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POTENTIAL ALTERNATIVES FOR RESOLVING BACTERIAL ANTIBIOTIC RESISTANCE

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ABSTRACT

Antibiotics are chemical substances that are used to kill or prevent the growth of microorganisms. Antibiotic resistance among pathogenic organisms has become a major impediment in the treatment of many infectious diseases. Several mechanisms have evolved in bacteria which make them resistant to antibiotics, such as, enzymatic inactivation of the antibiotic, chemical modification of the antibiotic, render it inactive through physical removal from the cell, or modify target site so that it is not recognized by the antibiotic. The most common mode is enzymatic inactivation of the antibiotic. Multidrug-resistant bacteria which are often resistant to many, if not all of the existing antibiotics are becoming more common. Since the level of development of novel antibiotics has severely dropped, alternatives to these antibiotics must be considered in the treatment of bacterial infections. There are various approaches and many research efforts at different stages of development in order to find substitutes to the antibiotics. These include the use of bacteriophages, antimicrobial peptides (AMPs), predatory bacteria, nanoparticles, vaccines, medicinal plants, among others. Therefore, this review focuses on the potentials of using these alternatives to resolve the antibiotic resistance in bacteria.

KEYWORDS: Bacteria, Antibiotic, Antibacterial-resistance, Multi-drug resistance, Alternatives.

1. INTRODUCTION

Bacterial antibiotic resistance is a type of drug resistance whereby some sub-populations of bacterial species are able to survive after exposure to one or more antibiotics (Sani, 2014). In other words, "antibiotic resistance means the ability of a microorganism to withstand the effect of an antibiotic" (Witte, 2004).

Antibiotics were first prescribed in the 1940s to treat serious infections (CDC, 2013). During the World War II penicillin was successful in managing bacterial infections among soldiers (Sengupta *et al.*, 2013). However, shortly afterwards, penicillin resistance became a considerable clinical problem, so that, by the 1950s, many of the advances of the earlier years were threatened (Spellberg and Gilbert, 2014). In response, new beta-lactam antibiotics were discovered, developed, and used, restoring confidence (Sengupta *et al.*, 2013). Still, the first case of methicillin-resistant *Staphylococcus aureus* (MRSA) was identified during that same time, in the United Kingdom in 1962 and in the United States in 1968 (Sengupta *et al.*, 2013; CDC, 2013). Unfortunately, resistance has ultimately been seen to nearly all antibiotics that have been developed (CDC, 2013).

Vancomycin was introduced into clinical practice in 1972 for the treatment of methicillin resistance in both *S. aureus* and coagulase-negative staphylococci (Sengupta *et al.*, 2013; CDC, 2013). It had been so hard to induce vancomycin resistance that it was believed doubtful to occur in a clinical setting (Spellberg and Gilbert, 2014). Still, cases of vancomycin resistance were reported in coagulase-negative staphylococci in 1979 and 1983 (Sengupta *et al.*, 2013). From the late 1960s through the early 1980s, the pharmaceutical industry introduced many new antibiotics to solve the resistance problem, but after that the antibiotic pipeline began to dry up, less new drugs were introduced (Spellberg and Gilbert, 2014). As a result, in 2015, many years after the first patients were cured with antibiotics; bacterial infections have again become a danger. So, antibiotic-resistant infections are already widespread across the globe (Golkar *et al.*, 2014).

There are high proportions of antibiotic resistance in bacteria that cause common infections (e.g. urinary tract infections, pneumonia, bloodstream infections) in all regions of the world. A high percentage of hospital-acquired infections are caused by highly resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) or multidrug-resistant Gram-negative

