Antimicrobial resistance (AMR) and plant-derived antimicrobials (PDA\textsubscript{ms}) as an alternative drug line to control infections

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Abstract Infectious diseases caused by antimicrobial-resistant microbes (ARMs) and the treatment are the serious problems in the field of medical science today world over. The development of alternative drug line to treat such infectious diseases is urgently required. Researches on ARMs revealed the presence of membrane proteins responsible for effusing the antibiotics from the bacterial cells. Such proteins have successfully been treated by plant-derived antimicrobials (PDA\textsubscript{ms}) synergistically along with the commercially available antibiotics. Such synergistic action usually inhibits the efflux pump. The enhanced activity of plant-derived antimicrobials is being researched and is considered as the future treatment strategy to cure the incurable infections. The present paper reviews the advancement made in the researches on antimicrobial resistance along with the discovery and the development of more active PDA\textsubscript{ms}.

Keywords Antimicrobial-resistant microbes · Efflux pumps · Antimicrobial resistance · Plant antimicrobial compounds

Abbreviations
MDR Multidrug-resistant
XDR Extensively drug-resistant
AMR Antimicrobial resistance
PDA\textsubscript{m} Plant-derived antimicrobials
ARM Antimicrobial-resistant microbes
EPI Efflux pump inhibitor
AMP Antimicrobial peptides

Introduction

Increasing antimicrobial resistance (AMR) among microbes caused the emergence of new resistant phenotypes and further caused the development of new antimicrobial compounds (Goossens 2013). Infectious diseases caused by antimicrobial-resistant microbes (ARM) have been frequently reported since last few years (Vila and Pal 2010). About 440,000 new cases of multidrug-resistant tuberculosis (MDR-TB) are recorded annually, causing approximately 150,000 deaths all over the world. Recently, a joint meeting of medical societies, the first ever in India was held to tackle the challenges of antimicrobial resistance in developing world (Ghafur 2013). As a result of this conference “Chennai declaration” came into existence, initiating efforts through a national policy to control the rising trend of AMR in India and abroad (Ghafur et al. 2012).

Multidrug-resistant (MDR) microbes are resistant to three or more antibiotics (Styers et al. 2006), however; strains of \textit{Mycobacterium tuberculosis}, resistant to virtually all classes of antimicrobials have also been identified in the Kwa Zulu Natal Province of South Africa (Gandhi et al. 2006), a typical example of Extremely Drug-Resistant...
Tuberculosis (XDR TB) reported in 64 countries to date (World Health Organization 2011). The global emergence of MDRs is increasingly limiting the effectiveness of the existing antibiotic drugs (Hancock 2005) for e.g. methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococci spp. (Norrby et al. 2005). The development of resistance among the microbes is the result of continuous selection pressure of antibiotics and their surroundings causing genetic alterations (Bush 2004) which, are transferred to the next generation and reach out to the wider range of other geographical regions through the transfer of genetic information exchange between microbes (Amábile-Cuevas 2003) (Table 1 presents the examples of some of the common MDRs). In this review, attempt has been made to understand specific issues such as factors causing resistance, the role of developing world with a quick overview of plant-derived antimicrobials (PDAm) and synergistic compounds as an alternative drug line.

Factors causing AMR

Microbes comprise 50% of total living biomass and are well-survived life forms on earth. There exists a sharp distinction between microbes as pathogenic and non-pathogenic although; one-way exchange of genetic elements (Amábile-Cuevas 2003) may confer the pathogenic characters to the non-pathogenic microbe. Pathogenic microbes cause infectious diseases in humans and animals and are treated with antibiotics. Antibiotics also known as antimicrobials are chemical substances, toxic for most of the life forms. Irrational and deliberate use of antibiotics, migration of infected individuals to other communities (Memish et al. 2003), prolonged use of medical health care systems in hospitals, hunger and malnutrition are some of the main causes of the development of resistance against antibiotics in the microbes (Byarugaba 2004; Vila and Pal 2010). Antimicrobial use in veterinary practices especially as food additives is one of the causes of development of AMRs in zoonotics that may spread to humans (Memish et al. 2003) through the food chain. In this connection, reports of Schlegelova et al. (2008) suggest, least chances of spreading of a resistant strain through the dairy products, however; improperly processed raw meat is strongly discouraged for human consumption in developed nations (Threlfall 2002).

Molecular understanding of AMR

Microbes attain resistance very rapidly against most of the currently available antibiotics because of the adaptability feature conferred by plasmids. Table 1 presents the examples of such plasmids carrying integron and gene cassettes in most common MDRs which on transfer, widespread the resistance (Kumarasamy et al. 2010). Gram-negative (Kumarasamy et al. 2010) and Gram-positive bacteria (Grohman et al. 2003) both exhibit conjugative transfer of plasmids, a natural way of horizontal gene transfer for e.g. the horizontal transfer of plasmid in between Vibrio fluvialis and Vibrio cholerae conferring resistance to V. fluvialis (Rajpara et al. 2009). Recent cases of AMR development include Pseudomonas aeruginosa and Acinetobacter baumannii resistant to nearly all

