

EDITORIAL

Medicinal plants to mitigate the problem of antibiotic resistance

Antibiotics, since their introduction to medicine in the 1940s, have been used to treat and prevent bacterial infections. The global use of antibiotics was estimated at 100,000 tons in 2010 and is projected to increase by two thirds in 2030. Currently, there are more than 15 structural types of antibiotics; the main types include β -lactams (e.g., penicillin), cephalosporins (cephalexin), macrolides (erythromycin), fluoroquinolones (ciprofloxacin), sulfonamides (co-trimoxazole), tetracyclines (tetracycline) and aminoglycosides (gentamicin). The most important sources of leading antibiotics in the pharmaceutical industry are natural products of microbial origin.

Antibiotics kill bacteria or prevent them from multiplying. Broad spectrum antibiotics affect a wide range of bacteria while narrow spectrum antibiotics affect a few types of bacteria. Their action sites are associated with physiological or metabolic functions essential to the bacteria. Penicillins and cephalosporins inhibit cell wall biosynthesis. Macrolides, tetracyclines and aminoglycosides inhibit protein synthesis. Fluoroquinolones interfere with nucleic acid metabolism and repair while sulfonamides interfere with folic acid biosynthesis. Polymyxins, a group of nonribosomal peptides, disrupt bacterial cell membrane.

Antibiotic resistance among bacteria occurs when an antibiotic loses its ability to control and kills bacterial growth. Widespread and inappropriate use of antibiotics leads to antibiotic resistance. Antibiotics are used not only in treating bacterial infections but also in preventing infections in surgical patients, cancer patients and immunocompromised patients. Some people, however, inappropriately consume antibiotics for viral and fungal infections; antibiotics do not respond to such infections. Today, far more antibiotics are used in animal production—to treat individual animals with bacterial infections, to prevent infections, and to promote growth—than in human health. Some of the antibiotics used by people and animals end

up in ground and surface water and soil, which eventually adds to the burden of antibiotic resistance.

Antibiotic resistance is a survival trait of bacteria. Exposure of bacteria to an antibiotic can cause modifications in bacterial physiology so that the antibiotic is no longer effective. Some bacteria develop resistance to many antibiotics becoming multidrug resistant (MDR) strains. The resistance mechanisms employed by bacteria are drug-specific and include the following: degradation of the antibiotic drug by enzymes of the bacteria, modification of the receptor site in the bacteria such that the efficiency of drug-binding is reduced and extrusion of the drug by multidrug efflux pumps of the bacteria. Resistant strains of bacteria have been found for almost all commercially available antibiotics. Their resistance levels appear to follow the frequency of antibiotic use. The highest resistance levels are observed for the most frequently used antibiotics such as β -lactams, tetracyclines, sulfonamides and aminoglycosides. Lower resistance levels are recorded for newer antibiotics.

The worldwide spread of MDR bacteria is a major health threat in the 21st century. Each year, over 13 million deaths in the world are attributed to new MDR pathogens. The emergence of MDR strains threatens the efficacy of antibiotics, leads to treatment complications, prolonged hospital stays, increased mortality and increased healthcare costs, and has become the major cause of failure in treating infectious diseases.

The bacterium *Staphylococcus aureus* is the most prevalent cause of bloodstream infection, skin and soft-tissue infection and pneumonia. The efficacy of β -lactams such as penicillin, methicillin, amoxicillin and oxacillin in the control of this bacterium is fading because of the rapid emergence of penicillin- and methicillin-resistant strains of *S. aureus* (MRSA). Vancomycin, a glycopeptide

antibiotic, is considered a last resort in the control of such MDR MRSA, but the emergence of vancomycin-resistant strains has also been observed. MRSA is sometimes called a 'superbug' since MRSA infections are often hard to treat. New antibiotics are required to treat infections caused by MDR bacteria.

The World Health Organization has recently announced the urgent need to develop new antibiotics to combat 12 MDR bacterial pathogens which include vancomycin-resistant MRSA and *Enterococcus faecium*, clarithromycin-resistant *Helicobacter pylori* and carbapenem-resistant *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacteriaceae*. However, many pharmaceutical companies are terminating their research and development (R&D) endeavours on new antibiotics. The R&D of a new antibiotic may cost as much as 1.5 to 2 billion US dollars. Eventual financial returns may not, however, compensate for the expenditure incurred in R&D because bacteria are likely to develop resistance to the new antibiotic in less than five years of its clinical use. The lack of financial motivation in developing new antibiotics and the widespread resistance to antibiotics in just sixty years of use mandate an extensive search for alternative approaches to effectively treat infectious diseases.

