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Review Article

ACTION MECHANISMS OF ANTIBIOTICS VS NATURAL INGREDIENTS AGAINST MICROBES

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ABSTRACT

Antimicrobial resistance is being identified as one of the major threats in the health sector and to humans. The main reason of development of the resistance is established as acceleration of the natural evolution of the bacteria due to unnecessary constraints provided by the antimicrobial agents. After exploiting and exhausting the available antibiotics, development of new antibiotics is proven to be an expensive and difficult task and therefore alternative solutions such as use of nanoparticles, bacteriophage, natural ingredients, and new mechanisms such as quorum sensing ability were staged. It is important to identify the mechanism by which each of these new ingredients act in bacteria and reaction in the host environment to avoid similar misuses and creation of resistance. This review focuses on summarizing action mechanisms of antibiotics and resistance mechanisms of microbes and gathering probable action and resistance mechanisms of herbal ingredients. Antibiotic action is mainly obtained by inhibiting a bacterial structure or specific metabolic activity that is necessary for survival of bacteria. Some plants in contrast do not focus on inhibiting bacteria but minimizing the effects on host by nullifying the toxins and improving the immunity. Some other plants can disrupt the communication between bacteria and biofilm formation. One of the most important ability of some herbal ingredients is to overpass the resistance and they are called inhibitors. With the inhibitors there are new possibilities of reintroducing antibiotics. Plants with bactericidal capacity must use carefully to avoid creating resistance and should conduct further research for calculating proper dosages.

KEYWORDS: Antibiotics, Multi Drug resistance, Bacteria, Plants.

INTRODUCTION

World Health Organization has issued an ultimatum on human health by highlighting the impending peril of accelerated Antibiotic resistance due to misuse of Antibiotics. The natural process of evolution which created the bacteria resistance to Antibiotic has increased its phase by several folds due to unnecessary and incorrect use of Antibiotics by the individuals, health professionals, agriculture and poultry sector.[1,2] New developments in antibiotics are slow[3] and not expected to be effective against most dangerous bacteria. Occurrence of multi drug resistance is common among most opportunistic and pathogenic bacteria.[4]

European Commission action plan against the rising threats from antimicrobial resistance (AMR) includes the "promotion of the appropriate use of antimicrobial agents in human and veterinary medicine, the prevention of microbial infections and their spread, the development of new antimicrobials, alternatives for treatment or diagnostic tools, and the harmonization of surveillance systems".[5]

Prevalence of Antimicrobial Resistance

Many survey studies have been conducted in recent past demonstrating the failure of Antibiotics or improved antimicrobial resistance. Study on fecal Escherichia coli isolated from healthy volunteers from developing countries shows highest percentages of resistance in the urban populations of Asia and South America.[6]

Causes of AMR in developing countries are different than those in developed contries. Common causes are acceleration of natural resistance by misuse and over use for various reasons including human consumption, farming and poultry. Specific reasons in developing countries can be identified in every step involved from manufacturer to the individual. Lack of drug quality and dosage by production, easy access due to lack of regulations, misuse by health professionals by wrong prescriptions and use of broad spectrum antimicrobial agents, lack of effective surveillance

systems, and lack of up to date information about AMR patterns.[7] In a Lebanese study, it was shown that in 52% of cases, the prescription dose was inappropriate while 63.7% of physicians prescribed antibiotics with wrong duration of treatment.[8]

Some studies focus on the danger of using traditional or alternative therapy as first line treatments for infections due to unknown composition and potency of these medicines. They may have a potential role in AMR if the dosage is not enough for the intended action while creating a multi facade common resistance such as reducing the permeability of the cell membrane.[7]

Identifying the method/s of spreading of Antibiotic Resistance Bacteria (ARB) and Antibiotic Resistance Genes (ARGs) are also important in provenance. Many studies have been done on this subject and in one study that had been conduction by Graham Environmental Sustainability Institute at the University of Michigan shows water distribution systems could serve as an incubator for growth of certain ARB populations and as an important reservoir for the spread of antibiotic resistance to the opportunistic pathogens.[9] Similar study had been done in Portugal regarding waste water and purified waste water and the conclusion was ARB was not eliminated by the purification process.[10]

Few examples of global epidemiology of AMR among disease causing bacteria is being listed and *Neisseria gonorrhoeae* is estimated as 60 million cases per year and *Haemophilus ducreyi* (Chancroid) is 7 million new cases per year around the globe. Quinolone resistance gonococci was first identified in 1992 and by the year of 1996, 50% of resistance was exhibited in Hong Kong, China, Korea, Cambodia, and the Philippine.[11] Prevalence of Macrolide Resistance in *Streptococcus pneumoniae* in United States in 1994-1995 ranged from 2.1% to 23% in 30 different medical centers.[12] In 2013 an estimated number of affected numbers of people with multi drug resistant tuberculosis was estimated at 630,000 and cases have been reported from more than 80 countries.[2]

Action and Resistance Mechanisms of Antibiotics

Action mechanisms from which antibiotics act against microbes are important for understanding resistance created by bacteria.

