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Emergence of Herbal Antimicrobial Drug Resistance in Clinical Bacterial Isolates

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Abstract

Alternative medicines have been practiced for centuries and remained as integral part of many civilizations around the globe. One important aspect of alternative medicine includes herbal medicines/drugs in which locally available plants or its parts are used in treating ailments. Herbal medicines are commonly used for treating both infectious and non-infectious diseases. On the other hand, Antimicrobials used to treat bacterial infections caused by multiple drug resistant (MDR) and total drug resistant (TDR) strains are becoming more common in the clinical setting and world is looking for alternative therapies to treat such infections. Herbal medicines are anticipated to protect us from infections as they are considered as better alternatives for existing and emerging antimicrobial drug resistant (ADR) pathogens. Herbal antimicrobials acts either by killing or restricting the bacterial growth through parallel mechanisms as antibiotics similarly there could be mechanisms of herbal drug resistance just like antibiotic resistance in microbes. However, lack of systematic and standard data on herbal antimicrobial activity neither we could understand the extent of herbal drug resistance nor the mechanism of resistance in microbes. The recent studies on antimicrobial properties of herbal drugs on clinical isolates indicated that there is some insensitivity or resistance in microbes towards some common herbal antimicrobial compounds. This review focuses on recent reports of herbal drug resistance among pathogenic microbes (clinical bacterial isolates) against herbal drugs.

Keywords: Herbal medicine; Antimicrobial resistance; ADR; TDR; Herbal antimicrobials; MHDR

Introduction

Antibiotic resistance is a serious and growing phenomenon in contemporary medicine and has emerged as one of the pre-eminent public health concerns in 21st century. World health organization's 2014 report on global surveillance of antimicrobial resistance states that "antibiotic resistance is a serious threat and no longer a prediction for the future; it is happening right now in every region of the world and has the potential to affect anyone, of any age, in any country". This jeopardizes the treatment of common infections in the community and hospitals [1]. It has also been predicted by several authors that the next pandemic will not be of some specific disease but due to ineffectiveness of available drugs to cure even small cuts and wounds.

Antimicrobial drug resistance (ADR) hampers the control of infectious diseases and has potential to threaten health security, damage trade and economies but it is difficult to think of "the world without antibiotics". It may be a deadly situation because the routine surgery, cancer treatments, organ transplants etc. become just impossible without antibiotics. So, we need to save antibiotics for certain therapeutic interventions. It is also important to take urgent and coordinated action to save the world from entering a post-antibiotic era, in which common infections and minor injuries can become life threatening.

Development of ADR is a natural phenomenon [2]. However, certain human actions accelerate the emergence and spread of ADR. Inappropriate therapeutic use of antimicrobial drugs, and use in agriculture, fish, poultry and animal farming, favours the emergence and selection of resistant strains. Besides, poor infection prevention & control practices further contribute for emergence and spread of ADR. Eminent organizations like WHO, World Organization for Animal Health (OIE) and Food and Agriculture Organization (FAO) of the United Nations have collaborated to promote best practices to avoid the emergence and spread of antibacterial resistance. All attempts are in progress to promote optimal use of antibiotics both in humans and animals to address problem of growing AMR.

Most of the pathogenic bacteria have developed resistance to modern antibiotics as a result of which we are evidencing multi drug resistance among bacteria. We are running out of antibiotics and could not add any new group of antibiotics since last three decades. At the same time, there is no potential antibiotic in pipeline for release in near future. As a result, research in alternative medicine has begun and one such alternative is use of herbal drugs to treat infections.

Since ancient times, herbs and their essential oils are known for their varying degrees of antimicrobial activity. Due to immense biodiversity, India is a vast repository of medicinal plants that are used in traditional medical treatments [3]. Almost, 70% modern medicines in India are derived from natural products and the various indigenous systems of India such as Siddha, Ayurveda, Unani and Allopathy use several plant species to treat different ailments [4]. Herbal medicine has always been a part of Indian culture and gaining popularity due to toxicity and side effects of allopathic medicines. This led to sudden increase in the number of herbal drug manufactures in India [5]. It's reported that more than 500 Indian traditional communities use about

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800 plant species for curing different diseases among 20,000 medicinal plant species that are available in the country [6].

