Journal of Medicinal Plants Research Vol. 3(13), pp. 1147-1152, December, 2009
Available online at http://www.academicjournals.org/JMPR
ISSN 1996-0875 © 2009 Academic Journals

Review

Use of bioactive plant products in combination with standard antibiotics: Implications in antimicrobial chemotherapy

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Accepted 23 October, 2009

Nowadays, multiple antibiotic resistance by disease-causing microorganisms are a major public health problem. Antimicrobial compounds from plants have been found to be synergistic enhancers in that though they may not possess any antimicrobial properties alone, but when used concurrently with standard drugs they enhance the activity of the drug. The synergistic effect of the association of antibiotic and plant extracts against resistant pathogens leads to new choices for the treatment of infectious diseases. Also synergy between bioactive plant product and antibiotics will confront problems of toxicity and overdose since lesser concentrations of two agents in combination are required, due to these reasons, there is need therefore, for continuous exploration of multidrug resistance modulating principles from plants sources.

Key words: Medicinal plants, infectious diseases, synergism, resistance, antimicrobial, chemotherapy.

INTRODUCTION

The plant kingdom has served as an inexhaustible source of useful drugs, foods, additives, flavouring agents, lubricants, colouring agents and gums from time immemorial (Parikh et al., 2005). The therapeutic power of herbs had been recognized since creation of the universe and botanic medicine is one of the oldest practiced professions by mankind (Kambizi and Afolayan, 2001). Medicinal plants have been found useful as antimalaria, antisickling, anti-helminthic, anti-microbial, anti-convultant, anti-hypertensive and anti-schistosomal (molluscicidal) agents (Prescott et al., 2002). The medicinal actions of plants are unique to particular plant species or groups, consistent with the concept that the combination of secondary products in a particular plant is taxonomically discrete (Parikh et al., 2005). Hugo and Russell (2003) asserted that 80% of the populations in developing countries use medicinal plants and as a result of the importance of herbs in the lives of people, the World Health Organization devoted 27 centers, out of 915 collaborating centers worldwide, for traditional medicine (WHO 2001).

The clinically useful antibiotics now in use have major setbacks. Apart from the narrow spectrum of anti-microbial activity many of them have been found to be neurotoxic, nephrotoxic, ototoxic or hypertensive and few others cause severe damage to the liver and cause bone-marrow depression (Chong and Pagano, 1997) and importantly; infectious pathogens have developed resistance to all known antibiotics.

Betoni et al. (2006) demonstrated that plants either contain antimicrobials that can operate in synergy with antibiotics or posses compounds that have no intrinsic antibacterial activity but are able to sensitize the pathogen to a previously ineffective antibiotic. Synergism is a positive interaction created when two agents combined and exert an inhibitory effect that is greater than the sum of their individual effects. Combination therapy can be used to expand the antimicrobial spectrum, to prevent the emergence of resistant mutants, to minimize toxicity and to obtain synergistic antimicrobial activity, it could be an alternative to monotherapy for patients with invasive infections that are difficult to treat, such as those due to multi-resistant species and for those

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who fail to respond to standard treatment (Kamatou et al., 2006). Antimicrobial compounds used in combination might promote the effectiveness of each agent, with efficacy being achieved using a lower dose of each drug. Pharmacological benefits would accrue, with one drug clearing infection from one body system while the other clears it from a different site (Williamson, 2001). In addition, synergism in antimicrobials could be utilized in an attempt to prevent or delay the emergence *in vivo* of resistant populations of the pathogenic organisms (Lupetti et al., 2002).

Abundant medicinal plants have been used in many forms over the years to treat, manage or control man's ailments (Prescott et al., 2002), therefore any effort to further explore the medicinal or natural products from man's botanical flora towards improving health care delivery deserves attention. This article presents an overview of the use of bioactive plant products in combination with standard antibiotics and its implications in antimicrobial chemotherapy.

