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Review Article

HARMONY OF PHYTOCHEMICALS AND ANTIBIOTICS: A BOON IN ANTIMICROBIAL THERAPY

***Bezalwar P.M[1]., Patil S.P[2] and Charde V.N[3]**

[1]Department of Microbiology, Chintamani College of Arts and Science, Gondpipri, Dist- Chandrapur (MS), India
[2]Department of Botany, Taywade College, Mahadula-Koradi, Dist-Nagpur (MS), India, 441 111
[3]Department of Microbiology, Taywade College, Mahadula-Koradi, Dist-Nagpur (MS), India, 441 111

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ABSTRACT

Plants contains bountiful of potentially useful constituents for the development of novel therapeutic agent, hence in recent years drug development in phytomedicine has gained considerable interest. With the emergence of MDR pathogens and insufficient treatment strategy with antibiotic, investigators turned eye in search of alternative potential approach for treatment. Phytochemicals is a unified and unique complex of natural components having therapeutic efficacy. Biological activity of phytochemical is associated with its chemistry. It elaborates the development of natural products, combining it with modern antibiotics to confer its action against MDR pathogens. Present review has been aimed to summarize past practices and latest issues of medicinal plants and its phytoconstituents in medical microbiology against MDR pathogens. It also deals with vast ancient knowledge and its diverse applications, and rejuvenation of therapy with synergistic action of antibiotics and phytochemicals, and its mechanism of action.

INTRODUCTION

The medicinal potentials of plants have long been recognized and to date plants remain the main source of drugs in the traditional medicine. Plants with curative potentials are known as medicinal plants and have been employed in the treatment of various ailments, and even poisonous properties of phytochemicals were used since pre-historic times for the control of disease causing agents and their vectors (Ghaleb *et al*., 2010, Olgica *et al*., 2009). Various plants and their extracts have been exploited for the treatment requiring antimicrobial activity. Since long, honey is being used as one of the popular natural antimicrobial substances, especially for throat infections (Rafa't and Jawad, 2011, Odunbaku and Ashidi, 2012). Most of the herbs have been employed in the traditional herbal medicine exclusively for curative purposes while others serve asfood, condiments in food and drugs to control pest, rodents, insects, etc (Hassain, 2002). Some herbs serve as food as well as medicine such as *Treculia africana* and other species of *Treculia* (Ogbonnia *et al*., 2008, Maryam *et al*., 2010).

Morphine was separated from *Papaver somniferum* L. (Opium) and its structure was studied in 1804 although earlier benzoic acid was isolated from plants in 1560 (Maryam *et al*., 2010). Since then plenty of drugs from plants have been discovered but less than 100 of drugs with defined structure are in use today. In western medicine tentatively 55 or more drugs are being widely employed. Some drugs with defined structure such asaspirin, atropine, artimesinin, colchicine, digoxin, ephedrine morphine, physostigmine, pilocarpine, quinine, quinidine, resperine, taxol, tubocurarine, vincristine and vinblastine are derived from medicinal plants (Gudrun ulrich-merzenich *et al*., 2010, UNESCO (1996)).

In the survey of WHO, IHO, almost 70-80% populations living almost solely on conventional medicine for their basic health care needs and nearly 61% of drugs marketed worldwide can be outlined to natural products. Natural product always considered a first choice in the global market. Abundance and availabilities have enforced in the development of native and

Corresponding author:* **Bezalwar P.M
Department of Microbiology, Chintamani College of Arts and Science, Gondpipri, Dist- Chandrapur (MS), India

regional therapy. Red ginger was a native plant to Southeast Asia which had been used in traditional Indian and Chinese medicine for centuries to strengthen gastric functions and to treat a wide range of gastro intestinal (GI) and gastric infection caused by *Helicobacter pylori* (HP) using aqueous ginger extract orally (Nahed *et al*., 2010, Tambekar and Khante, 2010). Likewise, Melghat forest (Amravati district, Maharashtra State, India) also preserves innumerable valuable medicinal plants which are being used traditionally without any documentation. Korkus, Bhumka, or Bhagats are few traditionally used plants used by local population for the treatments of diarrhea, dysentery, stomach ache, and any other enteric disorder but their antibacterial potential was not documented (Hemraj and Anil, 2012). Out of 250'000- 500,000 estimated plant species, only few percentage have been investigated for phytochemical analysis and the fraction of them are investigated for biological or pharmacological screening. Compound of natural or synthetic origin has been the source of innumerable therapeutic agents. A broad range of medicinal plants is used to get different formulations which hold different medicinal properties against different pathogens. Although hundreds of plants species have been tested for antimicrobial properties, the majority of these have not been adequately evaluated (Osman *et al*., 2005, Isam *et al*., 2009).