The burning question is now, if non-judicious use of antibiotics may lead to emergence and spread of ADR why it may not happen to herbal antimicrobials? In recent past, a few reports have already documented about prevalence of herbal antimicrobial drug resistance (HADR) in environmental and clinical strains of bacteria. However, either we fear to accept the existence of HADR (probably due to looking those as last resources) or due to poor understanding of HADR. Therefore, this review details about HADR from clinical bacterial isolates documented recently.

Drug Resistance in Bacteria

Emergence of drug resistance made treatment of infectious diseases more difficult. For instance, extensively drug-resistant tuberculosis (XDRTB) has been identified in 92 countries and there were about 4, 50,000 new cases of multidrug-resistant tuberculosis (MDR-TB) worldwide in the year 2012 [1]. Similarly, evolution of methicillin resistant *Staphylococcus aureus* (MRSA) and vancomycin resistant *Staphylococcus aureus* (VRSA) leads to nosocomial infections. It is alarming fact that fluoroquinolone and carbapenem resistance in *E. coli* and other commensal intestinal bacteria are on continuous rise [1]

Antibiotic resistance is a phenomenon in which some sub-populations of bacteria resist the presence of one or more antibiotics and pathogens that are resistant to multiple antibiotics are considered as multidrug resistant (MDR) or superbugs [7]. The evolution of resistant bacterial strains is a natural phenomenon which occurs when microorganisms replicate themselves erroneously or when resistant traits are exchanged between strains through horizontal gene transfer mechanisms. The use and misuse of antimicrobial drugs accelerates the emergence of drug-resistant strains. Poor infection control practices, inadequate sanitary conditions and inappropriate food-handling encourage further spread of the antimicrobial resistance [1]. Moreover, the scenario of AMR is not only restricted to human pathogens, but also common in veterinary pathogens. It has been reported that extended spectrum β-lactamase and metallo-β-lactamase producing strains are common in animals and also present in their environment [8].

Need for Revival of Herbal Antimicrobials

Herbal medicines are derived from the plants or plant extracts containing therapeutic substances [9]. The herbal medicine practice is generally called as complementary and alternative medicine (CAM). Many essential oils are relatively easy to obtain, have low mammalian cell toxicity, and degrade quickly in water and soil, making them relatively easy to use and environment friendly antibiotic alternatives [10].

Herbal drugs are used by physicians for hundreds of years as indigenous systems of medicine and about 80% of the world population still use them for primary health care [6]. Hippocrates (5th century B.C.) in his writings mentioned approximately 300 to 400 medicinal plants. Similarly, Dioscorides (1st century B.C.) wrote De Materia Medica, a medicinal plant treatise that outlined the medical use of numerous plant species [11]. China has history of 5000 years in use of herbal medicines [12,13]. The Holy Bible also describes many medicinal plant species, such as myrrh and frankincense, which were reported to have antiseptic and healing properties [11]. Around 250,000-500,000 plants species are found worldwide. Many of these plants are used for various purposes such as foods and medicines by both humans and animal species [14] but less than 10% of these plants have been scientifically investigated [11].

Herbal medicine is becoming more popular not only in developing countries but also in developed countries [15]. Many studies have been conducted across the globe to prove or find the antimicrobial efficiency and /or properties of herbal drugs [16,17,18, 19,20]. For example, *Achillea millifolium* (yarrow), *Caryophyllus aromaticus* (clove), *Melissa offficinalis* (lemon-balm), *Ocimun basilucum* (basil), *Psidium guajava* (guava), *Punica granatum* (pomegranate), *Rosmarinus officinalis* (rosemary), *Salvia officinalis* (sage), *Syzygyum joabolanum* (jambolan), *Thymus vulgaris* (thyme) and phytochemicals such as benzoic acid, carvacrol, cinnamic acid, eugenol and farnesol were found to contain antimicrobial properties [21]. Among herbal preparations, essential oils of several medicinal plants are often shown to possess antimicrobial activities. Among all the oils, the essential oil of cinnamon has been found to be the most effective, followed by the essential oil of oregano and thyme (the active ingredient in latter two plants is carvacrol) [22].