bacteria. The Center for Disease Control and Prevention (CDC) declared in 2013 that the human race is now in the "post-antibiotic era," and in 2014, the World Health Organization (WHO) warned that the antibiotic resistance crisis is becoming dire (Viswanathan, 2014). Among gram-positive pathogens, a worldwide pandemic of resistant *S. aureus and Enterococcus species* currently poses the biggest threat (CDC, 2013; Luyt *et al.*, 2014). MRSA kills more Americans each year than HIV/AIDS, Parkinson's disease, emphysema, and homicide combined (Gross, 2013; Golkar *et al.*, 2014) Vancomycin-resistant enterococci (VRE) and a growing number of additional pathogens are developing resistance to many common antibiotics (Golkar *et al.*, 2014). The worldwide spread of drug resistance among common respiratory pathogens, including Gram-negative pathogens are particularly worrisome because they are becoming resistant to nearly all the antibiotic drug options available, creating situations reminiscent of the pre-antibiotic era (CDC, 2013; Golkar *et al.*, 2014; Luyt *et al.*, 2014). In 2013, there were about 480,000 new cases of multidrug-resistant tuberculosis (MDR-TB). Extensively drug-resistant tuberculosis (XDR-TB) has been identified in 100 countries. MDR-TB requires treatment courses that are much longer and less effective than those for non-resistant TB. The emergence of MDR (and increasingly pan-resistant) gram-negative bacilli has affected practice in every field of medicine (Golkar *et al.*, 2014). The most serious gram-negative infections occur in health care settings and are most commonly caused by *Enterobacteriaceae* (mostly *Klebsiella pneumoniae*), *Pseudomonas aeruginosa*, and *Acinetobacter* (CDC, 2013; Luyt *et al.*, 2014). MDR gram-negative pathogens are also becoming increasingly prevalent in the community (Luyt *et al.*, 2014). These include extended spectrum beta-lactamase-producing *Escherichia coli* and *Neisseria gonorrhoeae* (Luyt *et al.*, 2014). Treatment failures due to resistance to antibiotics of last resort for gonorrhoea (third-generation cephalosporins) have been reported from 10 nations. In developing countries, MRSA is not a big problem as multi-resistant salmonellosis, shigellosis, and tuberculosis in the community setting and enteric bacteria and *Pseudomonas aeruginosa* infections in hospitals (Byarugaba, 2010).

2. Mechanisms of Antibiotic Resistance in Bacteria

Several mechanisms have evolved in bacteria which confer them with antibiotic resistance to ensure their survival. These mechanisms can chemically modify the antibiotic, render it inactive through physical removal from the cell, or modify target site so that it is not recognized by the antibiotic. The most common mode is enzymatic inactivation. An existing cellular enzyme is modified to react with the antibiotic in such a way that it no longer affects the microorganism (Toleman *et al*., 2006). An alternative strategy utilized by many bacteria is the alteration of the antibiotic target site (Alekshun and Levy, 2007).

The resistance mechanisms, therefore, depend on which specific pathways are inhibited by the drugs and the alternative ways available for those pathways that the organisms can modify to get a way around in order to survive (Byarugaba, 2010). One of the main mechanisms of defense is inactivation of the antibiotic. This is the usual defense against penicillin and chloramphenicol, among others. Another form of defense involves a mutation that changes the bacterial enzyme affected by the drug in such a way that the antibiotic can no longer inhibit it (Witte, 2004). This is the main mechanism of resistance to the compounds that inhibit protein synthesis, such as the tetracyclines (Witte, 2004).

All these forms of resistance are transmitted genetically by the bacterium to its progeny. Genes that carry resistance can also be transmitted from one bacterium to another by means of plasmids, chromosomal fragments that contain only a few genes, including the resistance gene. Some bacteria conjugate with others of the same species, forming temporary links during which the plasmids are passed from one to another (Sengupta *et al* 2013). If two plasmids carrying resistance genes to different antibiotics are transferred to the same bacterium, their resistance genes can be assembled onto a single plasmid (Witte, 2004). The combined resistances can then be transmitted to another bacterium, where they may be combined with yet another type of resistance. In this way, plasmids are generated that carry resistance to several different classes of antibiotic. In addition, plasmids have evolved that can be transmitted from one species of bacteria to another, and these can transfer multiple antibiotic resistance between very dissimilar species of bacteria (Alekshun and Levy, 2007).

