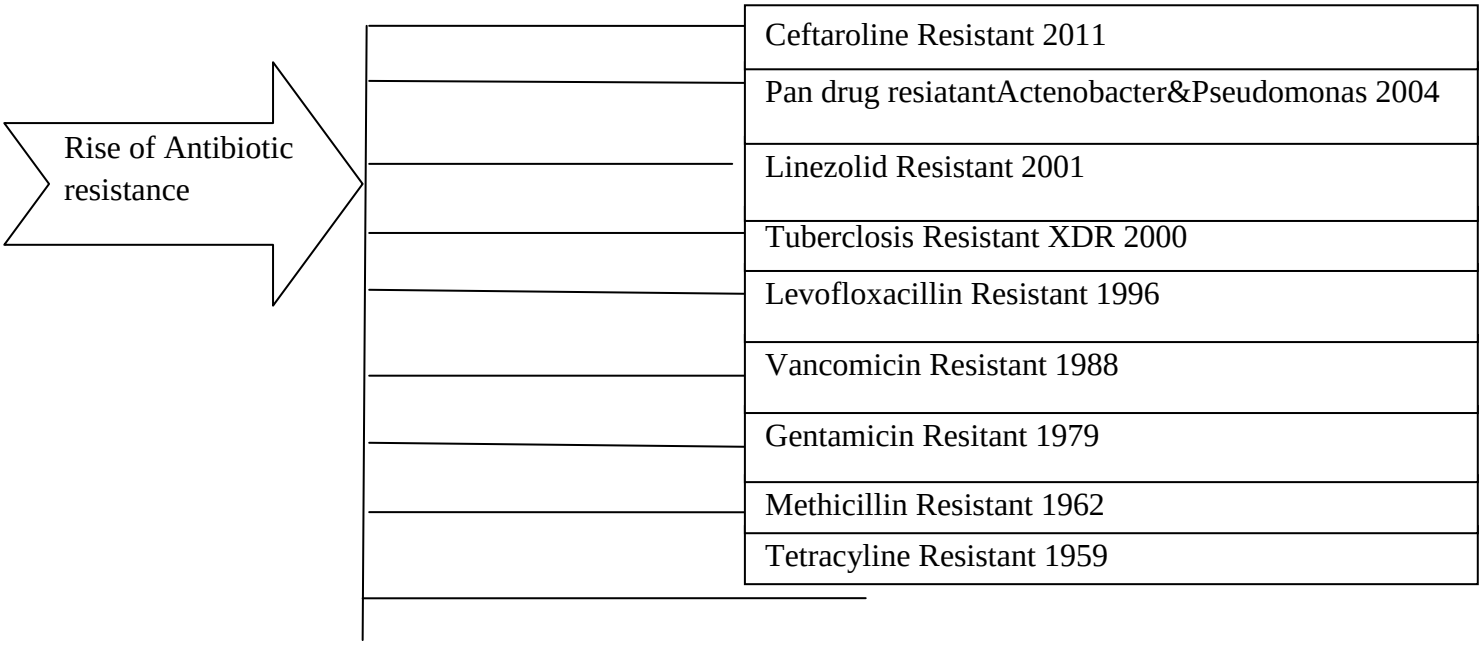

Figure 2: Antibiotics past to present

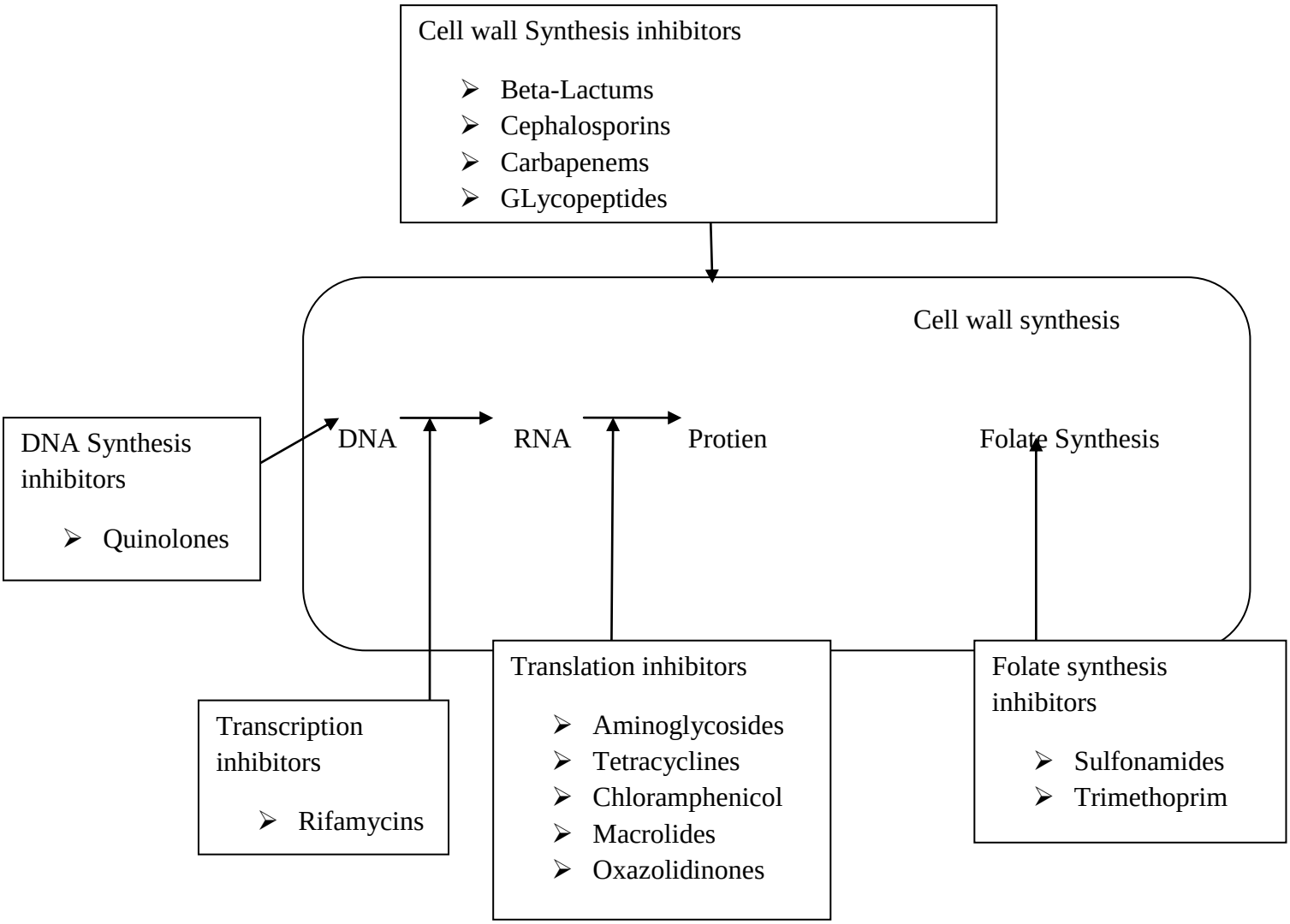

Figure 3: Classes of Antibiotics with their mode of action

Mechanism of Antibiotic Resistance

Antibiotics can kill or inhibit the growth of microorganism in different ways there are many mechanisms of resistance involved that microorganism developed over time during exposure to antibiotics. One organism can become resistant to various classes of antibiotics by one mechanism if their mode of actions is the same. Frequently Bacteria can share the resistance between the individual bacteria through the production of resistance plasmids. Understanding these mechanisms of antibiotics resistance is important to learn why Antibiotic Resistance is a major health concern (Jiregna, 2017).

- Modification of target site

Receptor modifications occur when the intracellular target or receptor of the antibiotics is altered by the bacteria which results in the lack of binding.Modifications in Penicillin-binding proteins leads to a ribosomal alteration which can effectaminoglycoside, macrolides and DNA gyrase,causedfluoroquinolones resistance to (Pandra*et al*; 2010).

- Efflux Pumps

Efflux pumps are those which export the antibiotics out from the cell and maintain their low concentrationwhen the anti-microbes are entering into the cell the efflux mechanism are forcing them out again so that they cannot reach the target site.Antibiotics of all class are subject to the efflux system (Kapoor*et al*; 2017).

- Modification of Antibiotics

When the antibiotics enter into the cell of bacteria, which is resistant will either degrade or modify enzymatically so that it cannot bind to its targetenzyme that degrade the antibiotics.Derivatives of Beta lactamases are encoded in bacteria each of which can degrade the number of beta-lactam antibiotics.There are few known enzymes which transfer chemical groups like phosphate,acyl,nucleotidyl etc.(Petchiappan, 2017).