The demand for the herbal drugs has increased in recent times, as many plants or herbs are scientifically proven to contain bioactive compound(s) and as alternatives to harmful synthetic drugs that cause side effects to biological system and environment [23]. The herbal drugs have been used for treatment of many infectious diseases in humans as well as in animals all over world [23]. In developing countries herbal medicines are now in great demand since they are not only inexpensive but also for better cultural acceptability, better compatibility with the human body and minimal side effects [24,6]. Other than antimicrobial therapy, herbal drugs are used for treatment of age-related disorders like memory loss, osteoporosis, immune disorders, etc [6]. The active ingredients of plants can also be used in laxatives, blood thinners, antibiotics and anti-malarial medications. Medicinal plants can also be used as sources of lead compounds for drug design and development [25,26,27,28]. It has been reported that volatile oils from plants have analgesic, antibacterial, deodorizing, febrifuge, fungicidal, antiseptic, antidepressant, astringent, diuretic, galactogogue, insecticidal, antipyretic, antimicrobial and sedative properties [29,30].

It is reported that the curcumin from turmeric inhibited the biofilm formation in *H. pylori* in cell cultures. However, *H. pylori* could restore ability to form biofilm during extended time of incubation [31]. Some essential oils have been reported to kill biofilms formed by *Pseudomonas aeruginosa* (PAO1), *Pseudomonas putida*, and *Staphylococcus aureus* [10]. There are innumerable uses of herbal medicines; therefore, there is a need to revamp research to develop alternative antimicrobial drugs for the treatment of infectious diseases. Of the several approaches, one is to screen local medicinal plants for possible antimicrobial properties and active molecules are important for the future. Another approach may be to find out the herbal molecules which potentiate the existing antibiotics through synergistic action or through inhibiting efflux pumps or inactivating antibiotic degrading enzymes of microbes.

Mechanism of Action of Herbal Drugs

Broadly, six possible mechanisms of antimicrobial action has been reported, they are: (1) disintegration of cytoplasmic membrane, (2) interaction with membrane proteins (ATPases and others), (3) disturbance of outer membrane of gram negative bacteria with the release of lipopolysaccharides, (4) destabilization of the proton motive force with leakage of ions, (5) coagulation of the cell content, and (6) inhibition of enzyme synthesis [32]. The effects of essential oils and their bioactive constituents mainly disrupt the bacterial cell membranes followed by release of membrane components [33]. However, it has

been reported that the components of lemongrass oil also inhibited biofilm formation, killed preformed biofilms and have multiple targets on the bacterial cell [33]. The lipophilic monoterpenes of essential oils deeply interact and affect the molecular structure of lipid bilayers. Some examples are myrtle essential oil which affects mainly cell wall and membrane structures leading to the release of intracellular contents accompanied by disruption of membrane function such as electron transfer, enzyme activity or nutrient absorption [34]. Carvacrol and pcymene get absorbed by lipid membranes thus affecting membrane lipid composition. The antimicrobial activity of terpenes such as thymol also damages lipid membranes [35,36]. Cranberry has also been reported to adhere to uroepithelial cells and change the physicochemical surface properties of uropathogenic *E. coli* [37].

Herbal Drug Resistance

The resistance to herbal drugs in various clinical and/ or non-clinical isolates of pathogenic organisms has been reported more recently from veterinary clinical isolates but this resistance or sensitivity is comparative and results vary with the concentration of drug used [38]. For example, studies on resistance to LGO and other herbal drugs showed varying degree of MIC [38,39] depending upon species of microbes tested or within same species among different strains, this suggests that microbes has mechanism to overcome the bactericidal concentration of herbal drugs also.