Thus, resistance can be of two types

a. Inherent or natural where by microorganisms naturally do not possess target sites for the drugs and therefore the drug does not affect them or they naturally have low permeability to those agents because of the differences in the chemical nature of the drug and the microbial membrane structures especially for those that require entry into the microbial cell in order to carry out their action.
b. Acquired resistance whereby a naturally vulnerable microorganism obtains ways of not being affected by the drug.

The mechanisms of acquired resistance can occur through various ways (Fluit *et al*., 2001) including:

i. The existence of an enzyme that inactivates the antibiotic agent.
ii. The occurrence of an alternative enzyme for the enzyme that is inhibited by the antibiotic agent.
iii. A mutation in the antibiotic's target, which reduces the binding of the antibiotic agent.
iv. Post-transcriptional or post-translational modification of the antibiotic's target, which lessens the binding of the antibiotic agent.
v. Reduced uptake of the antibiotic agent.
vi. Active efflux of the antibiotic agent.

vii. Over-production of the target of the antibiotic agent.
viii. Expression or suppression of a gene *in vivo* in contrast to the situation *in vitro.*
ix. Earlier unrecognized mechanisms.

3. Multidrug Resistance

Multidrug resistance among many organisms has become a big challenge to infectious disease management. It is increasingly being reported in bacteria and is often mediated by genetic mobile elements such as plasmids, transposons, and integrons (Schmieder and Edwards, 2012). Integrons are mobile DNA elements with the ability to capture genes, notably those encoding antibiotic resistance, by site specific recombination, and they have an intergrase gene (*int*), a nearby recombination site (attI), and a promoter (Hall, 1997). Integrons seem to have a major role in the spread of multidrug resistance in gram-negative bacteria but integrons in gram-positive bacteria have also been described (Dessen *et al.,* 2001). Class 1 integrons are often associated with the sulfonamide resistance gene *sul1* and are the most common integrons. Class 2 integrons are associated with Tn7. The majority of genes encode antibiotic disinfectant resistance, including resistance to aminoglycosides, penicillins, cephalosporins, trimethoprim, tetracycline, erythromycin, and chloramphenicol (Dessen *et al.,* 2001).

4. Causes of Antibiotic Resistance

The problem of resistance has been exacerbated by the use of antibiotics as prophylactics, intended to prevent infection before it occurs (Sani, 2014). Indiscriminate and inappropriate use of antibiotics for the treatment of the common cold and other common viral infections, against which they have no effect, removes antibiotic-sensitive bacteria and allows the development of antibiotic-resistant bacteria (Allen *et al.,* 2014). Incorrectly prescribed antibiotics also contribute to the promotion of resistant bacteria. Also, the use of antibiotics in poultry and livestock feed has promoted the spread of drug resistance and has led to the prevalent contamination of meat and poultry by drug-resistant bacteria (D'Costa *et al.,* 2011).

5. Some Alternatives for Resolving Bacterial Antibiotic Resistance

For antibiotic uses that target a primary bacterial infection, there are numerous approaches to either reduce the selection for antibiotic resistance or to replace the antibiotic altogether. Each approach has its own benefits and costs. The most useful replacements for antibiotics are, like antibiotics, natural compounds or agents that inhibit bacteria. Among others, these include bacteriophages (phages), antimicrobial peptides and predatory bacteria. Unlike antibiotics, such alternatives can be targeted to specific bacteria, which are often desirable so as to avoid selecting for resistance of non-targeted bacteria (Allen *et al.,* 2014). According to Allen *et al* (2014) one thing most scientists can agree on is that antibiotic resistance is not a single-solution problem and there are four strategies being explored to resolve even the most resistant bacteria:

a. Changing old compounds into entirely new classes of antibiotics;
b. Combining modern antibiotics in a one-two punch against infection;
c. Boosting existing antibiotics with adjuvants that can render resistant pathogens vulnerable once more and;
d. Restoring the field's roots by exploring the globe for novel antimicrobial compounds.