Invention of an antibiotic made a landmark contribution in the field of medical science because of high reactive value and early response; antibiotics catch population's interest in its use. Genetic engineering and advanced industrial technology increased the market demand. A major problem encountered with antibiotics in clinical use is drug resistance, which mostly leads to treatment failure. Different classes of antibiotics and modified antibiotics have been introduced. The extensive use of antibiotics in the treatment of bacterial infections has led to the emergence and spread of resistant strains. Frequent use of effective first-line drugs now lost their clinical efficacy towards most common bugs and treatment of such bugs shifted to second-line and third-line antibiotics that are often more expensive with numerous side effects. It has been nicknamed as 'superbug' by clinicians because of its rapid adaptive resistance through several mechanisms. Past records over study of antibiotic resistance shows that resistant strains often appear a few years after the first clinical use of any antibiotics (Vidal *et al*., 2012). Microorganisms have developed several mechanisms that confer them with antibiotic resistance property. These mechanisms can chemically modify the antibiotic, render it inactive through physical removal from the cell, or modify the target site so that it is not recognized by the antibiotic. They exhibit concentration-dependent bactericidal activity and intermittent doses overcome bacterial adaptive resistance (Olufunmiso and Anthony, 2013).

The present review has mainly highlighted the use of the ethnomedicinal plants against drug resistant bacteria as a source of bioactive compounds especially anti bacterially active and synergistically active plant derived products & antibiotics. Potential Indian medicinal plants with such activity have also been acknowledged. It is interesting to scrutinize that plant derived products with antibiotics exhibit broad spectrum antibacterial activity showed effective almost equally both against drug resistant and drug sensitive bacteria or decreasing virulence and pathogenicity against such super-bug. Present review also deals with the particular responsible phytochemical along with its specific mode of actions. Toxicity approach of phytochemicals also been tried to include with optimum extent.

Highlights on medicinal plants and phytochemicals

The increased prevalence of antibiotic resistance renders the current antimicrobial agents insufficient to control, at least, some bacterial infections (Himal, 2010; Shyamapada, 2010). Searches for substances with potent antimicrobial activity are frequent and used since past. Medicinal plants have been considered interesting as they are frequently used as remedies for many infectious diseases with surprisingly positive results (Singh, 2012).

Fruits of *Xylopia aethiopica* contain cardiac glycosides flavonoids, phlobatannins, tannins, phenol, anthraquinones, saponin and steroids which are active against ampicillin and gentamycin resistant *P. aeruginosa*, *B. subtilis* and *S. aureus* but administration of *X.aethiopica* with conventional antibiotics is still under contradiction because of varied results *in vivo* (Ilusanya, 2012). Phytochemical study of leaf extracts of *Senna obtusifolia* (L) revealed that the extracts contains phytoconstituents; saponins, tannins, alkaloids, flavonoids including other bioactive components like thiocynate, nitrate, chloride and sulphates, beside are known to be bactericidal, pesticidal or fungicidal in nature thus conferring the anti-microbial property to plants (Doughari *et al*., 2008, Cowan, 1999). Different bioactive compounds such as phenols, flavonoids, tannins, coumarins, alkaloids in *Clinopodium vulgare* confer its antimicrobial property. Phenols and flavonoids significantly contribute to the overall antibacterial activity against *B. subtilis* and *Klebsiella* which is resistant to gentamicin and cephalexin (Olgica *et al*., 2011). Chromatographic analysis of green and black tea extract reported the presence of polyphenols, gallic acid. Caffeine is the most abundant constituents of black tea, whereas epigallocatechin (EGC) and epigallocatechin gallate (EGCG) were the prominent polyphenols in green tea (Tirang *et al*., 2007). *Z. multiflora, R. officinalis, Artemisia* genus, *P. graveolens, Lavandula stoechas, Z. majdae, P. abrotanoides, D. anethifolia, Myrtus communis* (myrtle), *Ferula gummosa* (*Apiaceae*), and *Oliveria decumbens* essential oil showed microbicidal activity against bacteria and fungi (Mohaddese, 2013). The mixture of two plants, *Solanum trilobatum and Ocimum sanctum* extracts have antimicrobial activities against *Aeromonas hydrophila*, a bacterial pathogen (Subeena and Navaraj, 2012).