The ability of microorganisms to develop resistance to herbal drugs is not well studied. It is often stated that bacteria can not develop resistance to herbal medicines [40-43]. However, recent reports suggested that microbes can overcome bactericidal or bacteriostatic activities of the herbal drugs. Many of herbal drugs reported to contain better antimicrobial properties either alone or in combination with antibiotics but reports on ineffective herbal drugs on certain strains cannot be neglected. Khan *et al.* [39], reported many clinical and non-clinical bacterial isolates were sensitive to herbal drugs like *A. nilotica, T. arjuna, S. aromaticum* but study also revealed that some of the isolates such as *P. aeruginosa, E. coli, C. albicans*, *K. pneumoniae*, *E. coli* from nosocomial infections, and *E. coli*, *C. albicans, K. pneumoniae* isolated from community acquired infections were resistant to herbal drugs. Similarly, Singh et al. [44] reported that many bacterial strains isolated from different clinical conditions in animals and from post mortem cases were resistant to lemon grass oil. Fagbemi et al. [45] also reported resistance in *E. coli* ATCC 25922, and field isolates of *E. coli*, *P. aeruginosa* and *S. flexneri* against aqueous extracts of unripe banana (*Musa sapientum)*, lemon grass (*Cymbopogon citratus*) and turmeric (*Curcuma longa*). Lemon grass oil was reported to be effective against multi drug resistant bacteria except *P. aeruginosa* [46]. Moore-Neibel et al. 2011[33], reported that the antimicrobial activity of lemongrass oil against *Salmonella* Newport was concentration and time dependent. Among bacterial population, the enteric bacteria are often reported to be more resistant than other bacteria to herbal drugs [38,47,48,49]. High resistance was reported among bacterial strains of gecko origin to herbal antimicrobials, moreover, it is said that, herbal drug resistance varied among strains of bacteria and herbal drugs can be selective and may not have broad spectrum against large bacterial populations [50].

One important use of herbal medicines is to treat the multiple drug resistant pathogens but, some drug resistant or MDR strains have also been isolated from the herbal products. Brown and Jiang [51] could isolate ceftriaxone and tetracycline resistant bacteria from ground garlic samples at 1.1×10^2 CFU/g and 3.0×10^2 CFU/g, respectively. Similarly tetracycline-resistant bacteria were present in organic onion powder samples. The low levels of resistant bacteria were also isolated from other products such as ginger, rosemary, mustard, and goldenseal. High CFU count of enteric bacteria was found even in dry spice samples [52]. The presence of drug resistant bacteria in the herbal medicinal products can also become a source of antibiotic resistance to commensel bacteria in consumers [15]. Ogunshe and coworkers [53] confirmed that most indigenous orally consumed herbal medications in Nigeria harbor bacterial flora that exhibited multiple resistance to routinely used antibiotics. Besides being source of MDR strains, resistance to herbal drugs is not uncommon among bacteria [38,44,47,48].

Most herbal products on the market today have not been subjected to drug approval process to demonstrate their safety and effectiveness [24]. Though the guidelines for the assessment of herbal medicine are developed by WHO, but it has not systematically evaluated [6]. This may lead to indiscriminate or over use of these drugs which could cause herbal drug resistance. The ability of microorganisms to develop resistance to herbal drugs is not well studied. However recent reports suggested that microbes can overcome bactericidal or bacteriostatic activities of the herbal drugs, Table 1, gives some examples of resistant and sensitive bacteria against common herbal agents reported in recent studies.

Herbal Drug Resistant Mechanisms

Herbal drugs are often reported to be important alternatives for MDR strains, and it is shown that bacteria can not develop resistance to herbal medicines [40-43]. It has been reported that some bacteria has natural resistance to some of the herbal medicines [44] but there is no clear understanding about the resistance mechanisms of microorganisms against these naturally occurring antimicrobial compounds.