5.1 Bacteriophage Therapy

Phages are viruses that infect bacteria (Allen *et al.,* 2014). Part of the active phage lifestyle involves a lytic phase, which leads to the physical break down of host bacteria to allow escape of progeny virus. The application of lytic phages to kill pathogenic bacteria is called phage therapy (Allen *et al*., 2014). Lytic phages of particular pathogens have been cultivated and administered to treat infections in both humans and animals (Johnson *et al*., 2008). Although some evidence suggests that it is effective against systemic infections (Biswas *et al.,* 2002). Phage therapy has been primarily developed and used for accessible topical infections, such as in the paranasal sinus or on the skin (Chan *et al*., 2013). In the United States, phage therapy has been developed and used for treatment of foodborne pathogens in animals (Goodridge, and Bisha, 2011), and for biocontrol of plant pathogens, (Balogh *et al*., 2010) while use of phage therapies for human infections is limited to mainly Eastern European countries (Miedzybrodzki *et al*., 2012). The critical factor to consider is the possible development of bacterial resistance to phages, which, on the one hand, is a short-term problem for treatment (i.e., lost infectivity of the phage to a specific bacterial target) but, on the other hand, because the cellular modifications associated with phage resistance can also pose a long-term fitness cost to the host bacterium (which could lead to altered microbiota) (Levin and Bull, 2004).

5.2 Antimicrobial peptides (AMPs)

AMPs are increasingly of interest as alternatives to classic antibiotics. However, because many AMPs are toxic to mammalian cells, they are not good candidates for therapies (Allen *et al.,* 2014). A subcategory of AMPs that lacks this drawback is the bacteriocins. These compounds are commonly described as small ribosomally synthesized peptides that are secreted by bacteria and inhibit the growth of closely related species. Similar to phage-encoded endolysins, bacteriocins function by inserting themselves into the plasma membrane of target bacteria, forming pores and causing lysis (Allen *et al.,* 2014).

Bacteriocin production has been found throughout the major lineages of bacteria; by some estimates up to 99% of all bacteria produce at least one bacteriocin (Allen *et*

al., 2014). Many commensal bacteria endogenously produce bacteriocins, and thus exploiting or modulating such bacteriocins may be promising (Cotter *et al*., 2013). For example, one group of commensal microbes, the lactic acid bacteria (LAB), produce bacteriocin nisin A, which, owing to its bacteriodical activity, is currently used in some countries as a food preservative (Vollmer *et al.,* 2008). In addition to their food-safety applications, bacteriocins can be used effectively in treatment of human pathogens, including multi-drug resistant pathogens. For example, a bacteriocin produced by *Enterococcus faecium* is effective against vancomycin-resistant *Enterococcus* (VRE) strains (Shokri, *et al.*, 2013). Larger bacteriocins are quickly degraded by intestinal proteases, heat, and other stresses, and are less persistent in the environment than traditional antibiotics (Bastos *et al.*, 2010). As with phage therapy, one advantage of bacteriocins is that they are thought to have a lower potential to select for resistance than do antibiotics. Even with such widespread use of nisin A, for example, almost no developed resistance has been observed in routine use (Zendo, 2013).

However, resistance to bacteriocins has been observed *in vitro*; one study developed bacteriocin resistant strains of *E. coli* and *Listeria monocytogenes* through long-term exposure of gradually increasing concentrations (Naghmouchi, *et al.*, 2011). Thus, the use of bacteriocin therapies will need careful and controlled implementation to limit or delay the development of resistance. There have been three main reasons which limit the AMP group's clinical utility: - high susceptibility to proteolytic degradation by endogenous or microbial enzymes, possible toxicity due to large amounts of drug needed for treatment, and manufacturing costs (Peters, 2010). Other possible restricting characteristics that may also limit the utility of these agents include high protein binding and high metabolic clearance, leading to a relatively short half-life (Glenn and Nicolette, 2013). Efforts to overcome these hurdles have centered mainly on the synthesis of proteolytic resistant versions of natural peptides by either complete or partial substitution of L-residues with non-natural D- or B-residues (Glenn and Nicolette, 2013).