Table 1 Examples of plasmids carrying integron integrase carrying gene cassettes imparting resistance against antimicrobials

| Plasmid gene cassette | Resistance against | Microbes (isolation) | Conjugative transfer | References |
|-----------------------|--------------------|----------------------|----------------------|------------|
| pVN84                 | MDR                | Vibrio spp.          | ✓                    | Raipara et al. (2009) |
| MLSg [erm(B) & erm(C)]| Erythromycin       | Staphylococcus spp.  | x                    | Schlegelova et al. (2008) |
| gyrA or gyr A         | Ciprofloxacin      | Staphylococcus spp.  | x                    | Campion et al. (2004) |
| ppx2X                 | β-Lactam           | Staphylococcus spp.  | x                    | Coffey et al. (1991) |
| CTX-M                 |                    |                      |                      |            |
| aac(6’)-Ib            | Aminoglycoside     | Klebsiella pneumoniae| ✓                    | Soge et al. (2006) |
| emr(B)                | Macrolide-lincosamide-streptogramin B | K. pneumoniae | ✓ |
| pla TEM-1             | Ampicillin         | K. pneumoniae        | ✓                    |            |
| dfr                   | Trimethoprim       | K. pneumoniae        | ✓                    |            |
| p3iANG                |                    |                      |                      |            |
| dfr/A15               | Trimathoprinn      | Vibrio cholerae      | ✓                    | Ceccarelli et al. (2006) |
| bla PI                | β-Lactam           | V. cholerae          | ✓                    |            |
| qacH                  | Quaternary ammonia-compounds | V. cholerae | ✓ |
| aada8                 | aminoglycosides    | V. cholerae          | ✓                    |            |
| mecA                  | Methicillin (MDR)  | S. aureus            | x                    | Hiramatsu et al. (2002) |
| qnr (carried on class 1 integron) | Ciprofloxacin | V. Cholerae | x |
| blasMDL-1             | Carbapenem         | Enterobacteriaceae   | ✓                    | Kumarasamy et al. (2010) |
antibiotics including the carbapenems (Huang and Hsueh 2008). Antibiotic inactivation (degradation of antibiotics by the microbial enzymes e.g. transferase and β-lactamase) causes resistance in microbes (Wright 2005; Jacoby and Munoz-Price 2005), more than 1,000 such β-lactamases are identified till date (Bush and Fisher 2011). Different antibiotics have different mode of actions, therefore, their use is largely dependent on variety of traits other than resistance (Amabile-Cuevas 2010) which either undergo rapid enzymatic degradation or actively effused by the resistant bacteria. Efflux pump in MDRs was first described by Roberts (1996) for tetracycline and macrolide antibiotics. In general, efflux pumps act through membrane proteins of substrate specificity, effuse the antibiotics from the bacterial cell, resulting in a low intracellular ineffective concentration of the drug (Gibbons 2004; Throrold et al. 2007) altering the permeability of membrane. In a study, staphylococcal accessory regulator (sara) was reported to contribute promising role, imparting resistance in S. aureus (Riordan et al. 2006). In addition, Kuete et al. (2011) reported two efflux pumps viz., AcerAB-ToIC (Enterobacteriaceae) and MexAB-OprM (Pseudomonas aeruginosa) imparting resistance in Gram-negative bacteria against natural products. AMR is a genetically-modified manifestation, linked to the point mutation in bacterial non-chromosomal DNA. As in case of MRSA, the resistance to methicillin is associated with acquisition of a mobile genetic element, SCCmec, which contains mecA-resistant gene (Okuma et al. 2002). Analytical procedure followed on Escherichia coli showed reversible function of class 1 integron integrase gene machinery under selective pressure (Díaz-Mejía et al. 2008). Similar results were also observed by Hsu et al. (2006) whereby E. coli MDR was found associated with the class 1 integron gene. Detailed mechanism of development of AMR among microbes has been extensively reviewed by Byarugaba (2010).

Developing world: the factory of MDRs

Developing world especially the countries of South East Asia, Western and Central Africa, India and Pakistan are the most vulnerable for various infectious pandemic diseases. Byarugaba (2004) comprehensively reviewed and reported the AMR in developing countries. Several factors are associated with the AMR development including nosocomial infections, unsafe disposal of biomedical waste, inappropriately used antibiotics, self drug abuse, shortfall of antibiotic course and lack of mass awareness of infectious diseases and personal hygiene (Okeke et al. 2005a, b). In addition to these, lack of surveillance data, providing information of microbial infections common to a geographic location and the invasive microbial species have been suggested as the major causes of MDRs development in developing countries (Okeke et al. 2005a, b; Giske and Cornaglia 2010; Kartikeyan et al. 2010; Lalitha et al. 2013). Giske and Cornaglia (2010) emphasized on the surveillance practices especially the monitoring and sampling techniques of invasive microbial isolates. Surveillance of resistance in many developing countries is suboptimal (Okeke et al. 2005b) and unable to present the real picture of infectious diseases and the medication. Recent reports of Lalitha et al. (2013) showed the feasibility of proper surveillance of resistance by carrying experimental surveillance study on the school children in different geographic locations of Indian subcontinent. In India for Salmonella typhi, MDR has become a norm in strains. This widespread resistant bacterium is associated with contaminated water supply in developing countries and through food products such as contaminated meat in developed countries (Threlfall 2002). Remarkable report of Kumarasamy et al. (2010) provides sufficient evidences in support of the positive role of developing world in the development of ARMs. Resistance to carbapenem conferred by plasmid encoded New Delhi metallo-β-lactamase-1 (blaNDM-1) is a worldwide health problem, especially in UK, (Kumarasamy et al. 2010) having the roots in India and Pakistan. The selective pressure on the bacterial cells is associated with the adaptations causing resistance among microbes for multiple antimicrobials for e.g. genes encoding NDM-1, OXA-23 and OXA-51 enzymes (hydrolyzing specific antibiotics) were observed in three different isolates of Acinetobacter baumannii in India (Kartikeyan et al. 2010). Alterations in gene structure were reported in A. baumannii as a result of selection pressure of antibiotics (Kartikeyan et al. 2010). The literature suggest, substandard surveillance of resistance, non-prescribed antibiotic usage causes huge selection pressure resulting in the development of AMR in developing countries and their suburbs (Byarugaba 2004; Okeke et al. 2005b; Kumarasamy et al. 2010). Figure 1 shows a schematic diagram showing the development of MDR microbe in community.