Phytochemical screening of mature leaf extracts of *Vigna marina* revealed the presence of biologically active substances such as alkaloids, steroids, triterpenoids and flavonoids (Bandaranayake, 1995, Abeysinghe *et al*., 2003). In addition to these phytochemical groups; tannins, anthocyanins, polyphenols, coumarins and essential oils is also a potent antimicrobial agent (Abeysinghe and Wanigatunge, 2006). In the study of antimicrobial property of caffeine and its metabolites can be used against *Staphylococcus aureus* and *Pseudomonas aeruginosa.* Methylxanthines showed antibacterial properties against *Staphylococcus aureus* but methylxanthines plus levofloxacin have antagonistic effects (Taylor).

E. coli resistant to ciprofloxacin, levofloxacin, norfloxacin, nalidixic acid, gentamicin, amikacin, sulbactam/ampicillin which was treated with phytoconstituents of clove and active compound in clove was identified as eugenol when studied with HNMR and IR spectrum and have pronounced antiseptic, antimicrobial and anesthetic properties (Ghaly *et al*., 2009). Plants, *Euphorbiahirta* and *Phyllanthus amarus* prompted for *in-vitro* antibacterial activity and have synergistic effects of crude methanolic extracts of the plants with antibiotics against *Escherichia coli, Salmonella typhi* and *Klebsiella pneumonia* isolated from patients of diarrhea, dysentery, typhoid fever were effective, phytochemical analysis of the crude extracts revealed the presence of alkaloids, tannins, saponins, cardiac glycosides, and anthraquinones (Daniyan *et al*., 2013).

Menthol is one of the active compounds in peppermint in addition to many other potent compounds such as menthone, menthylacetate, menthofuran, and limnone and it is virucidal against influenza, herpes and few other viruses (Cai *et al*., 2007). *Allium sativum* and *Gongronema latifolium* have very high antimicrobial activity against Gram negative enteric bacterial pathogens, *E. coli*, and Gram positive bacterial pathogens, *S. aureus* (Tessema *et al*., 2006, Hughes and Lawson, 1991). The antimicrobial activity of the garlic has been attributed to its phytochemical component, allicin (a thiosulfonate) (Mitchel *et al*., 1977, Shahnaz *et al*., 2009) and allicin in combination with antibacterials, ciprofloxacin, enoxacin, vancomycin and clarithromycin against microorganisms *pseudomonas aureginosa* and *S. aureus* have strong synergistic effect of allicin in combination with ciprofloxacin and enoxacin against *pseudomonas aureginosa* and also have synergistic antibacterial effect with vancomycin and clari-thromycin against *S. aureus*.1, 8-dihydroxy-3-hydroxymethyl-9, 10-anthracenedione; 1, 8-dihydroxy-3-methyl-9,10-anthracenedione, and 10-C-b-D-glucopyranosyl - 1, 8-dihydroxy-3-hydroxymethyl-9-anthracenone, compounds from *Aloe feroxh*ave antibacterial action against *Bacillus subtilis, Staphylococcus epidermidis, Shigella sonnei* and *Escherichia coli.Aloe emodin*also have anticancer property against neuroectodermal tumors (Kambizi and Afolayan, 2001).