Antibiotic action mechanisms

Basic Anatomy of Bacteria cell wall

Basic anatomy of bacteria cell wall is important for understanding the mechanisms of action and resistance of Antibiotics. Bacteria are divided into two major groups depending on their cell wall structure and these differences caused differences in staining of the bacteria. A gram–positive bacterium consists of inner cytoplasmic membrane and outer cell wall made of thick layer of peptidoglycan. Gram- negative bacteria consist of thin peptidoglycan cell wall that is covered by the outer membrane and inner cytoplasmic membrane. Even though this additional membrane layer prevents the entering of foreign matters to the bacterium, channels referred as porins allows passage of some chemicals shush as specific drugs. Membranes are made of lipids. Space between membranes is called periplasm. Cell walls provide the shape and act against the mechanical and osmotic stress. Cell membrane keep ion balance of the cell as well as content of the bacteria contained inside.[13,14] Antibiotic action is mainly obtained by the inhibition of bacterial structure or metabolic activities.[14]

Inhibit cell wall synthesis

Cell wall made of peptidoglycan consists of long sugar polymers. The peptidoglycans cross-link to from the glycan strand by the action of transglycosidases enzyme. Then peptide chains extend from the sugars from the chain to another to make cross links between peptides. In the presence of penicillin binding proteins, a portion chain is cross linked by glycine residues and strengthens the cell wall. Beta- lactam antibiotics are targeting penicillin binding proteins (PBP). β-lactam ring mimics the part of the peptide chain that is normally bind to PBP and interfere with the synthesis of peptidoglycan and leads to the lysis of bacterium.[15,16]

Inhibit protein synthesis

Synthesis of protein in bacteria is similar to that of any animal cell and occurs through transcription and translation process. The bacterial 70S ribosome is made of two ribonucleo protein subunits known as 30S and 50S subunits. Protein biosynthesis of bacteria is inhibited by targeting these subunits. 30S subunits are inhibited by Aminoglycosides (AG's). Positively charged AG's enter the cell wall via membrane actively in aerobic conditions and interfere with the m-RNA translation of 30S unit. In anaerobic conditions AG's needs to be combined with the β-lactam and glycopeptides for an easy penetration of the cell wall. Tetracyclines are in this category. 50S subunits are inhibited by the chloramphenicol by interfering with the t-RNA binding site of the 50S unit. Macrolides affect the translocation of the 50S ribosomal subunit and leads to premature detachment of incomplete peptide chains. Oxazolidinones interfere with the several stages of protein synthesis by binding to 50S subunit and by inhibition of peptidyl t- RNA.[17-20]

Inhibit DNA replication

Quinilones inhibits the bacterial DNA gyrase and damage the double strand DNA. This is highly effective in Gram positive bacteria in which major target of action is topoisomerase IV having greater affinity to fluoroquinolones that nicks and separate's daughter DNA strand after DNA replication.[21]

Inhibits the Folic acid metabolism

Sulfonamides and trimethoprim inhibits specific steps in folic acid metabolism by inhibiting the specialized enzymes.

Biochemical resistance mechanisms

Antibiotic resistance can be either intrinsic (natural) or acquired.[14]

Antibiotic inactivation

β-lactamases, aminoglycoside – modifying enzymes, and chloramphenicol acetyltransferase (AACs) are produced by the bacteria and capable of inactivating the antibiotics.

β-lactamases are classified according to structure and function as Class A, B, C and D. Class A found in members of Enterobacteriaceae and resistant to penicillins, third generation cephalosporin etc, but those are sensitive to cephamycins and carbapenems such as clavulanic acid. Class B is resistant to clavulanate, aztreonam, and carbapenems. Class C are called cephalosporinases and produced by all Gram-negative bacteria except *Salmonella* and *Klebsiella*. These classes are resistant to all β-lactams except carbapenems and they are not inhibited by clavulanate. Class D found in Enterobacteriaceae and in P. aeruginosa. They are resistant to penicillin, Cloxacillin, Oxacillin, and Methicillin. They can be inhibited by sodium chloride.[18,22-24]

Target modification

This can occur due to natural mutation of binding sites. Even slightest changes can affect the sensitivity due to specific target mechanisms. Alteration of PBP, 30S binding site or cell wall precursors alteration, and DNA gyrase mutations are some examples for this.[22-25]