Plants derived antimicrobial (PDAm): a ray of hope

Antimicrobial resistance is rapidly increasing along with the development of classical antibiotics consequently, there is an urgent need to develop a different drug line to treat and control MDR bacterial infections. Medicinal values of plants were known to earlier traditional medical practitioners (Emeka et al. 2012). PDAm substances are plant-originated secondary metabolites and have great concern because of their antibiotic activity without conferring resistance (Baris et al. 2006; Palaniappan and Holley 2010).
PDA_m's are classified as antimicrobial on the basis of dose ranging from 100 to 1,000 μg ml⁻¹ for the minimum inhibitory concentration (MIC) susceptibility test performed on bacteria (Tegos et al. 2002). Table 2 presents few of the examples of plants and their active antimicrobial compounds. Plants have unlimited ability to produce wide variety of secondary metabolites most of which are aromatic compounds including alkaloids, glycosides, terpenoids, saponins, steroids, flavonoids, tannins, quinones and coumarins (Das et al. 2010) forming the basis of PDA_m compounds (Table 3). Target specific plant’s secondary metabolites having potential to treat and control the infection can be found in several species. For instance, Staphylococcus aureus and ineffective on Gram-negative bacteria (Lewis and Ausubel 2006). The literature such as Cowan (1999); Lewis and Ausubel (2006) and González-Lomothe et al. (2009) provides comprehensive information on the major secondary metabolites of plant origin. Precise mechanistic approach of PDA_m and their activity on microbes has been discussed by Lewis and Ausubel (2006). In general, PDA_m's (mostly secondary metabolites) are phenol derivatives, sufficiently able to control microbes by reducing pH, increasing membrane permeability, altering efflux pumping. Examples mentioned in Table 2 followed by recent studies of (Machado et al. 2003; Ram et al. 2004; McGaw et al. 2008; Renisheya et al. 2011; Ahmed et al. 2012; Emeka et al. 2012; Upadhyaya 2013) and the references there in, suggest the antimicrobial potential of various local and exotic plant species, although very few reports have suggested the mechanism of their actions. The affectivity of PDA_m's largely depends upon the extraction methods (Das et al. 2010). In a study carried out by our group, methanolic, ethanolic and water extracts of several plants species viz., Argemone maxicana, Callistemon lanceolatus, Allium sativum, Swietenia mahogani, Citrus colocynthis, Salvadora persica, Madhuca Indica, Acacia nilotica and Pongamia pinnata were assayed for their antimicrobial activity on most of the common MDRs viz., Staphylococcus aureus, Bacillus cereus, B. pumilus, Klebsiella pneumonia, Salmonella typhi, E. coli exhibiting...
activity of all the extracts, however; the target specificity of plant extracts could not be established because of uncertain mechanism of plant-derived antimicrobial compounds. A generalized mechanism of PDA\textsubscript{mp}s on microbes suggests the effects of efflux pumping on MDRs: increasing permeability and reduce selection pressure (Lewis and Ausubel 2006). Antimicrobial peptides (AMPs) are also produced by plants against the infections also called as defensins. Plant antimicrobials act well in combinations with other amphipathic compounds. In addition to this, resistance in MDRs conferred by efflux pumping can be treated with the synergistic combinations of antimicrobial with an efflux pump inhibitor (EPI) and altering outer membrane permeability of MDR bacteria providing an effective drug resistance of various degrees. For instance, unlike Gram-positive, MDR Gram-negative bacterial species have developed a sophisticated permeability barrier as outer membrane comprised of hydrophilic lipopolysaccharide restricting the entry of hydrophobic (quinones and alkaloids) and amphipathic antibiotic compounds (Lewis and Ausubel 2006). The biased effect of PDA\textsubscript{mp}s on Gram-positive and -negative species has been a key to the discovery of the synergistic compounds of plant origin (Lewis 2001).

### Table 2 Plant derivatives as antimicrobial for the treatment of microbial infections

| Plants | Plant derivatives | Effective against | References |
|--------|------------------|-------------------|------------|
| Medicago sativa | Saponins, canavanine | Enterococcus faecium, Staphylococcus aureus | Aliahmadi et al. (2012) |
| Onobrychis sativa | AMPs (antimicrobial peptides) | E. faecium, S. aureus | Aliahmadi et al. (2012) |
| Allium sativum | Organosulfur compounds (phenolic compounds) | Campylobacter jejuni | Lu et al. (2011) |
| Raphanus sativum | RsAFP2 (Antifungal peptide) | Candida albicans | Aerts et al. (2009) |
| Vetiveria zizanioides | Vetivone (vetiver oil) | Enterobacter spp. | Srivastava et al. (2007) |
| Chelidonium majus | Glycoprotein | B. cereus, Staphylococcus spp. | Janovska et al. (2003) |
| Sanguisorba officinalis | Alkaloids, antimicrobial peptides | Ps. aeruginosa, E. coli | Janovska et al. (2003) |
| Cinnamomum osmophloeum | Cinnamaldehyde (in essential oil) | Legionella pneumophila | Chang et al. (2008) |
| Ocimum basilicum | Essential oil | Salmonella typhi | Wan et al. (1998) |
| Micromeria nervosa | Ethanolic extract | Proteus vulgaris | Ali-Shtayeh et al. (1997) |
| Rhabdosia trichocarpa | Trichorabdal A | Helicobacter pylori | Kadota et al. (1997) |
| Melaleuca alternifolia and Eucalyptus sp. | Essential oil | Staphylococcus spp. and Streptococcus spp. | Warnke et al. (2009) |
| Anthrocephalus cadamba and Pierocarpus santalinus | Ethanolic extract | MDR\textsuperscript{M} | Dubey et al. (2012) |
| Lantana camara L. | Leaf extract in dichloromethane & methanol | MDRsG + ve and MDRsG—ve | Dubey and Padhy (2013) |
| Butea monosperma Lam. | Ethanolic and hot water extract of leaf | MDR\textsuperscript{M} | Sahu and Padhy (2013) |
| Jatropha curcas (Linn.) | Ethanolic and methanolic extract | MDRsG + ve + Micrococcus sp. & MDRsG—ve + Shigella sp. + Bacillus sp. | Igbinosoa et al. (2009) |
| Ficus exasperate and Nauclea latifolia | Methanolic extract of leaf and stem | E. coli, Shigella dysenteriae, S. typhi, C. albicans, P. aeruginosa | Tekwu et al. (2012) |
| Rhus coriaria | Ethanolic extract | MDR P. aeruginosa | Adwan et al. (2010) |

