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Herbal antibiotics: As alternative source of bacterial antibiotics resistance

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Abstract
Current century witness antibiotic resistance is becoming a major challenge to the global health care, particularly in the treatment of infectious diseases. A rational approach to deal with antibiotic resistance problems requires detailed knowledge of the different biological and non-biological factors that affect the rate and extent of resistance development. The dire need of health organizations and pharmaceutical industries all over the world to discover and production of more synthetic antibiotics against the fast growing antibiotics-resistant microorganisms, while there are significant alternative sources of natural antimicrobials from plants with different mode of actions, some of them are employed in traditional medicine for centuries and was found to have competitive effects compared to some commercial antibiotics. The available literature shows the potentiality of phytochemicals as effective antibacterial substances that could set off modern antibiotics and later reduce the bacterial resistance to antibiotics.

Keywords: resistance, antibiotics, phytochemicals

Introduction
Antimicrobial therapy is one of the key therapies used for treatment of infectious diseases and has extremely improved the health aspects of human life since its beginning. World Health Organization stated that the infectious diseases remain the second leading cause of death worldwide (WHO, 2002) [1]. Even with the advancements in this therapy, we still live in an era where incidents of antibiotic resistant infections are tremendously on rise (WHO, 2012) [1]. The significance of the role of antibiotics in nature remains unfounded due to the responses of bacteria through the manifestation of various forms of resistance following the introduction of a new antibiotic for clinical use. The most important factor influencing the emergence and spread of antibiotic resistance is the excessive bacterial exposure to antibiotics (Yap *et al.*, 2014) [2]. Moreover, the fight between man and microbes was began since his manifestation on earth. Fossil records revealed that the human being living sixty thousands years ago in Mesopotamia in city of Iraq, using a medicinal plant *Alcea rosea* L. is commonly known as Hollyhock. (Cowan, 1999) [3], indicating that perhaps the first weapon used by ancient human against illnesses was plants. Man used the antimicrobial drugs against microbes since times immemorial. The development and uses of these drugs against microbes continued throughout civilizations until the modern era. In the present era, the strategy has changed. Scientists relied executively more and more on synthetic and semi-synthetic antibiotics. Although, researchers of Gratia and Dath in 1924, resulted in the discovery of naturally derived actinomycetin from strains of Actinomycetes and some soil microbes that has sources of number of antibiotics since 1940 (Pelczar *et al*., 1986) [4].

The development of antibiotic resistance in pathogenic bacteria has led to transformed wave of interest in exploring the potential of plant-derived antimicrobials as an alternative therapeutic approach to combat microbial infections. Antibiotics constitute a group of chemotherapeutic agents, either may bactericidal or bacteriostatic, which are required for the management and prevention of microbial infections, for e.g., Beta-lactam antibiotics, Macrolide antibiotics, Aminoglycosides, Oxazolidinoes, Quinolones, Lincosamides, Tetracyclines, Sulfa drugs other cyclic peptides (Gilbert and McBain, 2003) [5]. Whereas, prolonged use of antibiotics led to bacterial adaptation, resulting in the development of multi-drug resistance in bacteria and significantly limited the efficacy of antibiotics or treatment failure, hoist alternative strategies to combat microbial infections (Abhinav *etal*, 2014) [6]. It may also result in increased treatment costs as well as the rate of fatalities, and creates even broader infection control problems, spreading resistant bacteria from hospital to community. Antibiotic resistance urges the need of finding the new therapies entity against the multi-drug resistant bacteria. The problem of resistance has been exacerbated by the use of antibiotics in prophylaxis intended to prevent infection before it occurs.

Specious and inopportune use of antibiotics for the treatment of the cold infections and other viral infections, against which they have no effect, this removes the antibiotic sensitive bacteria and allows the development of antibiotic resistant bacteria. However, the use of antibiotics in the feed of poultry and livestock has promoted the spread of antibiotic resistance and has led to the prevalent contamination of meat and poultry by antibiotic-resistant bacteria (Bello, 2016) [7].

As a potential alternative source of solution to the resistance to antimicrobial agents, plant based antimicrobial agents showed full potentiality in fighting bacterial agents with minimal or no resistance to these phytochemicals as documented, probably due to their multiple mechanisms of

action which potentially prevent the selection of resistant strains of bacteria. The significant antimicrobial effect, nontoxic nature, and affordability of these compounds have formed the basis for their wide use as effective antimicrobials and disinfectants in many industrial and clinical applications, particularly as a source for development of novel antibiotics. Medicinal plant products, mainly plants extract, either as pure compounds or as standardized extracts, provide unlimited opportunities for new drug discoveries because of the unmatched availability of chemical diversity (Essawi and Srour, 2000; Aiyegoro and Okoh,2009) [9, 10].

Natural product as alternative source of antimicrobials

Plants are the largest biochemical and pharmaceutical stores ever known on our planet. These living stores are able to generate endless biochemical compounds. These are rich in a numerous variety of secondary metabolites of antimicrobial properties such as saponines, tannins, alkaloids, alkenyl phenols, flavonoids, glycoalkaloids, phorbol esters, sesquiterpenes lactones and terpenoids (Abdallah, 2011; Tiwar and Singh, 2004) [11, 8]. Accordingly, since times immemorial, plants have been resisting the continuous attacks of microorganisms eg. Bacteria and Viruses by producing biochemical defense compound. On the other side, micro-organisms have continued trying to invade these plants by breaking down as many secondary metabolites as much as possible. According to this everlasting battle, plant kingdom develops a vast number of biochemical defense compounds. In a similar way, the conflict between humans and pathogenic microorganisms continues endlessly. As people develop new drugs to fight the disease, those microorganisms develop new ways to strengthen themselves and live longer. However, plants are able to develop new, faster and natural antimicrobials than man-made remedies (Farnsworth *et al*, 1985), and that is explained that plants succeed in its fighting against microbes since millions of years while human failed.