5.3 Bacteria Predators

Predatory bacteria are unconventional compared to the bacterial viruses and products but they present an interesting possibility for an antibiotic alternative. Many different types of predatory bacteria have been identified, but the *Bdellovibrio* and like organisms (BALOs) show particular promise. BALOs are motile Deltaproteobacteria that obligately predate Gram-negative bacteria for energy and nutrients (Dwidar *et al.*, 2012). The genomes of many BALOs encode numerous hydrolases (e.g., DNases and proteases), an enzymatic arsenal essential for prey digestion and sufficient for attacking even bacterial (Lambert and Sockett, 2013). The latter presents a therapeutic advantage over other antibiotic alternatives, and indeed over antibiotics themselves, because biofilms pose a treatment challenge in both human and animal infections, as bacteria living in biofilms are up to 1000 times less sensitive to antimicrobials than are planktonic cells (Costerton and Keller, 2007). They have also been explored in clinical settings for targeting another group of recalcitrant infections, the multidrug resistant pathogens that include *Acinetobacter baumannii, E. coli, K. pneumonia, P. aeruginosa, and P. putida* (Kadouri *et al.*, 2013). The use of BALOs to treat intractable pathogens might be far from widespread use clinically, but their properties and potential unique targets deserve further investigation on them. One concern about BALOs is how they persist in native microbial communities and interact with the host immune system (Allen *et al.*, 2014).

5.4 Increasing antibiotic efficiency (Adjuvant Effect)

In addition to other antibiotic alternatives, the use of antibiotic adjuvants is another strategy to preserve or enhance the current antibiotic repertoire (Allen *et al.*, 2014). Adjuvants include other antibiotics, synergistic non-antibiotics, and molecules that are inhibitors of resistance genes (Worthington and Melander, 2013). Antibiotic adjuvants are important because the initial boom of antibiotic discovery is long past, there is little confidence that generation of new antibiotics will keep up with the demand from emerging multidrug-resistant pathogens because few antibiotics are in development (Jabes, 2011). For example, development of new generations of the most commonly administered class of antibiotics, the β-lactams, has stagnated in recent years (Mundy *et al*., 2016), instead research has emphasized discovery and development of inhibitors of β-lactamases, the enzymes primarily responsible for resistance to β-lactams. Penicillin-type β-lactams are often administered with a β-lactamase inhibitor, such as co-administration of amoxicillin with clavulanic acid (Bush and Macielag, 2010).

The tradition of synergy in herbal medicine is also being used as a source of research ideas. The in vitro findings of most researchers reported synergy both within plants and between plants and antibiotics (Mundy *et al*., 2016). Whole plant extracts and combinations of compounds were shown to be more effective antimicrobials than isolated constituents (Mundy *et al*., 2016). Ahmad and Aqil, (2006) observed that crude extracts of Indian medicinal plants, *Acorus calamus*, *Hemidesmus indicus*, *Holarrhena antidysenterica* and *Plumbago zeylanica* showed synergistic interactions with tetracycline and ciprofloxacin against Extended Spectrum β-lactamase (ESβL) producing multidrug-resistant enteric bacteria with ciprofloxacin showing more synergy with the extracts than tetracycline.

Betoni *et al*., (2006), observed synergistic interactions between extracts of guaco (*Mikania glomerata)*, guava *(Psidium guajava*), clove *(Syzygium aromaticum*), garlic (*Allium sativum*), lemongrass (*Cymbopogon citratus*), ginger (*Zingiber officinale*), carqueja (*Baccharis*

trimera), and mint (*Mentha pieria*) from Brazil and some antibiotics which represented inhibitors of protein synthesis, cell wall synthesis, nucleic acid synthesis and folic acid synthesis against *Staphylococcus aureus*.