MDRs\textsuperscript{M} = Staphylococcus aureus + Acinetobacter sp. + Citrobacter freundii + Chromobacterium violaceum + Escherichia coli + Klebsiella sp. + Proteus sp. + Pseudomonas aeruginosa + Salmonella typhi + Vibrio cholera; MDRsG + ve = S. aureus (MRSA) + Streptococcus pyogenes + Enterococcus faecalis (VRE); MDRsG—ve = Acinetobacter baumannii + Citrobacter freundii + Proteus mirabilis + Proteus vulgaris + Pseudomonas aeruginosa |

### Synergistic actions of PDA\textsubscript{mp}s

The AMR is conferred by several factors which have already been reviewed in previous sections. Plasmid encoded resistance facilitate bacterial cells to develop resistance of various degrees. For instance, unlike Gram-positive, MDR Gram-negative bacterial species have developed a sophisticated permeability barrier as outer membrane comprised of hydrophilic lipopolysaccharide restricting the entry of hydrophobic (quinones and alkaloids) and amphipathic antibiotic compounds (Lewis and Ausubel 2006). The biased effect of PDA\textsubscript{mp}s on Gram-positive and -negative species has been a key to the discovery of the synergistic compounds of plant origin (Lewis 2001). Plant antimicrobials act well in combinations with other amphipathic compounds. In addition to this, resistance in MDRs conferred by efflux pumping can be treated with the synergistic combinations of antimicrobial with an efflux pump inhibitor (EPI) and altering outer membrane permeability of MDR bacteria providing an effective drug (Savage 2001; Gibbons 2004; Baskaran et al. 2009). Studies of Chusri et al. (2009) reported another example of synergistic effect of plant-derived phenolics such as Ellagic acid (a derivative of Gallic acid) a non-antimicrobial, administered as EPI in combination with classical antibi- otic to control Acinetobacter baumannii. Another example belongs to the well-studied plant Berberis fremontii and its
amphipathic cation berberine inhibits the NorA MDR pump of *Staphylococcus aureus* when applied in combination with 5\(^{-}\)-MHC (5\(^{-}\)-methoxyhydnocarpin, an amphipathic weak acid) a real inhibitor of the pump enhancing the activity of berberine (Stermitz et al. 2000). Similar non-antimicrobial compounds known to enhance effectivity of antimicrobials have been discussed by Lewis (2001). Detailed mechanism of PDAms on MDR *S. aureus* has been discussed in the review by Gibbons (2004). Wang et al. (2009) defined that the role of AMP plant defensin Ib-AMP1 isolated from plant *Impatiens balsamina* have a prime target, intercellular components, forming small channels that permit the transit of ions or protons across the bacterial membrane, the same activity was also observed in the linear analogs of this peptide.

### Future studies

Researches on the AMR and alternating drug system are endless and a lot of scope is there in the field of ethnomedicine. Scientists are working on the development of

| Table 3 | Examples of plant derivatives and their antimicrobial activities |
|---------|---------------------------------------------------------------|
| Plant-derived antimicrobial groups | Structure | Chemical properties | Effective on microbes | References |
| Quinones | Conjugated cyclic-dione structure with molecular formula C\(_6\)H\(_4\)O\(_2\) e.g. Anthraquinone from *Cassia italica* | *Pseudomonas pseudomallei*, *Bacillus anthracis*, *Corynebacterium pseudodiphthericum*, *Pseudomonas aeruginosa* | Kazmi et al. (1994) |
| 6-(4,7 Dihydroxy-heptyl)quinone | *Staphylococcus aureus*, *Bacillus subtilis*, *Proteus vulgaris* | Ignacimuthu et al. (2009) |
| Alkaloids | Naturally occurring amines having nitrogen in heterocyclic ring of compounds and are the derivative amino acids e.g. glabradine from tubers of *Stephania glabra* | *S. aureus*, *S. mutans*, *Microsporum gypseum*, *M. canis*, *Trichophyton rubrum* | Semwal and Rawat (2009) |
| L-Proline derived Monophyllidin from *Zanthoxylum monophyllum* | Enterococcus faecalis | Patino and Cuca (2011) |
| Lectins and polypeptides | Lectins are carbohydrate binding proteins (phytoaglutinin) with MW around 17,000–400,000 | *E. coli*, *P. aeruginosa*, *Enterococcus hirae*, *Candida albicans* (fungi) | Zhang and Lewis (1997) |
| Flavones/flavonoids/flavonols | Are ubiquitous in plant’s parts, fruits, seeds, flowers and even honey. Flavones are hydroxylated phenolics containing one carbonyl group | MDR *Klebsiella pneumoniae*, *P. aeruginosa*, *E. coli* | Özcçelik et al. (2008); Edziri et al. (2012) |
| Coumarins | Coumarins are phenolic substances made of fused benzene and alpha pyrone ring forming toxic compounds found in plants such as *Dipteryx odorata*, *Anthoxanthum odoratum* etc | *S. mutans*, *S. viridans*, *S. aureus* | Widelski et al. (2009); Lewis and Ausubel (2006) |
| Terpenoids and essential oils | Isoprene derivatives having a general formula C\(_{10}\)H\(_{16}\) therefore also called as Isoprenoids. Well-known examples include menthol | *S. viridans*, *S. aureus*, *e. coli*, *B. subtilis*, *Shigella sonnei* (highly active) *P. aeruginosa*, *E. coli*, *S. aureus*, *T. mentagrophytes* (low activity) | Banso (2009); Ragasa et al. (2008) |
| Tannins | Large polyphenolic compound containing sufficient hydroxyls and other suitable groups | *S. aureus*, *S. typhimurium*, *S. viridans* | Moneim et al. (2007) |