HIGHLIGHTS ON SOME ANTIMICROBIAL PHYTOCHEMICALS

The "phyto" of the word phytochemicals is derived from the Greek word *phyto*, which means plant. Therefore, phytochemicals are defined as bioactive nonessential plant compounds in fruits, vegetables, grains and other plant foods that have been linked to reducing the risk of major chronic diseases. However, more and more convincing evidences suggest that the benefits of phytochemicals in plants may be even greater than is currently understood (Ames and Gold, 1991). Phytochemicals can be grouped as carotenoids, phenolics, alkaloids, nitrogen-containing compounds and organosulfur compounds. The most investigated phytochemicals are the phenolics and carotenoids (Ames and Gold, 1991).

Plants have an almost infinite ability to produce aromatic substances, most of which are phenols or their oxygen-substituted derivatives (Kambizi and Afolayan, 2001). Most are secondary metabolites, of which at least 12,000 have been isolated, a number projected to be less than 10% of the total (Van Wyk et al., 1997). In many cases, these substances serve as plant defense mechanisms against predation by microorganisms, insects and herbivores. Some of the compounds like, terpenoids- give plants their odors and, quinones and tannins are responsible for its pigmentations. Many compounds are responsible for plant flavor (e.g., the terpenoid capsaicin from chili peppers) and some of the same herbs and spices used by humans to season food yield useful medicinal compounds (Pecere et al., 2000). The isoquinoline alkaloid emetine from the underground part of *Cephaelis ipecacuanha*- has been used for many years as an amoebicidal drug as well as for the treatment of abscesses due to the spread of *Entamoeba histolytica* infections (Iwu et al., 1999).

Another important compound of plant origin with a long history of use is quinine- an alkaloid which occurs naturally in the bark of *Cinchona* trees. Apart from its continued usefulness in the treatment of malaria, it can also be used to relieve nocturnal leg cramps (Iwu et al., 1999). Similarly plants have made important contributions in the areas beyond anti-infective, such as cancer therapies. Examples include the antileukaemic alkaloids, vinblatine and vincristine, which were both obtained from the Madagascan periwinkle (*Catharanthus roseus* syn. *Vinca roseus*) (Nelson, 1982). Other therapeutic compounds from plants include taxol, homoharringtonine and several derivatives of camptothein, which are all anti-cancer. A well known benzylisoquinoline alkaloid, papaverine, has been shown to have a potent inhibitory effect on the replication of several viruses including cytomegalovirus, measles and Human Immunodeficient Virus (HIV) (Turano et al., 1989).

Atropisomeric naphthyl isoquinoline alkaloid dimmers, michellamines A, B and C were isolated from *Ancistrocladus korupensis*, and the three compounds showed potential anti-HIV activities. Kambizi and Afolayan (2001) isolated three compounds from *Aloe ferox,* a plant traditionally used for the treatment of sexually transmitted infections. These compounds includes; 1, 8 – dihydroxy – 3 – hydroxymethyl - 9, 10 - anthracenedione (aloe - emodin); 1, 8 – dihydroxy – 3 – methyl - 9, 10 - anthracenedione (chrysophanol), and 10 – C – b – D – glucopyranosyl - 1, 8 – dihydroxy – 3 –hydroxymethyl - 9 - anthracenone (aloin A), and these three compounds exhibited antibacterial activities against *Bacillus subtilis, Staphylococcus epidermidis, Shigella sonnei* and *Escherichia coli.*

Aloe emodin has also been reported to be an anticancer agent with selective activity against neuroectodermal tumors (Pecere et al., 2000) and generally, both aloe-emodin and aloin A have been associated with other biological and medicinal activities that include laxative action (Van Wyk et al., 1997). Mangena and Muyima (1999) reported antimicrobial activities of essential oils in *Artemisia afra, Pteronia incana* and *Rosmarinus officinalis*. All these plants have been used in the treatment of common cold, diabetes mellitus, bronchial complaints and stomach disorder. The essential oils from these plants were reported to contain such components as Bornylacetate, Camphene, Camphor, 1-8-Cineole, o-Cymene, p-Cymene, Limonene + 1, 8 Cinole, Mycerene, α-Pinene, β-Pinene, α-Thujone, β-Thujone and Verbone to mention a few.