Combination therapy using more than one antibiotic is a viable option to manage drug-resistant bacteria. Antibiotics have different target sites and mechanisms of action. Thus, the chance that a pathogen could simultaneously develop resistance against more than one antibiotic is low. The drug co-trimoxazole, for example, is a combination of two antibiotics, sulfamethoxazole and trimethoprim, which separately inhibit two enzymes involved in the biosynthesis of folic acid in bacteria. Augmentin, a combination of amoxicillin and clavulanic acid, is effective against lactamase-secreting resistant bacteria. Clavulanic acid, which has negligible intrinsic antibacterial activity, inhibits the enzyme β -lactamase secreted by the resistant bacteria so that amoxicillin is not degraded and remains effective. Other approaches such as vaccines and bacteriophages will also be useful to maintain the efficacy of current and new antibiotics.

Another strategy is to restore or enhance the activity of antibiotics against drug-resistant bacteria by using the antibiotics together with compounds that inhibit resistance mechanisms. Plants have defended attack by microbes for millions of years and, over time, have experienced antimicrobial-resistance as well. Consequently, plants began to produce compounds that interfere with drug-resistance mechanisms of microbes and enhance the potency of the antimicrobials through synergistic combinations. For example, antimicrobial activity of berberine, which is formed in the barberry plant (*Berberis vulgaris*), is enhanced by another constituent of the same plant, 5'-methoxyhydruncarpin-D, which is a potent inhibitor of multidrug efflux pumps.

Antibacterial compounds isolated from plants are not as potent as the antibiotics derived from microbial sources. The synergistic interactions between various metabolites could, however, enhance the activity of the weak antibacterial compounds and contribute to a plant's defense against invading pathogens. Plants have different levels of defense against pathogens—constitutive chemical defense, direct inducible chemical defense and gene-level inducible chemical defense—thereby producing a range of structurally different secondary metabolites such as alkaloids, flavonoids, polyphenols and terpenoids. The defense strategies may involve the synergistic activity of two or more metabolites via different mechanisms and targets. Such metabolites can potentiate the activity of antibiotics.

Some plant compounds have shown considerable resistance-modifying activities *in vitro*. Epigallocatechin gallate (EGCg), a major polyphenol found in tea (*Camellia sinensis*), for example, interferes with some drug-resistant mechanisms invoked by MRSA; EGCg inhibits β -lactamases that degrade methicillin and penicillin, blocks multidrug efflux pumps, and binds to peptidoglycan inhibiting cell wall synthesis. Incubation of MDR MRSA with EGCg remarkably improves the potency of oxacillin against MRSA through time- and dose-dependent synergistic effects. Other tea compounds such as epicatechin and epigallocatechin also show resistance-modifying activity. Aqueous tea extracts can reverse the resistance in MRSA and the tea catechins apparently contribute to this effect.

Crude extracts of some medicinal plants have also been effective in potentiating the activity of commonly used antibiotics against drug-resistant bacteria. Examples include the extracts of *Alium sativum* (garlic), *Zingiber officinale* (ginger), *Syzygium aromaticum* (clove), *Cinnamomum zeylanicum* (cinnamon), *Punica granatum* (pomegranate), *Psidium guajava* (guava), *Mentha piperita* (mint), *Cymbopogon citratus* (lemon grass), *Hibiscus rosa-sinensis* (hibiscus), *Acorus calamus* (sweet flag), *Hemidesmus indicus* (iramusu) and *Plumbago zeylanica* (Ceylon leadwort). With some medicinal plants, the combined crude extracts have been more effective in inhibiting resistance mechanisms than the crude extracts of individual plants alone; examples include the combined extracts of *Aloe vera* (aloe) and *Curcuma longa* (turmeric) and those of *Azadirachta indica* (neem) and *Withania somnifera* (ashwagandha). An aqueous extract of Triphala has demonstrated synergistic activity with oxacillin against MRSA and with gentamicin against MDR *Serratia liquefaciens*, *S. marcescens*, *S. odorifera* biogroup 1, *Proteus* spp., *Klebsiella pneumoniae*, *Enterobacter cloacae* and *Pseudomonas aeruginosa*. Triphala is an indigenous medicinal product composed of dried pericarp of the fruits of the three plants, *Terminalia chebula*, *T. bellirica* and *Embllica officinalis*.

The use of compounds or their combinations involved in plant defense systems, together with common antibiotics, is a powerful strategy to mitigate the problem of antibiotic resistance. To realise this potential, the relevant synergistic interactions should be identified. Conventional procedures require isolation of the defense compounds in plants and subsequent evaluation of antibacterial activity corresponding to all possible combinations of the defense compounds and antibiotics against MDR bacteria. The methods in metabolomics with multivariate data analysis have been suggested as a more practical and convenient approach to identify the synergistic interactions than the conventional procedures. The potent combinations of plant compounds and antibiotics determined from *in vitro* experiments could then be assessed by *in vivo* studies to determine the clinical relevance of such combinations.

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