- Antibiotic Inactivation

Sometime the cell might achieve resistant to the antibiotics by producing an enzyme which makes the drugs inactive or which alters the antibiotic functionslike beta-lactam antibiotics which can inhibit the beta-lactam ring of penicillin It will be more uncertain that penicillin or other similar drugs will be capable of disrupt the cell wall,so long as the organism produces the beta-lactamases.This mode of resistance may be shared from one microorganism to another by the administration of R-plasmids and is generally recognizable in Methicillin-Resistant *Staphylococcus aureus* strains(Sageman, 2015).

Nanotechnology used to combat Antibiotic Resistance

Nanotechnology is the leading and the most promising technologies that help in controlling the Resistance to many bacteria. Nanoparticles are defined as solid particles ranging from 1-1000nm in size their small size and small range gives them an advantage like high surface area and enhanced reactivity. Nanoparticles consisting of metals and the metal oxide may be promising to antimicrobial agents to which pathogens are not developing any resistance because they inhibit the cell wall directly apart from that nanosized transporters are additionally accessible which can precisely control the antibiotics by improving the pharmacokinetics parameter of the drug(Ranghar, 2014 and Kumar *et al*; 2019). Nanomaterial's encapsulated with antibiotics can help in the increased concentration of antibiotics at the site of action and enhance the binding of antibiotics to the bacteria can combat the antibiotic resistance. Whereas the current antibiotics may have various disadvantageslike Low therapeutic index, Development of Resistance with time, cytotoxicity and side effects but these disadvantages may overcome a few amounts with the help of Nano Technology and the Nano-Materials. Below are some Nano-Materials are discussed that are used to combat Antibiotic Resistance (Sharma *etal*; 2012).

Nano-Materials to Combat Antibiotic Resistance

1. Chitosan: Chitosan is a natural carbohydrate polymer develops from the reaction of N – Deacetylation of chitin; Chitin is a biopolymer derived from the crustacean shells.chitosan offers various advantages as drug carriers in nanotechnology because of its good biocompatibility;Biodegradability, inexpensive and it can be readily modified. Chitosan is soluble in ph less than 6.5 and it is insoluble in phosphoric and sulphuric acid due to its higher surface area chitosan can enter the cell wallnucleus of bacteria and inhibits the mRNA and protein synthesis by getting attached to the microbial DNA.This Properties Offers

Chitosan as the best material for a drug delivery carrier. For many years from now, chitosan shows a promising approach in pharmaceutical applications(Chakraborty, 2012).

2. Liposomes: Liposomes are small lipids colloidal materials which consist of a central aqueous space surrounded by a lipid bilayer ranging from 20-100 nm in size. Thediameter of liposome varies between 0.02 – 10 mico meters in size. Liposomes are of two type's unilateral micelles (range 20nm) and bilayered vesicles (range 100nm). Due to phospholipid in nature liposomes are more biocompatible than any other nanoparticles(Culek, 2019). ThePharmacokinetics and the antibacterial effects of antibiotics can be improved by encapsulating a liposome in the antibiotics.Lipid vesicles are used as a drug carrier for encapsulating because most of the antibiotics have show toxicity and weak bio-distribution due to low permeability hence lipid vesicle isused to improve the Pharmacokinetic and Pharmacodynamic Properties**.**(Priyanka, 2017).

Drug encapsulation in liposomal encapsulations enhances the pharmacokinetics parameters and hence protects the antibiotics against the hydrolytic activity of the enzymes.The main advantage of the liposomal carrier is the sustained release of the antibiotics during drug circulations in the body and hence it allows retains the appropriate concentration for a long time.The liposomes which are administered intravenously are known as foreign antigens by the immunological system and are opsonised (a condition in which microorganism and inanimate colloids like liposomes or particulates are coated with proteins and lipids) thus stimulates the nonspecific defence mechanism and the liposomes are absorbed by the mononuclear phagocyte system thus helps in fast drug clearance due to lower blood circulation time which is caused by the mononuclear phagocyte table 1(Kawa, 2010). Utilizing liposome as a drug delivery system has shown an excellent result in eradicating the intracellular pathogens.The disease which is caused by in the intracellular bacteria, rigid conventional liposomes vesicles and PEG-coated has been preferred to enhance drug retention in proper tissues provide sustain release, decreased toxicity and improves the concentration at the site of infection. However, lipid-based drug delivery system has certain limitation and has low encapsulation efficiency, a short half-life,the hydraulic instability of lipid ester bonds, a fusion of lipids and temperature sensitivity hence these limitations can cause inadequate delivery drug leakage in circulations.These limitations can overcome with a variety of modifications like the incorporation of hydrophilic long-chain polymers in the lipid bilayer, cholesterol or anionic charged groups etc. to form stealth liposomes**.**Many studies are going to improve microbial killing, facilitated by nano-sized vehicles/liposomes are under development(Benjamin, 2014).