Dilika et al. (2000) also reported the antibacterial activities of linoleic and oleic acids isolated from the dry leaf of *Helichrysum pedunculatum,* a plant used to treat wound acquired during male circumcision rites in the Eastern Cape of South Africa and this study has been corroborated by Aiyegoro et al. (2008a). Two lipophilic

Table 1. Some major classes of antimicrobial compounds from medicinal plants and their mechanisms of actions (Cowan, 1999).

Class	Sub-class	Example(S)	Mechanism
Phenolics	Simple phenols	Catechol Epicatechin	Substrate deprivation Membrane disruption
Phenolics	Phenolic acid	Cinamic acid	Membrane disruption
Phenolics	Quinones	Hypericin	Bind to adhesins, complex with cell wall and inactivate enzymes.
Phenolics	Flavonoids	Chrysin	Bind to adhesins
Phenolics	Flavones		Complex with cell wall
Phenolics		Abyssinome	Inactivate enzymes, inhibit HIV reverse transcriptase
Phenolics	Tannins	Ellagitannins	Bind to proteins and adhesins, enzyme inhibitor, substrate deprivation, complex with cell wall, membrane disruption, metal ion complexation.
Phenolics	Coumarins	Warfarin	Interaction with eukaryotic DNA (antiviral activity).
Terpenoids, Essential oils		Capsaicin	Membrane disruption
Alkaloids		Berberine, Piperine	Intercalate into cell wall and/or DNA.
Lectins and Polypeptide		Mannose-specific agglutinin	Block viral fusion or adsorption
Lectins and Polypeptide		Fabatin	Form disulfide bridge
Polyacetylenes		8S-Heptadeca-2(z), 9(z)-diene-4, 6-diyne-1, 8-diol	Membrane disruption

phytoalexins: α-amyrin and β-amyrin that have anti-tuberculosis and generally antibacterial activities have also been isolated from *Helichrysum kraussii* (Prinsloo and Meyer, 2006). Many more compounds with antibacterial potentials from different species of plants have been isolated (Park et al., 2008; Tsao and Yin, 2001; Iwu et al., 1999; Smith et al., 2007). It is also notable that, more novel antibacterial compounds have been isolated from plants and their structures elucidated on daily basis but have not been documented in any pharmacopeia.

Many plant extracts clearly demonstrate antibacterial properties, although the mechanistic processes are poorly understood. Cowan (1999) describe the mechanism of action of various classes of active components of medicinal plants (Table 1).

ANTIMICROBIAL SYNERGISMS IN PLANTS PRODUCTS

Plants antimicrobials have been found to be synergistic enhancers in that though they may not have any antimicrobial properties alone, but when they are taken concurrently with standard drugs they enhance the effect of that drug (Kamatou et al., 2006). The synergistic effect from the association of antibiotic and plant extracts against resistant bacteria leads to new choices for the treatment of infectious diseases. This effect enables the use of the respective antibiotic when it is no longer effective by itself during therapeutic treatment (Nascimento et al., 2000). The application of synergistic principle is evident in commercial preparations for the treatment of various infections (e.g. the antibiotic Augmentin). Traditional healers often use combinations of plants to treat or cure diseases (Kamatou et al., 2006). One notable example from the ethnobotanical literature is the concomitant administration of various *Salvia* species with *Leonotis leonurus* to treat various infections (Masika and Afolayan, 2003).

Kamatou et al. (2006), confirmed the existence of synergism between *Salvia chamelaeagnea* and *L. leonurus*, when these two plants were combined together against *Bacillus cereus, S. aureus*, *E. coli* and *Klebsiella pneumoniae*. They as well reported synergism when the tincture of *L. leonurus* and various *Salvia* species were combined together against influenza. Boik (2001) conducted a large number of combination studies using various natural substances and their results strongly suggested that when used in combination, natural substances can produce synergistic effects. It is thought that phenolic compounds such as flavonoids may increase the biological activity of other compounds by synergistic or other mechanisms (Williamson, 2001). Experimental evidence of synergistic actions between plants was also shown in a clinical study on the formulation of Chinese herbs used to treat eczema (Williamson, 2001).