5.5 Vaccines

Vaccines are occasionally mentioned in the prudent use of antibiotics (Mishra *et al.,* 2012). Preventing viral and bacterial diseases through vaccination has been a highly successful approach for many human and veterinary diseases. It has been estimated that more than 100 million illnesses have be prevented since 1924 by vaccinations including smallpox, measles, mumps, rubella, diphtheria, hepatitis A, pertussis, polio, etc. (Ahmed *et al*., 2016). Although effective vaccines are not available for many human or animal infectious diseases, additional research and novel vaccination approaches could lead to important alternatives to prophylactic antibiotic treatment (Mishra *et al.,* 2012). Vaccines that targets primary infections would remove the need for antibiotics for preventing secondary infections, as would vaccines that target secondary opportunistic pathogens. Thus, new vaccines could be an additional approach for guarded use of antibiotics and an alternative to their use to prevent infection in humans, as well as lead to the reduction of disease in animals, which may be an explanation for the positive effect of in-feed antibiotics as growth promoters in agricultural animals (Ahmed *et al*., 2016).

5.6 Nanoparticles

Nanomaterials possess unique properties compared to their larger bulk counterparts. Metal oxide nanomaterials, such as zinc oxide (ZnO) and copper oxide (CuO), have been exploited in paints, cosmetics, textiles and plastics (Tran *et al.,* 2010). It is, however, the antibacterial activity, particularly against an array of pathogens, which has led to recent research in this field. Nanoparticles have received attention in several fields due to their unique physical, chemical and effective biological properties. The properties of nanoparticles can be altered by changing their size, especially when at the nanometer scale. Indeed, the smaller particles have been shown to have activity against *E. coli* and *S. aureus.* Interestingly, these species seem to be highly susceptible to ZnO and CuO nanoparticles. The bactericidal activity of these nanoparticles depends on size, stability and concentration in the growth medium. Bacterial cells are typically in the micrometer range in size with cell wall peptidoglycan pores being a nanometer in dimension, thus nanoparticles possess a unique ability to cross into the bacterial cell. Synthesis of silver nanoparticles is also of much interest because of their wide range of applications. These silver nanoparticles are being successfully used in the cancer diagnosis and treatment as well (Ahmed *et al*., 2016).

The use of plant extracts in the assembly of silver nanoparticles has also drawn attention, because of its rapid, eco-friendly, non-pathogenic, economical procedure and a single step technique for the biosynthesis and more efficient in a variety of applications especially in bactericidal activities (Ahmed *et al*., 2016). The green rapid syntheses of spherical shaped silver nanoparticles with dimensions of 50–100 nm were observed by Kumar *et al*., (2014) using *Alternanthera dentate* aqueous extract. The reduction of silver ions to silver nanoparticles by this extract was completed within 10 min. These silver nanoparticles exhibit antibacterial activity against *Pseudomonas aeruginosa*, *Escherichia coli, Klebsiella pneumonia* and *Enterococcus faecal*. Nakkala *et al.,* (2014), also used *Acorus calamus* for the synthesis of silver nanoparticles to evaluate its antibacterial effect.

In 2012, Gopinatha *et al.,* used the dried fruit extract of the plant; *Tribulus terrestris L*. mixed with silver nitrate in order to synthesize silver nanoparticles. The spherical shaped silver nanoparticles having size in range of 16–28 nm were achieved using this extract with antibacterial property observed by Kirby-Bauer method against multi-drug resistant bacteria such as *Streptococcus pyogens*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Escherichia coli* and *Staphylococcus aureus*. A silver nanoparticle of size 22 nm was synthesized using extracts of the tree *Cocous nucifera* in ethyl acetate and methanol (in ratio of 40:60 respectively). It showed significant antimicrobial activity against human bacterial pathogens; *Salmonella paratyphi*, *Klebsiella pneumoniae*, *Bacillus subtilis* and *Pseudomonas aeruginosa* (Mariselvam *et al.,* 2014). A stable and spherical shaped silver nanoparticle was also synthesized using extract of *Abutilon indicum* by Kumar *et al.,* (2015) these nanoparticles show high antimicrobial activities against *S. typhi, E. coli, S. aureus* and *B. substilus*.