Chemical structure given in front of corresponding group of antimicrobials is not to be considered as generalized one, the references are in correspondence with bacteria.
safe and effective antimicrobials all over the world. Future studies may involve the development of new plant-derived synergistic compounds capable of enhancing the activity of PDAms. A lot of research potential is also there to answer the questions for e.g. mechanism of resistance in different bacterial species, development of XDRs and their control.

Conclusion

AMR is a worldwide problem. Research literatures suggest that the standard living in major parts of developing world is one of the major causes of the development of resistance among bacteria. The developed world is also vulnerable of getting widespread infections for e.g. USA is surrounded by the developing countries having high rates of resistance development. Nosocomial, water borne, health care systems and food products especially meats are some of the most common means of widespread of resistant gene globally. Thanks to the modern molecular approaches for making better understanding of the pathways of resistance development and its remedy. Pharmacologists are developing new antibiotic drugs to treat and control various infections; however, the chances of the development of resistance are equal to the emergence of new drugs. In addition, research suggest that the combinations of PDAms and the synergistic compounds work efficiently on resistant strains ensuring no further resistance development. Moreover; concerted efforts have been solicited by the world community because poor countries are worst affected by the antimicrobial resistance and the developed countries are no longer safe (Díaz-Granados et al. 2008). In this regard, PDAms in combination with plant-derived synergistic compounds may be the cost-effective approach to deal with global antimicrobial resistance.

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References

Adwan G, Abu-Shanah B, Adwan K (2010) Antibacterial activities of some plant extracts alone and in combination with different antimi crobials against multidrug resistant Pseudomonas aeruginosa strains. Asian Pac J Trop Med 3(4):266–269
Aerts AM, Carmona-Gutierrez D, Lefevre S, Govaert G, François IE, Madeo F, Santos R, Cammue BP, Thevissen K (2009) The antifungal action of native fungal defensins RsAFP2 from radish induces apoptosis in a metacaspase-independent way in Candida albicans. FEBS Lett 583(15):2513–2516
Ahmed AS, Elgorashi EE, Moodley N, McGaw LJ, Naidoo V, Elloff JN (2012) The antimicrobial, antioxidative, anti-inflammatory activity and cytotoxicity of different fractions of four South African Bauhinia species used traditionally to treat diarrhea. J Ethnopharmacol 143(3):826–839
Alihamidi A, Roghanian R, Emizaji G, Mirzajani F, Ghasempour A (2012) Identification and primary characterization of a plant antimicrobial peptide with remarkable inhibitory effects against antibiotic resistant bacteria. Afr J Biotechnol 11(40):9672–9676
Ali-Shayeh MS, Al-Nuri MA, Yaghmour RMR, Faidi YR (1997) Antimicrobial activity of Microcormia nervosa from the Palestinian area. J Ethnopharmacol 58:143–147
Amábile-Cuevas CF (2003) Gathering of resistance genes in Gram-negative bacteria: an overview. In: Amábile-Cuevas CF (ed) Multidrug resistant bacteria. Horizon Scientific Press, Wymondham, pp 9–31
Amábile-Cuevas CF (2010) Global perspective of antibiotic resistance. In: de-J-Soso A et al (eds) Antimicrobial resistance in developing countries. Springer, New York, pp 3–14
Banso A (2009) Phytochemical and antibacterial investigation of bark extracts of Acacia nilotica. J Med Plants Res 3(2):82–85
Barlo O, Gulluce M, Sahin F, Ozer H, Kilic HH, Orkan H, Sokmen M, Ozbek T (2006) Biological activities of the essential oil and methanolic extract of Achillea biebersteinii Afan. (Asteraceae). Turk J Biol 30:65–73
Baskaran SA, Kazmer GW, Hinckley L, Andrew JM, Venkitanarayanan K (2009) Antimicrobial effect of plant derived antimicrobials on major bacterial mastitis pathogens in vitro. J Dairy Sci 92(4):1423–1429
Brouwer CPJM, Rahman M, Wellmg MM (2011) Discovery and development of a synthetic peptide derived from lactoferrin for clinical use. Peptide 32(9):1953–1963
Bush K (2004) Antibacterial drug discovery in the 21st century. Clin Microbiol Infect 10(S4):10–17
Bush K, Fisher JF (2011) Epidemiological expansion, structural studies, and clinical challenges of new β-lactamases from Gram-negative bacteria. Annu Rev Microbiol 65:455–478
Byarugaba DK (2004) Antimicrobial resistance in developing countries and responsible risk factors. Int J Antimicrob Agents 24(2):105–110
Byarugaba DK (2010) Mechanism of antimicrobial resistance. In: de-J-Soso A et al (eds) Antimicrobial resistance in developing countries. Springer, New York, pp 15–26
Campion JJ, McNamara PJ, Evans ME (2004) Evolution of ciprofloxacin-resistant Staphylococcus aureus in vitro pharamcokinet environments. Antimicrob Agents Chemother 48(12):4733–4744
Ceccharelli D, Salvia AM, Sami J, Cappuccinelli P, Colombo MM (2006) New cluster of plasmid-located class 1 integrons in Vibrio cholerae O1 and a dfrA15 cassette containing integron in Vibrio parahaemolyticus isolated in Angola. Antimicrob Agents Chemother 50:2493–2499
Chang C, Chang W, Chang S, Cheng S (2008) Antibacterial activities of plant essential oils against Legionella pneumophila. Water Res 42:278–286
Chusri S, Villanueva I, Voravuthikunchai SP, Davies J (2009) Enhancing antibiotic activity: a strategy to control Acinetobacter infections. J Antimicrob Chemother 61:1203–1211
Coffey TJ, Dowson CG, Daniels M, Zhou J, Martin C, Spratt BG, Musser JM (1991) Horizontal transfer of multiple penicillin-binding
protein genes and capsular biosynthetic genes in natural populations of Streptococcus pneumoniae. Mol Microbiol 5(9): 2255–2260