CDC [54] reported that alternative therapies and herbal drugs are also not the final shot to treat infections and patients with chronic diseases commonly follow herbal drugs for cure [24]. Bacteria, in general, have the genetic ability to transmit and acquire resistance to therapeutic drugs used against them [55]. Even in the food processing industries where herbal compounds are used since a long time, the most urgent problem is that there is still little understanding of the effectiveness of the use of classical preservatives and naturally occurring antimicrobial biomolecules (biological, "natural" preservatives) in conjunction with other common components of food preservation systems.

The genetic approach to reveal the herbal drug resistant genes are yet to be studied however, deletion of rpoS gene in *E. coli* was associated with decreased resistance to carvacrol similarly, deletion of the *sigB* gene in *Listeria monocytogenes* reduced the resistance to carvacrol [56]. However rpoS gene deals with survival of organisms under stress conditions which may or may not be directly involved in resistance to carvacrol. Many scientific reports are available regarding the application of herbal extracts for antimicrobial, therapeutic and other therapeutic purpose in human and animals. However, literature is scant on the herbal antimicrobial drug resistance (HADR) and still less on mechanism of HADR.

Quality Control of Herbal Drugs and WHO Recommendations

Many countries with rich biodiversity like Africa, China, and India practice herbal and traditional medicine since time immemorial. Among European countries, Germany alone reported that more than 70 % of its population uses natural products [57]. The herbal medicines as such have great potential in prevention and therapeutics and also