Table 1: Liposomes as Drug Delivery System

Formulation	Drug	Targeted Microorganism	Activity	Reference
Soyphosphatidycholine(PC),Cholesterol,Alpha-tocopherol	Cefepime,Ceftazidime	*Pseudomonas aeruginosa*	Incresed antibacterial activity against P.aeruginosa	Maria et al; 2012

Cholesterol and 1,2-Dimyristoyl-sn-glycero-3 phospphocholine	Gentamicin	*Pseudomonas aeruginosa*	Incresed Prolonged antimicrobial activity and killing time	Rukholm et al; 2005
Dipalmitoylphosphatidylcholine(DPPC),Cholesterol and Dimethylammonium ethane carbamoyl cholesterol (DC-chol)	Benzyl Penicillin	*Staphylococcus aureus*	Lower Drug Concentration	Kim,2004

3. Dendrimers: Dendrimers were first introduced in 1978 by Fritz Vogtle with his co-workers. Dendrimers are defined as the highly branched macromolecular that shows a controlled pattern of branching arises from the central core.The well-defined structures, lowpolydispersity index and a well-defined number of peripheral groups are the ideal properties of dendrimers which makes them as the best candidate for drug carriers(Elizabeth, 2005). Dendrimers possess various distinctive properties that make them an ideal drug carrier for combating antibiotic resistance.They are highly arranged and branched globular macromolecules provide them with a broad surface area which allows a better reactivity with the microorganism.Both the hydrophobic as well as hydrophilic drugs are loaded into the Dendrimers table 2.Hydrophobic drugs are loaded inside the cavity of the hydrophobic core and the hydrophilic drugs are attached to the surface of Dendrimers through covalent conjugation.Dendrimers Biocide which contains quaternary ammonium salts as a functional group have shown significant antimicrobial activity against bacteria than small drug molecules due to high density of active antimicrobials present on Dndrimers surface.PAMAM D(Polyamidoamine) Dendrimers are most widely used Dendrimerto study the antimicrobial activity due to higher density of functional groups which makes them more hydrophilic and most reactive with antimicrobial agents(Zhang, 2010).

Table 2: Preparation of Dendrimers and their use

Drug	Dendrimer	Activity	Reference
Vancomycin Hydrochloride	PAMAM (Polyamidoamine)	Vancomycin Dendrimer enhances the antibacterial activity against the gram positive bacteria	Azadeh et al; 2019
Ceftazidime	Propyleneimine (PPI-GI)	Enhances the antibacterial activity with sustained release against Pseudomonas aeruginosa	Aghayari et al; 2015

Erythromycin Tobramycin	PAMAM (Polyamidoamine)	To study the effect of dendrimer on antibacterial activity of two drugs with different solubility water profiles	Winnicka et al;2013

4. Polymeric Nanoparticles: Polymeric nanoparticles are defined as the submicron-sized polymeric- colloidal in which active ingredient is encapsulated in the polymer matrix. A polymeric nanoparticle offers various distinctive properties for antimicrobial agents as they are structurally stable and can be synthesized with a sharper size distribution due to their particle properties like size, zeta potential and drug release profiles can be turned by picking distinctive polymer lengths,surfactants for the duration of synthesis.The outside of polymeric nanoparticles has functional groups linked which can be changed chemically with drug moieties.For targeted delivery of antimicrobial polymeric nanoparticles have often enhanced with lecithin,a protein which binds to the simple or complex carbohydrates which are present on bacterial cell wall.The widely used polymer-based nanoparticle is poly-hydroxy acid, Polyanhydrides, polylactide, Poly-lactide-co-glycolide. Encapsulated polymeric nanoparticles also help to overcome cellular and tissue barrier by effective targeting to the bacterially infected microenvironment(Salouti, 2014).