An active components from *Humulus lupulus*: humolone (α acids), lupulone (β acids) and xanthohumol, have antimicrobial activity (Koetter and Biendl, 2010). Fig leaves contains phenolic compounds with pharmacological properties which includes furanocoumarins like psoralen and bergapten, flavonoidslike rutin, quercetin, and luteolin, phenolic acids likeferrulic acid, and also phytosterols like taraxasterol (Teixeira *et al*., 2006). *Mikania glomerata, Psidium guajava, Syzygium aromaticum, Allium sativum, Cymbopogon citratus, Zingiber officinale, Baccharis trimera,* and *Mentha piperita* have *in vitro* anti-*Staphylococcus aureus* activities and synergism was verified for all the extracts; clove, guava, and lemongrass presented the highest synergism rate with antimicrobial drugs, while ginger and garlic showed limited synergistic capacity (Joyce *et al*., 2006). Flavones and their derivatives, including alkylgallate, intensify the activity of beta lactam antibiotics against methicillin resistant S*taphylococcus aureus* (MRSA) and methicillin sensitive S*taphylococcus aureus* (MSSA) (Shibata *et al*., 2005).

The abietane diterpenes, (carnosic acid) a component of *Rosmarinus officinalis* potentiates the activity of erythromycin against strains of *S. aureus* that express efflux proteins MsrA and TetK. Additionally, carnosic acid was shown to inhibit ethidium bromide efflux in a NorA expressing *S. aureus* strain (Oluwatuyi *et al*., 2004). A penta-substituted pyridine, 2, 6-dimethyl-4-phenylpyridine-3, 5-dicarboxylic acid diethyl ester and proparcine compound isolated from rhizome of *Jatropha elliptica,* increase the activity of ciprofloxacin and norfloxacin against NorA expressing *S. Aureus* (Marquez, 2005). Ferruginol and 5-Epipisiferol active compounds from the cones of *Chamaecyparis Lawsoniana* increased the efficacy of tetracycline, norfloxacin, erythromycin and Oxacillin against resistant*S. aureus* (Smith, 2007). *Terminalia catappa* extract have good antimicrobial activity individually and in combination with standard antibiotics and have good synergistic activity. It also has good antioxidant activity (Sumitra, 2013). *Ocimum sanctum* has antibacterial properties (Aquil *et al*., 2005) and the antibacterial properties are due to glycosides, Phenols and tannins (Ahmad and Beg, 2001). *Carica papaya* extract have antimicrobial properties and have synergistic activity against Gram positive and Gram negative bacteria resistant to penicillin G, ampicillin, amoxyclave, rifampicin, amikacin, nilidixic acid, gentamicin, ofloxacin (Kalpna and Sumitra, 2012) and*Clinopodium vulgare* have synergistic interaction with gentamicin and cephalexin in treatment of *Staphylococcus aureus, Bacillus subtilis* and *Klebsiella pneumoniae in-vitro,* because of the highest amount of phenols and flavonoids (Olgica, 2011). Extract of *Achillea millifolium*, *Caryophyllus aromaticus*, *Melissa offficinalis, Ocimun basilucum*, *Psidium guajava*, *Punica granatum*, *Rosmarinus officinalis*, *Salvia officinalis*, *Syzygyum joabolanum* and *Thymus vulgaris* have synergistic action with frequently used uneffective antibiotics. The phytochemicals benzoic acid, cinnamic acid, eugenol and farnesol in their pure form potentiate the activity of antibiotics (Gislene, 2000).

Interaction of bioactive plant products and different classes of antibiotics

Sometimes, an antibioticalone have not been effective in treating infectious diseases (Pranay *et al*., 2012). One strategy employed to overcome these resistance mechanisms is the use of combination of drugs, such as b-lactams together with b-lactamase inhibitors.

Extended Beta lactamase (ESBLs) are enzymes conferring broad resistance to penicillin, cephalosporins, and monobactame but not to carbapenem. ESBLs are often plasmid mediated and most are membrane of TEM-1, TMH-2 and SHV-1 family enzyme. The methanol leaf extract of *C. odorata* contains potential efflux pump inhibitors, the synergistic effect of the extract was observed on both Gram-Positive and Gram-negative bacteria (Ajao *et al*., 2011). The ethanol extracts of *Corchorus olitorius* leaf extract in *in-vitro* interaction with ciprofloxacin, gentamycin, streptomycin, erythromycin and ampicillin/cloxacilin mixture against Methicillin sensitive *Staphylococcus aureus* and Methicillin resistant *Staphylococcus aurues* (MRSA), the extract synergized the activities of streptomycin and ciprofloxacin and antagonized the activities of gentamycin, erythromycin and ampicillin/cloxacilin mixture on MRSA (Ashidi *et al*., 2012).