Alkaloids are a group of organic nitrogenous compounds with broad antimicrobial activity, including morphine and codeine. Some alkaloids found in *Callistemon citrinus* and *Vernonia adoensis* have antibacterial activities against *S. aureus* and *P. aeruginosa*. The mechanism of action of aromatic planar quaternary alkaloids such as berberine and harmane is attributed to their ability to intercalate with DNA thereby resulting in impaired cell division and cell death (Bello *et al*., 2016) [7].

Quinones such as anthraquinone from *Cassia italica* possess bacteriostatic effects against pathogenic bacteria such as *Bacillus anthracis*, *Corynebacterium pseudo diphthericum*, and *Pseudomonas aeruginosa* and bactericidal against *Burkholderia pseudomallei*. Hypericin, an anthraquinone from *Hypericum perforatum* was reported by its antimicrobial properties (Kazmi *et al.,* 1994 and Duke, 1985) [16, 17].

Flavonoids are pigmented compounds found in fruits and flowers of plants and mainly consist of flavone, flavanones, flavanols, and anthocyanidins. Flavonoids are also hydroxylated phenolic substances but occur as a C6-C3 unit linked to an aromatic ring. More lipophilic flavonoids may also disrupt microbial membranes, affecting membrane integrity (Thomson, 1978 and Bello, 2016) [19, 7]. Catechins, a flavonoid compounds exhibit inhibitory activity against both Gram-positive and Gram-negative bacteria. These compounds inhibited *in vitro Streptococcus mutans*, *Shigella* and some bacteria. The catechins inactivated cholera toxin in *Vibrio* and inhibited isolated bacterial glucosyl transferases in *S. mutans*, possibly due to complexing activities similar to those observed in quinines (Nakahara *et al*., 1993) [21].

Coumarins substances made up by fused of benzene and α-pyrone rings. Some coumarins like scopoletin and chalcones have been reported as antitubercular constituents of the plant *Fatoua pilosa* (Garcia *et al.,* 2012) [22, 25]. Moreover, phytoalexins, which are hydroxylated derivatives of coumarins, are produced in plants in response to microbial infections. General antimicrobial activity was documented in woodruff (*Galium odoratum*) extracts (Thomson, 1978) [19].

Terpenes are large group of secondary metabolites consisting of five carbon isoprenoid units. qTerpenenes or terpenoids are active against bacteria (Bello, *etal.,* 2016) [7] and reported that 30% of terpenoid essential oil derivatives were active inhibitors of bacterial growth (Chaurasia and Vyas, 1977) [24]. Some terpenoids are methanol, camphor (monoterpenes), farnesol and artemisin (sesquiterpenoids). Sesquiterpenoids are reported to exhibit bactericidal activity against Gram-positive bacteria, including *M. Tuberculosis*. The mechanism of antimicrobial action of terpenoids is not clearly defined, but it is attributed to membrane disruption in microorganisms (Garcia *et al.,* 2012) [22, 25]. Some of the plant depicted in Table (1) presents antimicrobial activity against multidrug resistant strains.

Table 1: Some plant extracts having potential antimicrobial activity against multidrug resistant strains (Abdallah, 2011) [11]

Plant	Name/Type of extract	Susceptible microorganisms	References
Acacia nilotica Allium sativum Cinnamomum zeylanicum	**Ethanolic extract**	***E. coli, Klebsiella pneumonia Candida albicans***	**Khan *et al.*, 2009**
Bosellia papyrifera Commiphora molmol	Methanoilc extract	Meticillin-resistant *Staphylococcus aureus*	Abdallah *et al*., 2009
Cinnamomum cassia	Ethanol extract	Multidrug resistant *Pseudomonas aeruginosa*	Sharma *et al*., 2009
Caesalpinia coriaria	Methanoilc extract	*Klebsiella pneumonia*	Mohana *et al*., 2009
Garcinia mangostana	A-mangostin	Vancomycin-resistant enterococci	Sakagami *et al*., 2009
Psidium guajava	Methanoilc extract	Multidrug resistant *Staphylococcus aureus*	Anas *et al.,* 2008

Conclusion

Constant growth in clinical pharmacology and medicinal chemistry in producing new synthetic antibiotics with structural changes to existing antibiotics, appropriate enzyme targets, against which inhibitors can be developed via molecular research; current global drug development program, may not be able to provide new effective antibiotics in last two to three decades (Boucher *et al.,* 2009) [13]. Nowadays, medicinal plants are predictable to be the future alterative source of new antimicrobials. Recently, phytochemist of the

drug industry are aware of this potential and have introduced screening programs for untapped medicinal plants, particularly from tropical and sub-tropical regions (Hostettmann *et al*, 2000) [15]. The combinations of antibiotics between existing antibiotics, to get promising synergistic benefits is a current therapeutic target (Cottagnoud *et al*., 2000) [14]. Though, the combination among some medicinal plant extracts of antimicrobial potency with some existing antibiotics is of great value, as it may alter the mode of action.

Recently, advancement in methods of isolation, biotechnological, analytical or characterizations, genomics, metabolomics and proteomics are applied in natural product research and give to the advancement of alternative natural antimicrobial agents. Moreover, the global scientific organizations are necessary to build up standard technical guideline for analysis of plant extracts and isolated `compounds, to measure and compare results of the growing researches in this field.

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