5. Metallic Nanoparticles: Metallic Nanoparticles is one of the encouraging approaches for combating bacterial resistance. Due to their small size and have a large surface area, they have a broad contact area for microorganism and due to these properties; the metallic nanoparticles increase the biological and chemical properties and helps the nanoparticles to acquire high bacterial activity. Nanoparticles can inhibits the cell membranes functions like permeabilitywhen the MNP go through the bacterial cell they alter the function of sulphur-containing proteins and phosphorous-containing compounds like DNA. Due to the complicated mechanism of metals, the chances of developing bacteria resistance to them are very low. Due to their high bacterial properties nanoparticles of silver, gold, oxides of Copper are most commonly used nanoparticles in antimicrobial studies. (Adil *et al;* 2011)

Preparation of Nano medicines

I. Gold Nanoparticles

Gold nanoparticles have extensively used in various fields such as cancer diagnosis, DNA, Protein determination and drug delivery system etc. because of their small size and large surface area, high reactivity to the living cells, better stability above temperature makes them an ideal drug carrier. Gold nanoparticles are useful for the delivery of drugs to cellular target due to their biocompatibility and due to their better synthesis. (Salouti, 2014)

II. Silver Nanoparticles

Silver has been used in medical sciences for many centuries for the treatment of various infections. It has been found that due to their small size less than 10nm they are capable of to go through the bacterial cell wall and membranes as a mean of interaction with sulphur-have protein and thiol groups. Inside the cell silver and the silver ions targets and inhibits the bacteria and respiratory enzymes cause the cell to lose their replicating properties and this results in cell death. Due to their small size and large surface area of silver nanoparticles makes them effective against the variety of pathogens. Microbes are not able to develop resistance against silver due to their broad range of targets they require multiple and simultaneous Mutations. (Sharma *et al*; 2012)

III. Copper and Copper Oxide

Copper nanoparticles possess a higher affinity to carboxyl and amine groups on the cell surface of the pathogens when compare to silver nanoparticles. Copper can create harmful impacts at high concentration when in free ionic structure by creating ROS that kills the DNA and amino acid synthesis. Due to cheaper than silver-copper oxide can easily miscible with the polymer can be used as an alternative to Silver nanoparticles. (Ranghar *et al*; 2014)

IV. Solid Lipid Nanoparticles

Solid lipid nanoparticles were introduced in 1991 which serve as an alternative and better carrier system to conventional colloidal carriers such as emulsion, liposomes and polymeric nanoparticle. Solid lipid nanoparticles are defined as they are submicron-sized colloidal carriers ranging from 50-1000nm, which consists of high melting lipid core coated by an aqueous surfactant solution.SLN offers many advantages such as avoidance of organic solvents, High drug payload, Improved Bioavailability and incorporation of lipophilic and hydrophilic drugs and they have disadvantages also like Burst release, particle growth and poor loading capacity table 3.SLN's are prepared by High-Pressure Homogenization, Ultrasonication, Solvent Evaporation, Micro Emulsion Based method etc*(*Yadav, 2013).Tobramycin is an antibiotic which is given in *Pseudomonas aeruginosa* infection and is administered orally. P glycoprotein is an ATP dependent efflux pump which actively transports the drug through p-glycoprotein which results in the poor intestinal absorption of tobramycin. Tobramycin encapsulated SLN shows Better bioavailability and pharmacokinetic properties because tobramycin encapsulated SLN can automatically repress P-glycoprotein efflux pump can pass through the intestinal lining through endocytosis. (Priyanka, 2017)

Table 3: Solid Lipid Nanoparticles as Drug Delivery System

Formulation	Drug	Targeted Microorganism	Activity	Reference
Stearic acid,Poloxamer 407 and Lipoid S-100	Rifampicin	*Brucella abortus*	Enhances the antibacterial activity and the killing	Ghaderkhani, 2019

			time	
Stearic Acid	Pyrazinamide,rifapicin,isoniazid	*Mycobacterium Tuberculosis*	Shows increased residence time and drug bioavailablity	Pandey, 2005
Cetyl alcohol,Glycerol palmitostearate,glyceryl behenate,soya lecithin and propylene glycol	Miconazole nitrate	Fungi	Increased encapsulation efficiency and improve skin targeting effect	.Bhalekar ,2009