5.7 Application of Medicinal Plants

Biologically active compounds isolated from plant species used as medicines have received a great attention in recent times due to the side effects and the serious issues of resistance that pathogenic microorganisms develop against conventional antibiotics. Antimicrobials of plant source are also quite active in the treatment of infectious diseases while simultaneously easing the numerous side effects often associated with synthetic antimicrobials (Iwu *et al.,* 1999). The primary benefit of using plant medicines is that they are relatively safer and cheaper than their synthetic counterparts. In addition, plant medicine is a complex combination of different phytochemicals acting by different mechanisms, which makes it difficult for pathogens to develop resistance (Aiyegoro and Okoh, 2009).

According to WHO, medicinal plants would be the best source for obtaining variety of drugs. For this reason; researchers are increasingly turning their attention to herbal products, looking for new leads to develop better drugs against MDR strains. A huge number of medicinal plants have been recognized as valuable resources of natural antibacterial compounds (Mahady, 2005).

Considerable number of studies have been conducted on the antibacterial activity of medicinal plants which showed promising effectiveness against multi-drug resistant microorganisms after antibiotics failed to eliminate them (Sibanda and Okoh 2007).

In 2001, Ahmad and Beg studied the effect of alcoholic extract of forty five (45) medicinal plants against multi–drug resistance bacteria including *Staphylococcus aureus*, *Salmonella paratyphi*, *Escherichia coli* and *Shigella dysenteriae*. The result show 40 plants extract to have antibacterial activity against one or more tested bacteria. Aqueous extracts of tea (*Camellia sinensis*) was shown by Stapleton *et al.,* (2004) to reverse methicillin resistance in MRSA and also, to some extent, penicillin resistance in β-lactamase-producing *Staphylococcus aureus*. Forty (40) to one hundred (100) fold dilutions of tea extract was able to reduce the MICs of high- level resistant MRSA (≥ 256 µg/mL) to less than 0.12 µg/mL for methicillin and penicillin.

A study by Appendino *et al.,* (2008) found that cannabinoids have powerful anti-bacterial ability against MRSA. All five major cannabinoids (cannabidiol, cannabichromene, cannabigerol, Δ^9-tetrahydrocannabinol, and cannabinol) showed potent activity against a variety of methicillin-resistant *Staphylococcus aureus* (MRSA) strains of current clinical relevance. Also noteworthy is the potent activity demonstrated against EMRSA-15 and EMRSA-16, the major epidemic methicillin-resistant *S. aureus* strains occurring in U.K. hospitals. These activities compare highly favorably with the standard antibiotics for these strains.

Khan *et al.,* (2009) evaluated antimicrobial activities of the crude ethanolic extracts of five plants against multidrug resistant (MDR) strains of *Escherichia coli* and *Klebsiella pneumoniae.* The MDR strains were sensitive to the antimicrobial activity of *Acacia nilotica*, *Syzygium aromaticum* and *Cinnamum zeylanicum*, whereas they exhibited strong resistance to the extracts of *Terminalia arjuna* and *Eucalyptus globulus*. The most potent antimicrobial plant was *A. nilotica* with minimum inhibitory concentration (MIC) in the range of 9.75-313µg/mL, whereas other crude plant extracts in the report were found to exhibit higher MIC values than *A. nilotica* against community acquired as well as nosocomial infection.

In 2011, Hannan *et al.,* assessed the antimicrobial activity of garlic (*Allium sativum*) against non-multi-drug resistance and multi-drug resistance *Mycobacterium tuberculosis*. The result indicated that MIC of garlic extract was ranged from 1 to 3 mg/ml; showing inhibitory effects of garlic against both non-MDR and MDR *M. tuberculosis* isolates.

Sani, (2014), studied the effect of hexane extracts of *Allium sativum* bulbs, *Calotropis procera* leaves, *Acacia nilotica* pods, and *Mitracarpus scaber* whole parts to resolve the antibiotic resistance in some selected clinically isolated bacterial strains; *Staphylococcus aureus, Klebsiella pneumoniae and Streptococcus pneumoniae*. The results indicated that, all the plants extracts exhibited antibacterial activity against one or more tested pathogens. The hexane extract of *A. nilotica* showed stronger and broad spectrum activity against the tested isolates as compared to the other extracts that demonstrated moderate activity.