Chemical modifications in the antibiotic target may result in reduced affinity of the antibiotic to its binding site (Lambert, 2005). These mechanisms have been employed by a number of pathogens resistance to macrolides, lincosamide and streptogramin B antibiotics (MLSB resistance) in pathogenic *Streptococcus* species is a result of methylation of the N6 amino group of an adenine residue in 23S rRNA which cause conformational changes in the ribosome leading to reduced binding affinity of these antibiotics to their binding sites in the 50S ribosomal subunit (Seppala *et al*., 1998, Kataja *et al*., 1998). Beta-lactams antibiotics function by binding to and inhibiting the biosynthetic activity of Penicillin Binding Proteins (PBPs), thereby blocking cell wall synthesis (Stephen *et al*., 2012). A strategy of the production of hydrolytic enzymes and group transferases is employed by number of pathogens for its invasion (Wright, 2005). Antibiotic degrading genes mostly codes for enzymes which often carried on plasmids and other mobile genetic elements (Frere, 1995). Pathogenesis of bacterial strain in the presence lactum ring based antibiotics is due to hydrolysis of the amide bond of the four membered-lactam ring of antibiotics (Wilke *et al*., 2005) and resistance of Gram-negative pathogens to aminoglycosides is by modification of antibiotic molecule by acetylation, adenylation or phosphorylation (Over, 2001). Intrinsic antibiotic resistance confer by constitutive expression of efflux pump proteins is encoded by house-keeping genes (Lomovskaya and Bostian, 2006). Active efflux mechanism resist to almost antibiotics (Gill *et al*., 1999, Li *et al*., 1994, Lin *et al*., 2002). Majority of the efflux systems in bacteria are because of non-drug-specific proteins that can recognize and pump out abroad range of chemically and structurally unrelated compounds from bacteria in an energy-dependent manner, without drug alteration or degradation (Kumar and Schweizer, 2005, Kaatz, 2002).

An antibacterial-hydrophilic ingredients derived from Kumazasa can be used against antibiotic-resistant bacteria. The combination of Kumazasa-cytoplasmic extract with a cell wall synthesis inhibitor (extract with ampicillin or with vancomycin) will be a highly efficient treatment for infections caused by MDR MRSA, methicillin-resistant *Staphylococcus aureus* and VRE, vancomycin-resistant Enterococci strains (Shoichi *et al*., 2009, Helen *et al*., 2009, Ashidi *et al*., 2012). Methanol leaf extract and the solvent fractions of *Phyllanthus muellerianus* (Kuntze) and their combinations with ciprofloxacin against various isolates of *Staphylococcus aureus* have anti bactericidal activity because of presence of glycosides, alkaloids, steroids, terpenoids and flavonoids. Lipophilic flavonoids disrupts microbial membranes. Besides, alkaloids have been demonstrated to intercalate between DNA strands (Ofokansi *et al*., 2012). Phytochemical such as tannins phlobaphenes, tannins, pyrogallates, anthocyanins, flavones, flavonols, flavonones, aurones, proanthocyanidins, alkaloids and terpenes showed greater sensitivity to *E. coli* and *K. pneumonia*. One of the classes with the most active compounds with diverse chemical structure is the terpenoids. It is most active due to their high medicinal value speculated to involve membrane disruption by the lipophilic compounds, with permeability enhancement. This property can facilitate the antimicrobial agents to penetrate into a cell, leading to an activity enhancement (Vidal *et al*., 2012, Mishra and Sharique, 2011, Calvo, 2006).

Extracts of *Foeniculum vulgare* seeds have synergistic effect on various classes of antibiotics, against resistant *Pseudomonas* spp. (Charde, 2014). *Escherichia coli*, *Pseudomonas aeruginosa* and *Proteus mirabilis* resistance to streptomycin, chloramphenicol, tetracycline, amoxicillin, rifamycine became sensitive to extract of (phenol fraction and flavonoid content) *Melissa officinalis* in synergism with antibiotics (Olgica, 2012). MDR Gram-negative bacteria with over expressing active efflux pump phenotypes became sensitive to methanol extracts of *Citrus medica*, the bulbs of *Allium sativum* and *Allium cepa*, the seeds of *Carica papaya*, *Cola acuminata*, *Buchholzia coriacea*, *Garcini kola*, and *Garcinia lucida*, the seeds and fruits of *Picralima nitida* in associations with currently used antibiotics on multidrug resistant. The association ofphenylalanine arginine *β*-naphthylamide (PA*β*N or efflux pumps inhibitor) to different extracts modify their activities at typical concentration (Stephen *et al*., 2012).