S.No	Herbal drug/ Essential oils tested	Effective on	Ineffective against	References
1	Lemon grass oil *(Cymbopogon Spp)* (Important constituents- citral geraniol, myrcene, neral, limonene, piperitone, citronellal)	*S. aureus, B. cereus, B. subtilis, E. coli, K. pneumoniae*	*P. aeruginosa*	[46]
		Majority of *Bacillus* spp., *Streptococcus* spp., *Aeromonas* spp., *Edwardsiella, Budvicia aquatica* and *Leminorella ghirmontii*	*majority of Staphyloccous* spp., *Enterococcus* spp., *Salmonella enterica, Citrobacter* spp., *Providencia spp, Kluyvera cryocrescens, Enterobacter* spp., *Proteus* spp., *Escherichia* spp., *Serratia* spp., *Erwinia ananas, Pragia fontium, Klebsiella* spp.	[38]
2	Sage essential oil (*Savia officinalis* L.) (Important constituents: pinene, camphene, myrcene, limonene, 1,8-cineole, thujone, camphor, linalool, bornyl acetate and borneol)	*Dermatophilus congolesis, Pasteurella canis, Plesiomonas shigelloides and Streptococcus* spp.	*Staphylococcus aureus, Bacillus subtilis, E. coli, Pseudomonas aeruginosa, Salmonella enterica* ssp. *enterica* serovar Typhimurium	[61,62,63,43]
3	*Artemesia vulgaris* (Important constituents: Germacrene, Caryophyllene, Zingiberene, Borneol)	Yeast, mold and *Bacillus* strains	*Staphylococcus aureus*, *Streptococcus* spp., *E. coli, Salmonella* and *Klebsiella pneumoniae, A. hydrophila, E. tarda* strains.	[44]
4	Caraway essential oil *(Carum carvi* L.) (Important composition: Acetaldehyde, Cumuninic aldehyde, Furfurol, Carvone, Limonene)	*Bacillus cereus, Bordetella bronchiseptica, Brucella abortus, Dermatophilus congolensis, Erwinia ananas, Escherichia coli* (two), *Moraxella canis* (two), *Moraxella osloensis, Pasteurella multocida, Proteus penneri, Pseudomonas aeruginosa, Raoultella terrigena* and *Streptococcus pyogenes.*	Aeromonads	[60]
5	Nutmeg essential oil *Myristica fragrans* (Important composition: Sabinene, Camphene, d-Pinene, Dipentene, d-Linalool, d-Borneol, i-Terpineol, Geraniol, Myristcin)	*Shigella dysenteriae, Proteus mirabilis, Escherichia coli, Enterobacter aerogenes, Pseudomonas aeruginosa*	*Klebsiella pneumoniae, Salmonella typhi, Bacillus subtilis, Proteus vulgaris*	[64]
6	*Selinum wallichianum* Essential oil (or) Milk Parsley (Important composition: α-bisabolol, farnesol, germacrene D, citronellyl propanoate, α-bisabolol oxide B, sabinene, β-farnesene, limonene)	Reference strains of *E. coli*, (E3376 and E3382), *Edwarsiella tarda*	*Bacillus coaggulans, E. coli, Aeromonas hydrophila, Lactobacillus acidophilus, Klebsiella pneumoniae, Enterococcus*	[48]
7	*Pelargonium* species Rose geranium oil (Important composition: a-pinene, myrcene, limonene, menthone, linalool, geranyl acetate, citronellol, geraniol and geranyl butyrate)	*Streptococcus equi* ssp. *equi, S. pyogenes, S. pneumoniae*	*Streptococcus equi* ssp. *zooepidemicus* *Staphyloccoccus* spp.	[65]
8	*Myrtus communis* L. (Important constituents: Myrtenyl acetate, 1,8-cineol, α-pinene, linalool, limonene, linalyl acetate, geranyl acetate, and α-terpineol)	*S. aureus, Micrococcus luteus, Streptococcus pneumoniae, S. pyogenes, S. agalactiae, Listeria monocytogenes, E. coli, Proteus vulgaris, Pseudomonas aeruginosa*	*Campylobacter jejuni*	[34]
9	*Acacia nilotica* (Important constituents: Menthol, limonene, Pinene)	*Streptococcus mutans* ATCC-700610, *S. bovis* ATCC 9809, *Staphylococcus aureus* ATCC-29213, *Enterococcus faecalis* ATCC-29212, *Pseudomonas aeruginosa* ATCC-27853, *Salmonella* Tphimurium ATCC-13311, *E. coli* ATCC-25922, *C. albicans* ATCC-10231, *K. pneumoniae* ATCC-700603, *E. coli* (isolate of nosocomial infection), *E. coli* (isolates of community acquired infection), *C. albicans* (isolates of community acquired infection), *K. pneumonia* (isolates of community acquired infection)	*E.coli* (isolates of community acquired infection)	[39]
10	*Terminalia arjuna* (Important constituents: Tannins, triterpenoid saponins (arjunic acid, arjunolic acid, arjungenin and arjunic acid), flavonoids, gallic acid, ellagic acid, phytosterols.)	*Streptococcus mutans* ATCC-700610, *S. bovis* ATCC 9809, *S. aureus* ATCC-29213, *E. faecalis* ATCC-29212.	*P. aeruginosa* ATCC-27853, S. Typhimurium ATCC-13311, *E. coli* ATCC-25922, *C. albicans* ATCC-10231, *K. pneumonia* ATCC-700603, *E. coli* (isolate of nosocomial infection), *E. coli* (isolates of community acquired infection), *C. albicans* (isolates of community acquired infection), *K. pneumoniae* (isolates of community acquired infection)	[39]