Cowan MM (1999) Plant products as antimicrobial agents. Clin Microbiol Rev 12(4):564–582

Das K, Tiwari RKS, Shrivastava DK (2010) Techniques for evaluation of medicinal plant products as antimicrobial agent: current methods and future trends. J Med Plant Res 4(2):104–111

Díaz-Granados CA, Cardo DM, McGowan-Jr JE (2008) Antimicrobial resistance: international control strategies with a focus on limited resource settings. Int J Antimicrob Agents 32(1):1–9

Díaz-Mejía JJ, Amábile-Cuevas CF, Rosas I, Souza V (2008) An analysis of the evolutionary relationships of integron integrases with emphasis on the prevalence of class1 integron in Escherichia coli isolates from clinical and environmental origins. Microbiol 154:94–102

Dubey D, Padhy RN (2013) Antibacterial activity of Lantana camara L. against multidrug resistant pathogens from ICU patients of a teaching hospital. JHerb Med (In press). doi:10.1016/j.hermed.2012.12.002

Dubey D, Sahu MC, Rath S, Paty BP, Debata NK, Padhy RN (2012) Antimicrobial activity of medicinal plants used by aborigines of Kalahandi, Orissa, India against multidrug resistant bacteria. Asian Pac J Trop Biomed 2(2):S846–S854

Edziri H, Mastouri M, Mahjoub MA, Mighri Z, Mahjoub A, Versчаeve L (2012) Antibacterial, antifungal and cytotoxic activities of two flavonoids from Retama raetam flowers. Molecules 17:7284–7293

Emeka PM, Badger-Emeka LI, Fateru F (2012) In-vitro antimicrobial activities of Acalyphaorna leaf extracts on bacterial and fungal clinical isolates. J Herb Med 2(4):136–142

Fonseca EL, dos Santos Freitas FF, Vieira VV, Vicente ACP (2008) New qnr gene cassettes associated with superintegron repeats in Vibrio cholerae O1. Emerg Infect Dis 14:1129–1131

Gandhi NR, Moll A, Sturm AW, Gandhi NR, Moll A, Sturm AW, Govender T, Laloo U, Zeller K, Andreas J, Friedland G (2006) Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. Lancet Infect Dis 368:1575–1580

Ghafur A (2013) The Chennai declaration: an Indian perspective on the antimicrobial resistance challenge. Global Antimicrob Resist 1(1):5–6

Ghafur A, Mathai D, Muruganathan A, Jayalal JA, Kant R, Chaudhary D, Prabhahashh K, Abraham O, Gopalakrishnan R, Ramesubrmanian V, Shah SN, Pardeshi R, Huligol A, Kapil A, Gill JPS, Singh S, Risam HS, Balakrishnan P, Kumar AV, Maharajan S, Mushtaq S, Noorie T, Paterson DL, Pearson A, Perry C, Pike B, Rao B, Rizvi U, Sarma JB, Sharma M, Sridhan E, Thirunarayan MA, Turton J, Upadhyay S, Warner M, Welfare W, Livemore DM, Woodford N (2010) Emergence of a new antibiotic resistance mechanism in India, Pakistan and UK: a molecular, biological and epidemiological study. Lancet Infect Dis 10(9):597–602

Gibbons S (2004) Anti-staphylococcal plant natural products. Nat Prod Rep 21:263–277

Giske CG, Cornaglia G (2010) Supranational surveillance of antimicrobial resistance: the legacy of the last decade and proposals for the future. Drug Resist Update 13(4–5):93–98

González-Lomothe R, Mitchell G, Gattuso M, Diarra MS, Maloum F, Bourarab K (2009) Plant antimicrobial agents and their effects on plant and human pathogens. Int J Mol Sci 10:3400–3419

Goossens H (2013) The Chennai declaration on antimicrobial resistance in India. Lancet Infect Dis 13(2):105–106

Grohman E, Muth G, Espinosa M (2003) Conjugalative plasmid transfer in Gram-positive bacteria. Microbial Mol Biol Rev 67(2):277–301

Hancock EW (2005) Mechanisms of action of newer antibiotics for Gram-positive pathogens. Lancet Infect Dis 5(4):209–218

Hiramatsu K, Katayama Y, Yuzawa H, Ito T (2002) Molecular genetics of melliicillin-resistant Staphylococcus aureus. Int J Med Microbiol 292:67–74

Hsu S, Chiu T, Pang J, Hsu-Yuan C, Chang G, Tseng H (2006) Characterization of antimicrobial resistance patterns and class1 integrons among Escherichia coli and Salmonella enterica serovar choleraesuis strains isolated from humans and swine in Taiwan. Int J Antimicrob Agents 27(5):383–391

Huang Y, Hsueh P (2008) Antimicrobial drug resistance in Taiwan. Int J Antimicrob Agents 32(3):S174–S178

Igbinosoa OO, Igbinosoa EO, Aiyegoro OA (2009) Antimicrobial activity and phytochemical screening of stem bark extracts from Ijatropa curcas Linn. Afr J Pharma Pharmacol 3(2):58–62