COMBINATIONS OF BIOACTIVE PLANT PRODUCTS AND DIFFERENT CLASSES OF ANTIBIOTICS WITH SPECIFIC MECHANISM OF ACTION

In the treatment of drug resistant infections, combinations of antibiotics have often been used as this takes advantage of different mechanisms of action. The use of

antimicrobial agents displaying synergy is one of the well established indications for combination antimicrobial therapy (Rybak and McGrath, 1996). Combinations of antimicrobials that demonstrate an *in vitro* synergism against infecting strains are more likely to result in successful therapeutic result. Thus, evidence of *in vitro* synergism could be useful in selecting most favorable combinations of antimicrobials for the practical therapy of serious bacterial infections (Hooton et al., 1984).

It has been proven that, in addition to the production of intrinsic antimicrobial compounds, plants also produce Multi-Drug Resistance (MDR) inhibitors which enhance the activity of the antimicrobial compounds (Stermitz et al., 2000a). Tegos et al. (2002) showed that the activity of presumed plant antimicrobials against gram positive and gram negative organisms was significantly enhanced by synthetic MDR inhibitors of MDR efflux proteins. The findings provided a basis that plants can be prospective sources of natural MDR inhibitors that can modulate the performance of antibiotics against resistant strains.

The screening of crude plant extracts for synergistic interaction with antibiotics is expected to provide ways for the isolation of MDR inhibitors. The ability of crude extracts of plants to potentiate the activity of antibiotics has been observed by some researchers (Aiyegoro et al., 2008b, 2009; Sibanda and Okoh, 2008; Betoni et al., 2006; Darwish et al., 2002; Isogai et al., 2001; Ahmad and Aqil, 2006), and it is anticipated to form the basis for the bioassay directed fractionation of potential resistance modulators from plants. Darwish et al. (2002) carried out a study on some Jordanian plants and they demonstrated that the efficacy of the antibiotics, gentamycin and chloramphenicol against *S. aureus* were reportedly improved by the use of plant materials. Ahmad and Aqil (2006), also reported that crude extracts of Indian medicinal plants demonstrated synergistic interaction with tetracycline and ciprofloxacin against extended spectrum β-lactamase (ESβL)-producing multidrug-resistant enteric bacteria. Betoni et al. (2006) also observed synergistic interactions between extracts of Brazilian medicinal plants and eight antibiotics on *S. aureus.* The use of *Catha edulis* extracts at subinhibitory levels, has been reported to reduce the Minimum Inhibitory Concentration (MIC) values of tetracycline and penicillin G against resistant oral pathogens, *Streptococcus oralis*, *Streptococcus sanguis* and *Fusobacterium nucleatum* (Al- hebshi et al., 2006).

A number of compounds with an *in vitro* activity of reducing the MICs of antibiotics against resistant organisms have also been isolated from plants. Polyphenols (epicatechin gallate and catechin gallate) have been reported to reverse beta-lactam resistance in Methicillin Resistant *S. aureus* (MRSA) (Stapleton et al., 2004). Diterpenes, triterpenes, alkyl gallates, flavones and pyridines have also been reported to have resistance modulating abilities on various antibiotics against resistant strains of *S. aureus* (Marquez et al., 2005; Smith et al., 2007; Shibata et al., 2005; Oluwatuyi et al., 2004).

The synergies detected in these studies as enumerated above were not specific to any group of organisms or class of antibiotics. This suggests that plant crude extracts is a blend of compounds that can enhance the activity of different antibiotics. Plants have been known to contain myriads of antimicrobial compounds (Iwu et al., 1999) such as polyphenols and flavonoids. The antimicrobial and resistance modifying potentials of naturally occurring flavonoids and polyphenolic compounds have been reported in other studies such as Cushnie and Lamb (2005), Sato et al., (2004).

Some of these compounds like polyphenols have been shown to exercise their antibacterial action through membrane perturbations. This disruption of the cell membrane coupled with the action of beta-lactams on the transpeptidation of the cell membrane could lead to an enhanced antimicrobial effect of the combination (Esimone et al., 2006). It has also been revealed that some plant derived compounds can improve the *in vitro* activity of some peptidoglycan inhibiting antibiotics by directly attacking the same site (that is, peptidoglycan) in the cell wall (Zhao et al., 2001).