II. EMERGING APPROACHES TO COMBAT ANTIBIOTIC RESISTANCE

Bacteriophage therapy

The first use of phage therapy was first commenced in France in 1919 to treat bacterial infection with the help of bacteriophages (Casto, 2016). Bacteriophages are commonly refereed as Phage and are defined as viruses that affects and reproduce within the bacteria. These viruses are consists of proteins which encloses a DNA or RNA genome which reproduce within the bacteria. This property can kill the bacteriophage occupied bacterial cells**(**Eric, 2012).Phage's were earlier used as an antibiotic before the discovery of penicillin there are various type of phage viruses lytic phages was the most common method used for bacterial therapy. In lytics phagesthe phage will bind to the bacteria and it uses a host enzyme and a cofactor to reproduce inside the bacteria lytic Phages consist of lysine enzyme that engulfs bacterial proteins which causes terminal damage (Stephen, 2018).There are several benefits are presents which are offered by the phage therapywhich makes them a ideal choice to treat the disease which are caused by the bacteria and they also contributes to deals against the emergence of bacterial resistance. They offer many advantages like they can quickly proliferate inside the host cells, can be administered in low doses (Domingo, 2018).There are many drawbacks of using phage therapy like it cannot be used against the intracellular pathogens like *Salmonella species* because intracellular pathogens survive in the host cells where they are inaccessible to phage due to inability of phage to enter into the eukaryotic cells, human immune system recognize phage as an foreign antigens and hence respond by producing phage neutralizing antibodies.(Doss, 2107)

Antimicrobial Peptides

Antimicrobial peptides are defined as low molecular proteins having broad spectrum of antimicrobial and immune modulatory against bacteria, fungi and viruses. These peptides are classify on the basis of their physiochemical properties , they are having both the hydrophobic and hydrophilic which enables these peptides to be soluble in environmental conditions like most of the antibiotics antimicrobial peptides they does not inhibit

the peptidoglycan synthesis by binding with proteins(Kaur, 2020).Antimicrobial peptides are develops from all species like peptides from bacteria,fungi and insects etc. The antibacterial activity of antimicrobial peptides is that when comparing to the eukaryotes they show selective toxicity against the bacteria because they have negatively charged phospholipid membrane when compare to eukaryotes cells which consists of lipid without having any net charge, this difference can leads to the electrostatic interactions between cationic antimicrobial peptide and cytoplasmic membrane of bacteria, Unlike novel antibiotics they target microbial cell membrane which are diversein many bacteria,Due to these peculiarity of antimicrobial peptide antibiotics effectively reduced the possibility of development of resistance against them(Mehrzad, 2015).It is believe that the antimicrobial peptides can that they act on cell wall, inhibit the protein folding or they act intracellular but the main mode of action of these antimicrobial peptides is still unclear(Bechinger, 2017).Like,most of the novel antibiotics which are available they act synergistically with these antibiotics by enhancing the antimicrobial properties of the peptides by reducing the dose and the membrano-lytic effect and they also act by neutralizing lipo-sacchrides more studies are required to approve them for their use in clinical practices(Kaur, 2016).

Biofilm Targeting Approaches

Biofilms are defined as combination of microbial cells which are enclosed by a self produced polymer matrix, both the monospecies and polyspecies biofilms exist they may or may not observe to the surfaces, but these are widely placed on the tissues and components from the host(Hoiby, 2017).They are either single ormulti-layered Biofilms consists of homogenous or heterogeneous culture of bacteria which stays in the matrix built of extracellular polymer matrix (Satpathy, 2016).The extra cellular polymer matrix consists of polysaccharides, the water and the nutrients are enclosed inside these biofilms which are important of microbial growth thus,the EPS inhibits the penetration of antibiotics which renders the antibiotic resistance to the microorganism(Tiwari, 2018**).**The complicated structure of the biofilm and the consistent adjustment in the biofilm structure makes them more tolerant against the antibiotic(Mulinti, 2018). Biofilms formation can occur in five steps these are reversible attachment,irreversible attachment, maturation stage 1,2 and the dispersion. In the first stage there is the communication between the adsorption surface and the planktonic cells during this phase the bacterial cell get removed from the surface for short period of time.In the second phase there is permanent attachment of bacteria to the surface occurs which results in the production of bacteria small clustersthird phase involves the development of extracellular polymer matrix due to hike in the bacteria clusters to 10micrometer and in the last phase there is accumulations of water channels in the bacterial cells which helps them to improved contact to nutrients.

III. Conclusion

Change is the law of life and universe follow one rule i.e., survival for the fittest. In the continuation every living thing present on the earth will change with time like Antimicrobial resistance is the one of example which we are facing globally, due to overuse and lack of development of new antibiotic. Currently, pharmaceutical sector facing Multidrug resistant, which cause health and economic burden. However, Progress in this area is going on and soon we will resolve this problem and get new agents to treat various bacterial infections.

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