Ignacimuthu S, Pavunraj M, Duraipandiyarn V, Raja N, Muthu C (2009) Antibacterial activity of a novel quinone from the leaves of Pergularia daemia (Forsk.). A traditional medicinal plant. Asian J Trad Med 4(1):36–40

Jacob GA, Munoz-Price LS (2005) The new B-lactamases. N Engl J Med 352:380–391

Janovska D, Kubikova K, KokoLSa K (2003) Screening for antimicrobial activity of some medicinal plants species of traditional Chinese medicine. Czech J Food Sci 21(2):107–110

Kadota S, Basnet P, Ishi E, Tamura T, Namba T (1997) Antibacterial activity of trichoradial A from Rhabdosia trichocarpa against Helicobacter pylori. Zentralbl Bakteriol 286(1):63–67

Kartikeyan K, Thirunayanan MA, Krishnan P (2010) Coexistence of blaOXA-23 with blaMDR and armA in clinical isolates of Acinetobacter baumannii from India. J Antimicrob Chemother 65:2253–2254

Kazmi MH, Malik A, Hameed S, Akhtar N, Noor AS (1994) An anthrquinone derivative from Cassia italica. Photochemistry 36:761–763

Kuete V, Ailbert-Franco S, Eystng KO, Ngameni B, Folefoc GN, Ngueveing JR, Tangmoyo JG, Fatso GW, Konguem J, Ouahouo BMW, Bolla JM, Chevalier J, Ngadju BT, Nkengfack AE, Pages JM (2011) Antibacterial activity of some natural products against bacteria expressing a multi-drug-resistant phenotype. Int J Antimicrob Agents 37(2):156–161

Kumarasamy KK, Toleman MA, Walsh TR, Bagaria J, Butt F, Balakrishnan P, Chaudhury U, Domsel M, Giske CG, Irfan S, Krishnan P, Kumar AV, Maharajan S, Mushtaq S, Noorie T, Parson DL, Pearson A, Perry C, Pike B, Rao B, Ray U, Sarmal J, Sharma M, Sheridan E, Thirunarayan MA, Turton J, Upadhyay S, Warner M, Welfare W, Livemore DM, Woodford N (2010) Emergence of a new antibiotic resistance mechanism in India, Pakistan and the UK: a molecular, biological and epidemiological study. Lancet Infect Dis 10(9):597–602

Lalitha MK, David T, Thomas K (2013) Nasopharyngeal swabs of school children, useful in rapid assessment of community antimicrobial resistance patterns in Streptococcus pneumoniae and Haemophilus influenzae. J Clin Epidemiol 66(1):44–51

Lewis K (2001) In search of natural substrates and inhibitors of MDR pumps. J Mol Microbiol 2:347–254

Lewis K, Ausubel FM (2006) Prospects for plant–derived antimicrobials. Nat Biotechnol 24:1504–1507

Li Y, Xiang Q, Zhang Q, Huang Y, Su Z (2012) Overview on the recent study of antimicrobial peptides: origin, functions, relative mechanisms and application. Peptides 37(2):207–215

Lu X, Rasco BA, Jabil JM, Aston DE, Lin M, N Korea ME (2011) Investigating antibacterial effects of garlic (Allium sativum) concentrate and garlic-derived organosulfur compounds on Campylobacter jejuni by using fourier transform infrared
spectroscopy, Raman spectroscopy, and electron microscopy. 
Appl Environ Microbiol 77(15):5257–5269

Michaëlo TB, Pinto AV, Pinto MC FR, Leal ICR, Silva MG, Amaral 
ACF, Kuster RM, Netto-dossantos KR (2003) In-vitro activity of 
Brazilian medicinal plants, naturally occurring naphthoquinone 
and their analogues, against methicillin resistant Staphylococcus 
aureus. Int J Antimicrob Agents 21(3):279–284

McGaw LJ, Lall N, Meyer JJM, Effon JN (2008) The potential of 
South African plants against Mycobacterium infections. J Ethno-
pharmacol 119(3):482–500

Memishi ZA, Venkatesh S, Shibi AM (2003) Impact of travel on 
international spread of antimicrobial resistance. Int J Antimicrob 
Agents 21(2):135–142

Moneim A, Suleman E, Issa FM, Elkhalifa EA (2007) Quantitative 
determination of tannin content in some sorghum cultivars and 
evaluation of its antimicrobial activity. Res J Microbiol 
2(3):284–288

Norbury RS, Nord CE, Finch R (2005) Lack of development of new 
antimicrobial drugs: a potential serious threat to public health. 
Lancet Infect Dis 5(2):115–119

Okeke IN, Laxaminaran Y, Bhutta ZA, Duse AG, Jenkins P, O’Brien 
TF, Pablos-Mendez A, Klugman KP (2005a) Antimicrobial 
resistance in developing countries. Part I: recent trends and 
current status. Lancet Infect Dis 5(8):481–493

Okeke IN, Klugman KP, Bhutta ZA, Duse AG, Jenkins P, O’Brien 
TF, Pablos-Mendez A, Laxaminaran Y (2005b) Antimicrobial 
resistance in developing countries. Part II: strategies for 
containment. Lancet Infect Dis 5(9):568–580

Okuma K, Iwakawa K, Tumidei JD, Grubb WB, Bell JM, O’Brien 
FG, Coombs GW, Pearlman JW, Tenover FC, Kapi M, Tiens-
asitorn C, Ito T, Hiramatsu K (2002) Dissemination of new 
methicillin resistant Staphylococcus aureus clones in the 
community. J Clin Microbiol 40(11):4289–4294

Ozcelik B, Deliorman OD, Ozgen S, Ergun F (2008) Antimicrobial 
activity of flavonoids against Extended Spectrum β-Lactamase 
(ESBL) producing Klebsiella pneumoniae. Trop J Pharma Res 
7(4):1151–1157