Terminalia arjuna (Combretaceae), *Moringa oleifera* (Moringaceae), *Azadirachta indica* (Maliaceae) and *Curcuma longa* (Zingiberaceae) extract in different effective against bacterial strains of *Bacillus subtilis*, *Escherichia coli* and *Klebsiella pneumonia* and fungal strains of *Aspergillus niger* and *Candida albicans* (Hariharan *et al*., 2012). *Staphylococcus aureus* resistant to chloramphenicol became sensitive in association with the ethanolic extracts of stem and leaf extract of *Olea europaea* but the combination of stem and leaf extract with penicillin does not produce the same inhibitory effect as that of chloramphenicol and *Olea europaea* stem and leaf extracts (Zafar *et al*., 2010). The synergistic action of the rosemary extract is due the presence of carnasol, diterpenoid present in the leaves of Rosemary. Carnosol has the ability to enhance the activity of antibiotics against drug resistant effluxing strains (Kumiko *et al*., 2007). Itis an efflux pump inhibitor of Tet(K) and Msr(A) efflux pump in *S. aureus* (Oluwatuyi *et al*., 2004). The combine effects of the leaf extract of *Jatropha curcas* L. with antibiotics on certain selected microorganisms *Salmonella typhi, Staphylococcus aureus, Pseudomonas aeruginosa, Proteus mirabilis, Klebsiella pneumonia, & Bacillus subtilis* were used for bactericidal effect, and anti-fungal activity was encountered for *Candida albicans*. The antimicrobial activity of ciprofloxacin was increased significantly (MICs reduced significantly) when combined with the plant extract whereas that of tetracycline was reduced (Akanwariwiak *et al*., 2012).

The methanolic extracts of fruit of *Xylopia aethiopica* separately and in combination with antibiotics: gentamycin, ofloxacin and ciprofloxacin; and two antifungal antibiotics: fluconazole and ketoconazole were active against *P. aeruginosa*, *B. subtilis*, *S. aureus*, *A. flavus* and *C. albicans*. Extracts showed little effect against *Klebsiella pneumoniae*and no activity against *E. coli* (Emeka and Micheal, 2010). In the formulation of the frontal leaves extract of *Tectona grandis* (Verabinaceae) and tetracycline have fair synergistic activity against *Salmonella typhimurium*, *Klebsiella pneumoniae*, and lowest synergistic against *Escherichia coli*. No synergistic activity for *Citrobacter freondii* was found. Thus stronger synergistic effect with folic acid and bacterial cell wall synthesis inhibitors where asinhibitors of the nucleic acid synthesis showed weak synergism with plant extracts (Purushotham *et al*., 2010). Treatment with manuka honey at

10% led to a down regulation of mecR1, which codes fora two-component sensor/signal transducer protein that regulates the expression of mecA (encoding a penicillin-binding protein that mediates the oxacillin resistance [Jenkins *et al*., 2012].