While the above explanations may account for the synergy between the extracts and beta-lactam antibiotics that act on the cell wall, it might not apply in the case of the observed synergy with other classes of antibiotics with different targets such as tetracyclines, erythromycin, ciprofloxacin and chloramphenicol. Bacterial efflux pumps are responsible for a considerable level of resistance to antibiotics in pathogenic bacteria (Kumar and Schweizer, 2005). Some plant derived compounds have been observed to augment the activity of antimicrobial compounds by inhibiting MDR efflux systems in bacteria (Tegos et al., 2002). 5'-methoxyhydnocarpin is an example of an inhibitor of the NorA efflux pump of *S. aureus* isolated from *Berberis fremontii* (Stermitz et al., 2000b). Such compounds are likely to be broad spectrum efflux inhibitors considering that the synergistic effect of the extract was observed on both gram positive and gram negative organisms as well as in combination with, cell wall inhibiting and protein synthesis inhibiting antibiotics. Importantly, some broad spectrum efflux pump inhibitors have been isolated from some plants. Smith et al. (2007) reported one efflux inhibitor (ferruginol) from the cones of *Chamaecyparis lawso-niana*, which inhibited the activity of the quinolone resistance pump (NorA), the tetracycline resistance pump, (TetK) and the erythromycin resistance pump, (MsrA) in *S. aureus*.

PERSPECTIVES

Traditionally used medicinal plants have received the attention of the pharmaceutical and scientific communities. This involves the isolation and identification of the secondary metabolites produced by the plants and used as the active principles in medical preparations (Taylor et al., 2001). Historically, many plant oils and extracts, such

as tea tree, myrrh and clove, have been used as topical antiseptics, or have been reported to have antimicrobial properties. It is important to scientifically investigate those plants which have been used in traditional medicines as potential sources of novel antimicrobial compounds. Also the resurgence of interest in natural therapies and increasing consumer demand for effective, safe, natural products means that quantitative data on plant oils and extracts are required.

The primary benefits of using plant derived medicines are that they are relatively safer than synthetic alternatives, offering profound therapeutic benefits and more affordable treatment (Van Wyk and Gericke, 2000). Plants based antimicrobials represent a vast untapped source for medicine. Continued and further exploration of plant antimicrobials needs to occur because plant based antimicrobials have enormous therapeutic potentials. They are effective in the treatment of infectious diseases while simultaneously mitigating many of the side effects that are often associated with synthetic drugs. Various reports have documented the enhanced antimicrobial activities (that is, synergistic potentials) of standard antibiotics in combinations with plant extracts even when the organisms are no more susceptible to the drug.

Synergistic interactions are of vital importance in phytomedicine, to explain the efficacy of apparently low doses of active constituents in an herbal product. This concept, that a whole or partially purified extract of a plant offers advantages over a single isolated ingredient, also underpins the philosophy of herbal medicine. Both literature reports and ethnobotanical records indicate a general consensus on the use of antimicrobially active medicinal plants to provide cheaper drugs that may complement existing supplies from orthodox medicine in the Primary Health programme and/or provide novel or lead compound that may be employed in controlling infections in our communities (Betoni et al., 2006).

Conclusion

With the relative absence of new antimicrobials coming to market and with the new threats arising from the microorganisms, the number of drug options leaves us perilously close to none or only a single effective agent for some life-threatening infections. Plants, the sleeping giants of pharmaceutical industry, are an inexhaustible source of natural drugs that may be employed in combating ailments and inconveniences resulting from microbial attacks. Assessing the therapeutic potentials of plants from the traditional African system of medicine could insight us as to how best these plants can be used in the treatment of diseases, especially, when the synergistic prowess between plants and standard antibiotics is optimally resourced. An important aspect of the research focus of our laboratory involves definite studies of the antimicrobial synergistic potentials of South African medicinal plants. The search for more natural antimicrobial substances is an ongoing exercise.

ACKNOWLEDGEMENT

We thank the National Research Foundation of South Africa for financial support.

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