11	*Eucalyptus globules* (Important constituents: α-pinene, 1,8-cineol, pinocarveol-trans)	*S. mutans* ATCC-700610, *S. aureus* ATCC-29213, *E. faecalis* ATCC-29212, *S. bovis* ATCC 9809.	27853, S. Typhimurium ATCC-13311, *E. coli* ATCC-25922, *C. albicans* ATCC-10231, *K. pneumoniae* ATCC-700603, *E. coli* (isolate of nosocomial infection), *E.coli* (isolates of community acquired infection), *C. albicans* (isolates of community acquired infection), *K. pneumoniae* (isolates of community acquired infection)	[39]
12	*Syzygium aromaticum* (Important constituents: eugenol, β-caryophyllene, eugenyl acetate)	*S. mutans* ATCC-700610, *S. aureus* ATCC-29213, *E. faecalis* ATCC-29212, *S. bovis* ATCC 9809, *P. aeruginosa* ATCC-27853, *S.* Typhimurium ATCC-13311, *E. coli* ATCC-25922, *C. albicans* ATCC-10231, *K. pneumoniae* ATCC-700603, *E. coli* (isolate of nosocomial infection), *E. coli* (isolates of community acquired infection), *C. albicans* (isolates of community acquired infection), *K. pneumoniae* isolates of community acquired infection).	*E. coli* (isolates of community acquired infection)	[39]
13	*Cinnamomum zeylanicum* (Important constituents: eugenol, linalool, piperitone)	*S. mutans* ATCC-700610, *S. aureus* ATCC-29213, *E. faecalis* ATCC-29212, *S. bovis* ATCC 9809, *P.aeruginosa* ATCC-27853, *S.* Typhimurium ATCC-13311, *E. coli* ATCC-25922, *C. albicans* ATCC-10231, *K. pneumoniae* ATCC-700603, *E. coli* (isolate of nosocomial infection), *E. coli* (isolates of community acquired infection), *C. albicans* (isolates of community acquired infection), *K. pneumoniae* (community acquired infection)	*E. coli* (isolates of community acquired infection)	[39]
14	Unripe banana (*Musa sapientum)* (Important constituents: Polyphenols, Phytosterols, starch, fructants)		*E. coli* ATCC 25922, *E. coli*, *P. aeruginosa* and *Shigella flexneri*	[45]
15	Turmeric (*Curcuma longa*) (Important constituents: phenols and terpenoids)		*E. coli* ATCC 25922, *E. coli*, *P. aeruginosa, S. flexneri*	[45]

Table 1: Herbal drug resistance in microbes of clinical importance reported in recent years.

have huge demand as herbal-derived remedies. So, it is need of the hour for powerful and deep assessment of pharmacological qualities and safety of herbal drugs [58].

The safety in use of herbal medicine is a very important public health aspect as the population using these medicines around the globe is enormous. The poor quality and lack of knowledge on usage of herbal drugs can be associated with adverse effects such as increased prothrombin times, severe kidney failure, fatal case of interstitial pneumonia, intracranial hemorrhages etc [59]. Herbal drugs more commonly found to be effective in combination with synthetic drugs to treat the MDR pathogens in vitro [39] however, the adverse reactions due to combination of these drugs in vivo are yet to be analyzed for final use. Many WHO member countries are bound to regulate herbal medicines. Though the WHO, 2004 [59] discussed and documented about the safety monitoring of the herbal medicines with respect to adverse reactions but could not analyze the development of herbal drug resistance in pathogens. Therefore, it is must to decide the amount of herbal product(s) to be used for determining herbal drug sensitivity similar to the standards available for antimicrobial drugs. In lack of standards, confusing literature will keep on emerging giving false impression of affectivity of herbal drugs on microbes. Besides, the lot of data generated in different labs using different standards poses difficulty in meta-analysis of the information to draw a useful conclusion for future clinical use of herbal antimicrobials [60]

Conclusions

The review casts some light about the importance of herbal drugs in treatment of animal and human infections and implies the need to find out the reasons for insensitivity/ tolerance/ resistance of certain bacteria to common herbal drugs. Many studies report the use of herbal drugs but there is hardly any study that concentrates on mechanism of their tolerance/ resistance in microbes. So, it is important to study and understand the mechanism of such tolerance/ resistance to herbal drugs among different isolates of bacteria. This may give the scientific community an opportunity to explore more about this area and also about the adaptability and co-existence between these complex microbes and the rich fauna of our biome.

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