Rifampicin and oxacillinare members of different antibiotic classes and the resistance mechanisms. Rifampicin resistance is typically due to a single-point mutation in the rpoB gene, resulting in an amino acid substitution in the rifampicin-binding site on RNA polymerase (Feklistov *et al*., 2008, Aubry-Damon *et al*., 1998, Wichelhaus *et al*., 1999). In *Thuja* extract, a synergistic action due to the damage occurring in the cell wall and in the cell membrane caused by epigallocoatechin gallate and an increase in the permeability responsible for the potent synergy (Shimizu *et al*., 2001). Active efflux pump is one of the mechanisms of resistance for almost all antibiotics. Inhibition of efflux pumps significantly decreases the level of intrinsic resistance, reverses acquired resistance and results in decreased frequency of emergence of resistance to efflux pump substrates (Charde *et al*., 2014). Different solvent extracts of Ajwain showed synergistic effect on susceptibility of previously resistant antibiotic. The hot extract in chloroform found to potentiate the susceptibility of antibiotics, Rifampicine, Amikacin, Ampicillin, Sparfloxacin, Ceftizoxime, Cephalothin, Gentamicin, Linezolid, Moxifloxacin and Oxacillin to greater extent [Cushnie and Lamb, 2005]. Synergyoccurs between flavonoids and chemotherapeutics (Sato *et al*., 2004, Dickson *et al*., 2006) and potentials of flavonoids and polyphenols, combining with the antibiotics alter the inherent resistant properties in the bacteria (Sibanda and Okoh, 2007, Gibbons, 2008, Phillipson *et al*., 1987). Aromatic planar quaternary alkaloids in extracts intercalate with DNA (Tsuchiya *et al*., 1996), lipophilic flavonoids can disrupt microbial membranes (Prasad *et al*., 2008), Tannins precipitate microbial protein, saponins can dislocate lipid (Abukakar *et al*., 2008). Dual action of extracts and antibiotics exerts its activity on different target microbe differently (Esinome *et al*., 2006), hindering inhibitory action of defensive enzymes (Aburjai *et al*., 2001, Darwish *et al*., 2002), phytochemicals can block the active site of peptidogly can inhibiting antibiotics [Zhao *et al*., 2001].

Biosafety

WHO proposed herbal drugs to be relatively safer and published a standard for herbal safety to minimize abuse and adulteration.

Phytochemicals as an antimicrobial chemotherapeutic agent, a future perspective

Natural products have few disadvantages of nonspecific concentration of phytoconstituents and slow curing properties but the major advantage of natural product is their abundance. Many natural-drug-derived compounds are under process (Polly *et al*., 2014, Igor *et al*., 2012). Antibacterial, antifungal, anti-arthropod, anti-helminthic, anti-cancer and many physiological defects cardiovascular also been cured by use of phytochemicals. Very few of the total herbs present on the earth are explored for the screening and for bioactivity against known pathogens (Ahmed *et al*., 2013). The overall antibiotic resistant profile shows resistant to often used antibiotics, ampicillin, tetracycline, rifampicin, amoxicillin, chloramphenicol, cefotaxime, erythromycin, penicillin, neomycin, streptomycin, trimethoprim and gentamycin, and sensitive to only ciprofloxacin and have significant role of plasmid DNA in drug resistance (Sima *et al*., 2012).

Investigation have reported that patients with nosocomial infections and have developed ESBLs activity and they figure out, plasmid DNA analysis is of great use in detection and treatment of MDR strains (Elizabeth and Vincent, 2010). The emergence of drug resistance in the antimicrobial agents being routinely used for treatment, and suggested the likely presence of co-selected traits that result in highly virulent and resistant strains which revealed the existence of a non-clonal population structure and multiple drug resistance, and virulence determinants are recommended to monitor routes of infection and changes in drug resistance patterns (Mesaros *et al*., 2007). Due to developed and developing diverse resistance mechanisms & their effect on global fitness, importance of appropriate empirical therapy, combination therapy versus monotherapy, economic impact; these highly resistant bacteria requires a multidisciplinary team approach that involves clinicians, laboratory staff, infection prevention specialists, and pharmacists (Gislene *et al*., 2000, Ghaleb *et al*., 2009). The synergistic effect from the association of antibiotics with 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 (Fabiola *et al*., 2010).

Synergistic interaction of phytomedicine with antibiotics can explain efficacy with respect to its action. Varied action of purified extract and crude one reports the need of study at high level. Abundance and cheaper value complements the use of herbal drug at large scale. Despite of increased interest in medicinal plant research very few formulations are available in market worldwide as compared to chemical based chemotherapeutic formulations.

Outlook

Due to decreasing efficacy of antibiotic, drug development from natural products renowned interest in natural products and analysis of new structure and systematically exploration of combinatory drug regime. Plants are a mine of inexhaustible source of natural drug. Numerous plants have been tested for antimicrobial properties and lots more yet to be investigated. Synergistic action is of key importance in phytomedicine to study the efficacy of apparently low dosage of active component in herbal product. Synergistic action of phytochemical and antibiotics have shown mark positive effect, in *in-vitro* study. Synergistic action of phytochemicals and antibiotics is therefore a successful attempt for annihilation of MDR pathogens.

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