Palaniappan K, Hollay RA (2010) Use of natural antimicrobials to 
increase antibiotic susceptibility of drug resistant bacteria. Int J 
Food Microbiol 140(2–3):164–168

Patino OJ, Cuca LE (2011) Monophyllidin, a new alkaloid 1-Proline 
derived from Zanthoxylum monophyllum. Phytochem Let 
4:22–25

Ragasa CY, Ha HKP, Hasika M, Maridable J, Gaspio P, Rideout J 
(2008) Antimicrobial and cytotoxic terpenoids from Cymbopo-
gen citratus. Stapf. Philippin Sci 45(1):111–122

Rajpara N, Patel A, Tiwari N, Bahuguna H, Antony A, Choudhury I, 
Ghosh A, Jain R, Bhardwaj AK (2009) Mechanism of drug 
resistance in a clinical isolate of Staphylococcus aureus. Asia Pac J 
Trop Biomed 1(1):S76–S78

Roberts MC (1996) Tetracycline resistance determinants: mechani-
isms of action, regulation of expression, genetic mobility, and 
distribution. FEMS Microbiol Rev 19:1–24

Sahu MC, Padhy RN (2013) In vitro antimicrobial potency of Butea 
onosperma Lam. against 12 clinically isolated multidrug 
resistant bacteria. Asia Pac J Trop Disease 3(3):217–226

Savage PB (2001) Multidrug resistant bacteria: overcoming antibiotic 
permeability barriers of Gram-negative bacteria. Ann Med 
33:167–171

Schlegelova J, Vlkova H, Babak V, Holasova M, Jaglic Z (2008) 
Resistance to erythromycin of Staphylococcus spp. isolates from 
the food chain. Veterinarni Med 53(6):307–314

Semwal DK, Rawat U (2009) Antimicrobial hasubanalactam alkaloid 
from Stephania glabra. Planta Med 75(4):378–380

Sorge OO, Adeniyi BA, Roberts MC (2006) New antibiotic resistance 
genes associated with CTX-M plasmids from uropathogenic 
Nigerian Klebsiella pneumoniae. J Antimicrob Chemother 
58:1048–1053

Srivastava J, Chandra H, Singh N (2007) Allelopathic response of 
Vetiveria zizanioides (L.) Nash on members of the family 
Enterobacteriaceae and Pseudomonas spp. Environmentalist 
27:253–260

Sternitz FR, Lorenz P, Tawara JN, Zenewicz LA, Lewis K (2000) 
Synergy in a medicinal plant: antimicrobial action of berberine 
potentiated by S’-methoxyhydrocarpin, a multidrug pump 
inhibitor. Appl Biol Sci 97(4):1433–1437

Styers Da, Sheehan DJ, Hogan P, Sahm DF (2006) Laboratory-based 
surveillance of current antimicrobial resistance patterns and 
trends among Staphylococcus aureus: 2005 status in the United 
States. Ann Clin Microb Antimicrob 5:2

Tegos G, Stermitz FR, Lomovskaya O, Lewis K (2002) Multidrug 
pump inhibitors uncover remarkable activity of plant antimicro-
bials. Antimicrob Agents Chemother 46(10):3133–3141

Tekwu EM, Pieme AC, Beng VP (2012) Investigations of antimicro-
bial activity of some Cameroon medicinal plant extracts 
against bacteria and yeast with gastrointestinal relevance. 
J Ethnopharmacol 142(1):265–273

Thomas BPTH, Cammure BPA, Thevissen K (2002) Plant defensins. 
Planta Med 71:193–202

Thorrold CA, Letsoalo ME, Duse AG, Marais E (2007) Efflux pump 
activity in florouquinolone and tetracycline resistant Salmonella 
and E. coli implicated in reduced susceptibility to household 
antimicrobial cleaning agents. Int J Food Microbiol 
118(3):315–320

Threlfall EJ (2002) Antimicrobial drug resistance in Salmonella: 
problems and perspective in food and water-borne infections. 
FEMS Microbiol Rev 26(2):141–148

Upadhyaya S (2013) Screening of phytochemicals, nutritional status, 
antioxidant and antimicrobial activity of Vetiveria zizanioides (L.) 
Nash. Int J Food Microbiol 118(3):315–320

Vila J, Pal T (2010) Update on antimicrobial resistance in low income 
countries: factors favouring the emergence of resistance. Open 
Infect Dis J 4:38–54

Wan J, Wilcock A, Coventry MJ (1998) The effect of essential oil of 
basil on the growth of Aeromonas hydrophila and Pseudomonas 
fluorescens. J Appl Microbiol 84:152–158

Wang PD, Bang JK, Kim HJ, Kim JK, Kim Y, Shin SY (2009) 
Antimicrobial specificity and mechanism of action of disulfide— 
removed linear analogs of the plant derived cyste-rich antimicro-
bial peptides Ib-AMP1. Peptides 30(12):2144–2149

Warneke PH, Becker ST, Podschun R, Sivanathan S, Springer IN, 
Russo PAI, Wiltfang J, Fickenscher H, Sherry E (2009) The 
battle against multi resistant strains: renaissance of antimicro-
bial essential oils as a promising force to fight hospital 
acquired infections. J Cranio Maxillofac Surg 37(7): 
392–397
WHO (World Health Organization) (2011) Combat antimicrobial resistance. http://www.who.int/world-health-day/2011

Widelski J, Popova M, Graikou K, Grownia K, Chinou I (2009) Coumarins from Angelica lucida L.—antibacterial activities. Molecule 14:2729–2734

Wright GD (2005) Bacterial resistance to antibiotics: enzymatic degradation and modification. Adv Drug Deliv Rev 57(10):1451–1470

Zhang Y, Lewis K (1997) Febatins: new antimicrobial plant peptides. FEMS Microbiol Lett 149:59–64