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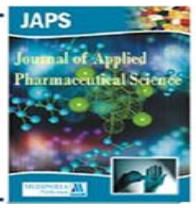

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Plants: An alternative source for antimicrobials

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ABSTRACT

No doubt that antibiotics are a miracle drugs. They stands against various infectious diseases for decades and saved millions of lives. However, the recent failure of antibiotics due to the dramatic emergence of multidrug resistant pathogens and the rapid spread of the new infections, urge the health organizations and pharmaceutical industries all over the world to change their strategy and stop going on the slow growing production of more synthetic antibiotics against the fast growing antibiotics-resistant microorganisms, while there are considerable 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. This review presents the potency of plants as alternative source for antimicrobials.

Key words: Antibiotics, Antimicrobials, medicinal plants, multi-drug resistant, Ethnobotany, Traditional medicine.

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INTRODUCTION

Although this era witness amazing success in development of technology, Science and medicine, but we failed to control the dramatic spread of infectious diseases. WHO stated that the infectious diseases remains the second leading cause of death world wide (WHO, 2002a). Though, The need for new antimicrobial agents is greater than ever.Microbes are exist in earth since million years ago, being one of the oldest creature in this planet. These tiny microorganisms are adapted, developed and survived in this changing nature throughout the eras, while other advanced huge ancient animals and plants perished. Though, microbes considered as one of the most adaptive and successive creatures in nature. These microbes were already-since that time- subjected to antibiotics produced from other microorganisms such as *Penicillium notatum*, as example. And they produces antibiotic resistant mechanisms, naturally (Opalet al, 2000). So, it is not surprising that microbes are developed resistant in the modern era against our synthetic and semi-synthetic antibiotics.

On the other hand, the struggle between man and microbes was began since his appearance on earth. Fossil records revealed that the human being living 60 000 years ago in Mesopotamia (Iraq), using a medicinal plant named Hollyhock (*Alcea rosea* L.) (Cowan, 1999), 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 employment and development of these drugs against microbes continued throughout civilizations until the modern era. In the modern era, the strategy changed. Scientists relied executively more and more on synthetic and semi-synthetic antibiotics. Although, researches of Gratia and Dath in 1924 resulted in the discovery of naturally derived actinomycetin from strains of Actinomycetes and some soil microorganisms that has given us a number of antibiotics since 1940 (Pelczar et al., 1986).

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In 1929, Alexander Fleming isolated antibacterial compounds from *Penicillium sp.*, and he called this antibiotic penicillin, by 1940 penicillin was one of the most famous antibiotics. Many scientists isolated antibiotics from other microorganisms, for example; René Dubos who isolated two antibiotics, gramicidin and tryocidine, from a soil bacterium, *Bacillus brevis* (Pelczar et al., 1986).

Afterwards, interest in this magic drug "antibiotics" increased leading to new waves of synthetic antibiotics. Being the golden era of these remedies. Since the last four decades and up to now, macrolide antimicrobial agents (which were originally isolated from various *Streptomyces* species) have been widely used in the treatment of infections caused by susceptible gram-positive organisms (Auckenthaler et al., 1988). Recently, the global problem of dramatic development of bacterial resistance to synthetic antibiotics has led researchers to consider the use of other natural products with antibiotic actions e.g. medicinal plants.

Interestingly, traditional medicine (including herbal medicine) is currently considered as a rapidly growing health system worldwide, it remains widespread in developing countries and it is increasing greatly in developed countries (WHO 2002). The applications of traditional medicinal plants have been employed as remedy long before the development of western medicine with the advent of science and technology. Though, it could be effective alternative source for many therapeutics, particularly after the recent dramatic failures of antibiotics against multi-drug resistant microorganisms.

HOW FAST ARE MICROBES DEVELPING RESISTANT

Antimicrobial resistance is an immense and serious global challenge and could endanger the lives of future generations. The phenomenon of antibiotic resistance was anticipated by Alexander Fleming, since the discovery of penicillin in 1940s (Levy, 2002).

As author mentioned in the introduction, microbes knew how to develop resistance against antibiotics in nature since million years ago. Now, scientists knows that, When antibiotics are used incorrectly, the target bacteria will directly adapt and develop resistance. Then, with its rapid multiplication, bacteria passes resistant genes through plasmid exchange, leading to an increasing prevalence of multi-drug resistant infections. However, not all microorganisms are equal in inducing resistance against antibiotics, this is related to many factors, such as whether the antibiotic is a concentration or time-dependant killing agent, its effects against the population of bacteria and its duration of the serum concentration in patient (Coates et al, 2002).

Ironically, the misuse of antibiotics by Human, the employment of antibiotics in veterinary practices and the growing presence of antibiotics in water, soil and food are contribute to the problem of antibiotic resistance (Moshirfar et al., 2006).