Altered permeability

Decreased number of porin channels reduces the entry of β-lactam antibiotics and FQ to the cell. *Pseudomonas aeruginosa* has acquired resistance to all the antibiotic classes via low outer membrane permeability.[23,24,26] Efflux mechanism of the bacteria includes where inner cytoplasmic membrane proteins remove or export antibiotics from the cell at increased speeds before they reach the target. Antibiotics of all the classes except polymyxin can be export through efflux system and can be specific or multidrug resistant.[22] Study on multi drug resistance *Mycobacterium tuberculosis* shows up regulation of Efflux gene by identifying relevant point mutations that create resistance to variety of antibiotics.[27]

Bypassing the metabolic pathway

Bacteria resistance acquired by avoiding inactivation of specific enzymes that can obstruct bacterial metabolic actions is known as bypassing metabolic pathway. Some trimethoprim and sulfonamide resistant bacteria shows this variety of resistance by producing a second enzyme that can achieve the same action in metabolic pathway but has lower affinity to target specific enzyme inactivation of given antibiotic.[4]

Biocides and biocides antibiotic cross resistance

Biocides do not have a specific target in the bacteria cell. Enzyme resistance and target modification are less likely to occur due to this reason. Resistance occurs due to improved tolerance and non specific changes such as improved lack of permeability, improvement of efflux capacity. Eg; triclosan.[24]

Alternative Therapies

Due to an increase of antimicrobial resistance (AMR) for traditional antibiotics and lack of development of new antibiotics, alternative therapies are considered for controlling microbial growth and virulence without gaining resistance.

Nanoparticles as potential antimicrobials

Nanosized (1-1000 nanometers) organic and inorganic particles are use as antimicrobial agents due to specific physicochemical properties such as large surface volume ratio provided by nanoparticle size in comparison with the regular chemical antimicrobial agents. Metallic nanoparticles such as copper, aluminum, gold, silver, magnesium, zinc and titanium work through various mechanisms as bactericidal chemicals. Nano size and large surface area improve the interaction with the microorganism and some resistance techniques such as permeability is not an issue for nanoparticles. For example, silver has a high affinity towards the sulphur and phosphorus and large content of sulphur containing protein of the cell membrane and phosphorus in DNA attracts Ag+ particles and therefore it increases the permeability and then destruction of the cells. This is purely chemical and physical reaction and enzymes have little to do with it. Thus development of resistance is difficult. However host cell may have similar reactions to the nanoparticles and therefore suitable particle size and quantities should be carefully calculated.[28]

Using bacteriophage

Specific bacteriophages that can invade and induce the lysis of pathogenic bacteria are used as a new treatment technique.[29]

Quorum Sensing Inhibitors (QSI)

QSI can decrease the bacterial virulence by disrupting the communication system between bacteria without killing the cells and therefore reduce the unnatural selective pressure on bacteria and will decelerate the phase of evolution of AMR.[30] Opportunistic and pathogenic bacteria use QS system to coordinate their virulence expression.

Probiotics

Use of probiotics or a fecal transplant therapy (FTT) is uncommon but emerging practice in which fecal matter from pathogen free healthy donors are use to repopulate the microbiota of a recipient.[31]

Herbal treatments

Bacteria cannot easily develop a resistance to plant materials due to complex and multiple chemicals that are introduced by the plant materials and therefore multiple assaults produce by the variety and due to lack of repetitions of the treatments.[32] However, some research data shows the ability of bacteria to develop resistance during long term use of isolated herbal materials such as essential oil or powders. Also some bacteria may have natural resistance to some plant materials.[33]

Plants Action Mechanisms

Antimicrobial resistance modifying agents MDR inhibitors

MDR bacteria are capable of developing safety mechanisms for a number of structurally and chemically unrelated medical compounds. The ability of modifying one or all of this chemical compounds to break this barrier in some herbal ingredients are been observed and these drugs that can work with antibiotics in synergism are called MDR inhibitors.[34]

Plants as antibiotic resistance modifying agents/ Efflux pumps Inhibitors

As previously mentioned many antimicrobial agents work by destroying the cells and therefore creating a selective pressure towards creating antimicrobial resistance. Efflux pumps are one of the common mechanisms developed by bacteria towards resistance. Due to non selective efflux process they are capable of creating multi drug resistance. Some plants material has the natural capacity to inhibit those pumps and therefore known as antibacterial resistance modifying agents. Barberine is one of the successful natural ingredient that has been used at a sub- inhibitory as an Efflux pump inhibitor to help re-introduction of antibacterial agent back to the bacterial cells.[35]