Demetrio *et al*., (2015) evaluated crude ethanolic extracts of twelve (12) Philippine medicinal plants for their antibacterial activity against methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, extended spectrum β-lactamase-producing, carbapenem-resistant *Enterobacteriaceae* and metallo-β-lactamase-producing *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. The leaf extracts *of Psidium guajava, Phyllanthus niruri, Ehretia microphylla* and *Piper betle (P. betle)* showed antibacterial activity against the Gram-positive methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus*. *P. betle* showed the highest antibacterial activity for these bacteria with MIC of 19–156 mg/mL and minimum bactericidal concentration (MBC) of 312 mg/mL. *P. betle* leaf extracts only showed remarkable antibacterial activity for all the Gram-negative multidrug-resistant bacteria (extended spectrum β-lactamase-producing, carbapenem-resistant Enterobacteriaceae and metallo-β-lactamase-producing) with MIC (312–625 mg/mL) and MBC (312–625 mg/mL).

Djeussi *et al.,* (2016) assessed the antibacterial properties of the methanol extracts of six (6) medicinal plants (*Anthocleista schweinfurthii, Nauclea latifolia, Boehmeria platyphylla, Caucalis melanantha, Erigeron floribundus* and *Zehneria scobra*) and the effects of their associations with antibiotics on Multi-Drug Resistant (MDR) Gram-negative bacteria over-expressing active efflux pumps. All tested extracts displayed moderate to low antibacterial activity on at least 14.3% of the 28 tested bacteria, with MIC values ranging from 128 to 1024 µg/mL. The best antibacterial spectrum was observed with *Naulcea latifolia* stem-bark extract. Extracts from *A. schweinfurthii* fruits, *N. latifolia* stem-bark, *Z. scobra* and *N. latifolia* leaves showed synergistic effects with many antibiotics against MDR bacteria.

Some isolated pure compounds of plant origin have been reported to have resistance modifying activities *in vitro* (Sibanda and Okoh, 2007). According to Shibata *et al*., (2005) ethyl gallate, a conginer of alkyl gallates purified from a dried pod of tara (*Caesalpinia spinosa*) native to South America, intensified β-lactam susceptibility in MRSA and MSSA strains. A study by Oluwatuyi *et al.,* (2004) indicated that the abietane diterpenes, (carnosic acid carnosol) isolated from the aerial parts of *Rosmarinus officinalis* by fractionation of the chloroform

extract at 10 μgmL^{-1}, potentiated the activity of erythromycin (16 -32 fold) against strains of *S. aureus* that express the two efflux proteins MsrA and TetK. Additionally, carnosic acid was shown to inhibit ethidium bromide efflux in a NorA expressing *S. aureus* strain.

Smith *et al*., (2007) screened active compounds from the cones of *Chamaecyparis Lawsoniana* for resistance modifying activities and observed that Ferruginol and 5-Epipisiferol were effective in increasing the efficacy of tetracycline, norfloxacin, erythromycin and Oxacillin against resistant *S. aureus*.

6. CONCLUSION

The importance of antibiotics cannot be overrated, as we are absolutely reliant on them for the treatment of infectious diseases. It is actually the time to admit on the mismanagement of these antibiotics over the decades of years. The current situation of antibiotic resistance is dingy, as resistance mechanisms are pandemic and this creates a huge clinical and financial burden on the healthcare system worldwide. If it continues, it may result in pathogens that evade all existing therapeutic agents. This prediction is consistent with evolutionary theory and the consequences of non-prudent antibiotic use. The prevalent dissemination of antibiotic resistance genes should provide sufficient caution for implementation of new antibiotic alternatives, such as, the use of bacteriophages, antimicrobial peptides (AMPs), predatory bacteria, nanoparticles, vaccines, medicinal plants, among others. We must consider our antibiotics as a limited valuable resource, and like all limited resources conserve, restore and value them. The search for new antibacterial agents must be continued, novel mechanisms and innovative bold solutions must be obtained if we are to slow down the rate of resistance. If not, the pre-antibiotic era awaits our descendants.

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