PREVALENCE OF MULTI-DRUG RESISTANT MICROORGANISMS

Unfortunately, new infectious diseases reveals (e.g. mad cow infections, West Nile viruses) in harmony with coming back of old infections (e.g outbreaks of *E. coli* O157:H7, MRSA, Salmonellas and Tuberculosis). At present most clinical isolates of *S. aureus*, *S. Pyogenes*, *Mycobacterium tuberculosis* are considered as highly resistant to most commercially known antibiotics (Sibnda and Okoh, 2007). In the last decades, prevalence and outbreaks of the multi-drug resistant bacterial strains have been increasingly documented throughout the world. As example, *Streptococcus pneumoniae* (Appelbum, 1992), *Helicobacter pylori* (Ndip et al., 2008; Boyanova, 2009), Haemophilus influenzae (Doern et al., 1986), *Pseudomonas aeruginosa* (Olayinka et al., 2004), *Vibrio cholerae* (Ranjbar et al, 2008), *Tuberculosis* (Ormerod, 2005) *Escherichia coli* (Manges et al., 2006), *Klebsiella pneumoniae* (Webster et al., 2011) and etc. It is believed that this phenomena is encountered with virtually every infectious disease ever known. More recently (2009), an isolate of *Klebsiella pneumoniae* from a Swedish patient of Indian origin' who had been admitted to a hospital in New Delhi, India, were shown to be resistant to most commonly used antibiotics and even to the last discovered antibiotics, carbapenems (Balaram 2010). Moreover, the employment of antibiotics in veterinary practices and the growing presence of antibiotics in water, soil and food are contribute to the problem of antibiotic desistance (Moshirfar et al., 2006). Regretfully, quantitative data regarding the clinical implications of resistance are lacking for many common infections (Metlay and Singer, 2002).

HOW SLOW ARE ANTIBIOTICS LAUNCHED INTO MARKETS

Despite the urgent need for new antimicrobial drugs, the development of these drugs is declining. The United States Food and Drug Administration (FDA) approval of new antibacterial agents decreased by 56% over the past 20 years (1998–2002 vs. 1983–1987) (Spellberg et al, 2004), see (Table 1). In this way, the supply of new effective antibiotics is expected to diminish in the future. additionally, based on the fact that, since 37 years ago, no new classes of antibiotics were discovered and all antibiotics that entered the markets since this period were modification of existing molecules (Coates et al, 2002), it seems there is no obvious hope to new antibiotic generations in the near future.

In economical view, the antibiotics industry faces significant obstacles, Pharmaceutical research and development is highly expensive compared to other drug industries, estimated to be in range of 400 to 800 million U.S. dollars per approved agent (DiMassa et al., 2003), this incurred by the late-stage failure of developmental candidates (Metlay et al, 2006).

PLANTS 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. In their living, human and animals are using only a small portion (1 to10%) of plants available on Earth (250,000 to 500,000 species) (Borris, 1996, Cowan, 1999).

Table 1. History of antibiotics approach in the US (source Shlaes, 2010).

New antibiotic class	Year approved
Sulfonamides	1935
Penicillin	1941
Aminoglycosides	1944
Cephalosporins	1945
Chloramphenicol	1949
Tetracyclines	1950
Macrolides/Lincosamides/Streptogeamins	1952
Glycopeptides	1956
Rifamycins	1957
Nitroimidazoles	1959
Quinolones	1962
Trimethoprim	1968
Oxazolidinones	2000
Lipopeptides	2003

Although, plants have many other defense mechanisms against micro and macro organisms, but in this review we focus only on their chemical products of important pharmaceutical characteristics (secondary metabolites). Medicinal plants are rich in a numerous variety of secondary metabolites of antimicrobial properties such as saponines, tannins, alkaloids, alkenyl phenols, glycoalkaloids, flavonoids, sesquiterpenes lactones, terpenoids and phorbol esters (Tiwari and Singh, 2004, Lewis and Ausubel, 2006). Here, studies should correlated between the plant extract of antimicrobial activity and its major secondary metabolites. Accordingly, since times immemorial, plants have been resisting the continuous attacks of microorganisms (Parasites, fungi, Bacteria and Viruses) by producing endless secondary metabolites. On the other side, micro-organisms have continue 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 develops new ways to strengthen themselves and live longer. However, plants are able to develop new, faster and natural antimicrobials and than man-made remedies (Fransworth et al, 1985), and that is explaining why plants succeed in its fighting against microbes since millions of years while human failed. Historically, The ancient civilizations considered plants as the main source of new leads for antimicrobial remedies and pharmaceutical development (McChesney et al, 2007). The first ancient record written, on hundreds of Sumerian clay tablets in cuneiform, are from Mesopotamia (Iraq) dated from about 2600 BC. Egyptian medicine dates from about 2900 BC and Egyptian pharmaceutical record “Ebers Papyrus” dating from 1500 BC; which documented over 700 drugs, mostly plants (Newman et al., 1999). These ancient medical knowledge have been transferred to us in what known today as traditional medicine (Fransworth, 1993). And until 1990's , approximately 80% of all remedies were produced from roots, barks and leaves of plants (McChesney et al, 2007).