Quorum sensing inhibiting action

Plants have lived with micro organisms as long as they existed and battled against pathogenic bacteria and survived in balance without killing or being killed. Therefore many have suspected they might have developed methods to manipulate the pathogenic bacteria into coexistence. QS system inhibitors are one of these mechanisms developed by nature. There are some chemical compounds that can inhibit QS, but most of the available QS inhibitors are natural products. N-acylhomoserine lactonase enzyme from bacillus sp., is capable of hydrolyzing lactone bond of the N-acelhomoserine signaling compound and thus disrupting the QS ability of other bacteria.[36,37] This method do not induce selective pressure which may give rise to acceleration of bacterial resistance. Attenuation *Pseudomonas aeruginosa* virulence by medicinal plant extracts is an example for the possibility of involvement of QS inhibition.[38] Studying plant volatiles against QS using *Chromobacterium violaceum* and *Pseudomonas aeruginosa* shows positive results by inhibiting QS with twenty two compounds while enhancing QS with seven compounds.[39]

Inhibition of biofilm formation

Biofilm formation is considered as an antimicrobial resistance method developed by bacteria. Plant derived materials role on inhibiting biofilm formation and related genes changes shows possibility of reduction of virulence factors by plant materials. One study shows epigallocatechin- gallate (EGCG) from tea is capable of inhibiting biofilm formation and reducing hemolytic activity of food borne pathogen *Listeria monocytogenes* in vitro conditions. Also in the same study observations include up regulation of the virulence genes, quorum sensing genes and transcription activator SOS genes and positive relationship between QS gene and biofilm formation.[40]

Antitoxin

Using plant compounds against bacteria without killing them (Sub- inhibitory levels) is a technique to reduce the development antimicrobial resistance while reducing the adverse effect to the patient. Carvacrol, a monoterpenoid from oregano and thyme oil and Trans- cinnamaldehyde, an aromatic aldehyde from cinnamon bark test against *Clostridium difficile* anaerobic gut bacteria proves to be effective in inhibiting toxin production and also affecting the related gene.[41] *Aegle marmelos* unripe fruit affect the production of cholera toxin *E.coli* heat labile toxin and their binding to gut receptors. Also it significantly reduce the bacterial adherence and invasion in the gut epithelium.[42] Sub–inhibitory concentration of Eugenol subsides the toxic

Hemolytic and Necrotic effect induced by the *Staphylococcus aureus.*[35] Immobilization of microbial toxin using plants and food are widely tested and succeeded in vitro conditions. However introducing these compound to host body in accurate non toxic but effective dosages to avoid widely spread symptoms and discomfort caused by infection is yet to be studied.[43]

Immunomodulatory/Stimulant activity

Immuno-stimulants are a type of immuno-modulatory compounds that can enhance body resistance against infections. The compounds that do not have any microbial activities or little but can help the immune system to fight against the infection and therefore render the microbial activity minimum and enhance the action of active drugs are considered as immuno-stimulants. Herbal ingredients that are well known for enhancing strength and vitality such as *Withania somnifera* and *Tinospora cordifolia* show immuno-stimulatory activity in vitro. However combine test in clinical settings have not done.[44]

Antimicrobial resistance is resulted from misuse of medicine and creating a selective pressure on microbes. Due to current dilemma of possibility of the complete failure of existing medicines it has become necessity to explore and invent new treatment methods, invention of new molecules that can work through different mechanisms, alteration of protective responds that has raised from microbes, and methods to improve human resistance to the pathogenic bacteria.[3]

Use of herbal or natural treatment for one of those purposes is a popular research area. Invention of possible natural microbial killing agents, understanding their mechanisms, using those microbial agents without creating selective pressure, inventing natural agents that are capable of enhancing immune response in humans, using herbal drugs for altering or bypassing resistance mechanisms have been studied to a certain extent.

However the possibility of creating herbal drug resistance through overuse due to falls safety feeling that comes with natural terms cannot be ignored.[33] Also the possibility of Antibiotics having different outcome than in inhibition in sub-inhibitory concentration via alteration of protein transcription cannot be ignored. Those outcomes changes with the media bacteria is grown and the presence of internal factors that affect outer environment like biofilm formation, and other external and environmental factors.[45]

Other aspects such as cultivation possibilities, cost effectiveness, environmental hazards are also to be considered on the development of potent natural products.

CONCLUSIONS

In conclusion natural or plant derivatives can be the solution for the bacterial infectious diseases in failure of synthetic antibiotics. However identification and use of those natural ingredients are of utmost importance to avoid exploitation of the plants as well as to avoid exploitation of medicinal aspects of the plants.

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