Even after the antibiotic era and till now, many effective drugs traded globally were from plant origin such as Atropine, Ephedrine, Digoxin, Morphine, Quinine, Reserpine and Tubocurarine (Gilani and Atta-ur-Rahman, 2005). Nowadays, a greater emphasis has been given towards the researches on traditional medicine, particularly medicinal plants that deals with microbial diseases management. As antimicrobials, based on ethno-botanical data, considerable number of studies have been conducted on the antimicrobial activity of medicinal plants and showed promising potency against multi-drug resistant microorganisms after the current antibiotics failed to eradicate them. Table (2) presents some of these plants. However, it is impossible to include all the plant of potent antimicrobial activity in this review, but an idea will be given towards discovery of new plant-derived antimicrobials.

Table2. Some promising plants having antimicrobial activity against multidrug resistant strains.

Plant	Name/Type of extract	Susceptible microorganism	Reference
Garcinia mangostana	alpha-mangostin	vancomycin-resistant enterococci (VRE)	Sakagami et al., 2005
Caesalpinia coriaria	Methanolic extracts	Klebsiella pneumoniae	Mohana et al., 2008
Psidium guajava	Methanolic extracts	MDR Staphylococcus aureus	Anas et al., 2008
Commiphora molmol and Boswellia papyrifera	Methanolic extracts	methicillin-resistant Staphylococcus aureus (MRSA)	Abdallah et al., 2009
Centratherum punctatum	Methanolc and ethyl acetate extracts	MDR-Acinetobacter baumannii	Pawar and Arumugam, 2011
Pelargonium sidoides	Ethanolic extracts	Aspergillus niger	Mativandlela et al, 2006
Thonningia sanguinea	Aqueous extract	ESBL-producing E. coli	N’guessan et al., 2007
Acacia nilotica, Cinnamomum zeylanicum and Syzygium aromaticum	Ethanolic extracts	Escherichia coli, Klebsiella pneumoniae and Candida albicans.	Khan et al., 2009
Allium sativum	Ethanolic extract	Extensively drug-resistant M. tuberculosis (XDR-TB)	Hannan et al., 2011
Cinnamomum cassia	Ethanol extract	multi-drug resistant Pseudomonas aeruginosa	Sharma et al., 2009
Prosopis juliflora	Alkaloid fraction	Acinetobacter	Singh et al., 2011

THE FUTURE

Despite progress in pharmacology and conventional chemistry in producing new synthetic antibiotics, such as Structural changes to existing antibiotics, finding suitable enzyme targets against which inhibitors can be developed via genome research; current global drug development program, may not be able to provide new effective antibiotics in 10 to 20 years (Boucher et al, 2009). Though, medicinal plants is expected to be the future alterative source of new antimicrobials. Recently, some representatives of the pharmaceutical industry are aware of this potential and have introduced screening programs for medicinal plants, particularly from tropical regions (Hostettmann et al., 2000). The antibiotic combinations between existing antibiotics of synergistic benefits is a current new approach (Cottagnoud et al.,

2000). However, the combination between some medicinal plant extracts of antimicrobial potency with some antibiotics is of great value, as it may alter the mode of action.

Fortunately, advanced methods of analytical, biotechnological, genomics, proteomics and metabolomics are nowadays applied in medicinal plant research and contribute to the advancement of alternative natural antimicrobial. Also, the global scientific organizations are required to develop standard technical guideline for analysis of plant extracts, in order to be able to measure and compare results of the growing researches in this field.

CONCLUSION

The 21st century witnesses major global health care problem which threaten the entire human life, the appearance and prevalence of multi-drug resistant microorganisms. We should understand that the battle against these microorganisms is never ending, but we can beat them by changing our strategy and returning back to nature, using active ingredients from plants that survived against microbes since millions of years. Currently, after the fall of antibiotics, considerable number of studies have been conducted on antimicrobial activities of selected medicinal plants against MDR or non-MDR microorganisms. However, little of them are attracting of pharmaceutical companies. Serious interests should be focusing on extracting drugs from medicinal plants, particularly those mentioned in the traditional and folk medicine. Hopefully, the area of antimicrobial research based on medicinal plant might be prove fruitfully.

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