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Evidence Based Antibacterial Potentials of Medicinal Plants and Herbs Countering Bacterial Pathogens Especially in the Era of Emerging Drug Resistance: An Integrated Update

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Abstract: Owing to rising incidences of antimicrobial resistance against various chemotherapeutic and antimicrobial agents, the treatment of bacterial infections requires special consideration that may otherwise lead to grave prognosis. Simultaneously, evolution of many a Multiple Drug Resistant (MDR) bacterial strains have further aggravated the present situation. In this scenario, scrutinizing for some alternative yet effective antibacterial therapeutics like herbs, nutritional immunomodulators, bacteriophages, avian egge antibodies and others have become need of the day. Herbs have been a valuable source of medication in virtually all cultures and societies worldwide due to their important antimicrobial principles and phytoconstituents and wider therapeutic potentials. As various extracts of herbs and medicinal plants are being reported with antibacterial activities, much effort should be made in their identification, studying biologically active ingredients, efficacy and potency testing and scientific validation for their significant and practical multi-beneficial uses. The present review elaborates the potential role and applications of several herbs in treating bacterial infections and various types of bacterial diseases for safeguarding health of humans and their companion animals. It highlights the salient beneficial applications of traditional herbs and novel phytomedicines, from ancient periods to modern usages. Due emphasis has been given regarding scientific approaches to be followed and future perspectives with a vision to counter the emerging antimicrobial resistance. The review will certainly promote and popularize herbs as alternatives to conventional antimicrobials, particularly in the event of emerging MDR bacterial infections. Global usages of herbs as alternative and complementary medicines to various antimicrobials would lead not only to safeguard health issues and obtain optimum production from animals but will also ensure the public health issues including of food safety concerns viz., antibiotic residual effects in animal products (milk, meat) and zoonotic threats.

Key words: Medicinal plants, herbs, phytoconstituents, biological activity, pharmacological principles, bacterial pathogens, antibiotic resistance, multiple drug resistance, antibacterial effects, treatment, herbal therapy

INTRODUCTION

Initiation and development of a bacterial infection in an animal requires a three dimensional interaction between bacterial agents, environment and the immune status of the animal (Rahal *et al.*, 2014a). A bacterial disease can be initiated only when pathogenic bacteria comes in contact with a susceptible host in a disease favouring

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environment (Engering *et al*., 2013; Kuehn and Kesty, 2005; Jelsbak *et al*., 2012). The environment plays a crucial role in modulating the virulence of the pathogens as well as reducing the host defence (Martinez and Baquero, 2002; Rahal *et al*., 2014a) and thus increases the susceptibility of the host towards various pathogens. A pathogenic agent can enter the animal body via., various possible routes of exposure (Kumar *et al*., 2011; Dhama *et al*., 2014; Verma *et al*., 2014a) but the immune system of host can certainly phagocytise the pathogen (e.g., by secreting chemical factors) and thus checks the disease progress. Moreover, alterations in the microenvironment such as abrasions, wound, malnutrition, pathophysiological conditions may further facilitate the disease development (Madenspacher *et al*., 2013).

For development of a disease, immune status of the animals and human population is an important issue. A susceptible host population can favour even a mild pathogen to produce an epidemic form of disease while immunocompetent population can resist even highly pathogenic microbial strains. The immune status of the animals depends on a number of environmental variables for its fluctuations (Rahal *et al*., 2014a). Animals with immunocompromised lungs usually show higher incidences of pathophysiology due to leukotoxins and lipopolysaccharide exposures (Panayotova-Pencheva and Alexandrov, 2010). Both these toxins act as chemotactic factors for inflammatory cells and promote inflammation and severe damage in the lung tissues. In immature animals, such outbreaks may take an acute form but with high mortality rates. Both these mechanisms of initiation of inflammation as well as cellular damage are pharmacologically well understood and can be counteracted with the use of phytoconstituents of herbs and plants (Rahal *et al*., 2009, 2014a,b).

Even today, due to high cost of effective antibiotics and the predicament of antibiotic resistance microbial strains worldwide, about 60-85% of the population of developing world relies either on herbal or on indigenous forms of Complementary and Alternative Medicine (CAM) medicines for their various general health related issues and countering several diseases/disorders (Kochnar, 1981; Okeke *et al*., 1999; Ernst, 2000; Archana *et al*., 2011; Umashanker and Shruti, 2011; Mahima *et al*., 2012; Tiwari *et al*., 2012, 2013a, b; Yarney *et al*., 2013; Midrarullah *et al*., 2014). Herbal plants have been used as a source of valuable medication in virtually all cultures worldwide due to presence of important antimicrobial principles, immunomodulatory activities, maintenance of general health, precious therapeutic properties and healing potentials; thus ensure prevention and cure for several diseases and disorders of humans and animals (Baquar, 1995; Rios and Receo, 2005; Mahima *et al*., 2012; Rahal *et al*., 2014b). The healing properties of these medicinal plants and herbs were well accepted by our ancestors and nowadays also being scientifically proven as well (Sharma *et al*., 2014). Extracts or phytoconstituents derived from various parts of medicinal plants for prevention and cure of several diseases provide therapeutic modalities with broad spectrum antimicrobial activities against various pathogenic microorganisms (Suck, 1989; Gilani and Atta-ur-Rahman, 2005; Khan *et al*., 2006; Oyetayo and Oyetayo, 2006; Sudhakar *et al*., 2006; Kumar *et al*., 2013a; Vashney *et al*., 2012; Bhatia *et al*., 2013a; Sharma *et al*., 2014). In last few decades, there has been an upsurge in demand and delivery of various herbal products for multifaceted health benefits. In first world country like the United States, herbal remedies still continue as dietary supplements. A variety of herbal therapies have stood the test of time because of their efficacy and potency in the treatment of various bacterial infections with a few having scientific evidences of significant usefulness (Blumenthal *et al*., 1998; Bisset and Wicht, 2001, Mahima *et al*., 2012; Tiwari *et al*., 2012; Rahal *et al*., 2014b).

Currently, the focus on herbal therapy is not only in third world developing countries but also in developed countries. The studies regarding their assessment of risks and benefits, identifying pharmacologically active components/principles and biological activities; scientific validation and revealing ethnomedical values are going on worldwide with regards to thousands of herbs and their extracts, preparations and products which altogether would play vital role in perpetuating, propagating, popularizing and promoting the wider usages of drugs/medicines based on herbs. Active research on various aspects of herbs is being carried out in Nigeria, Rawanda, Maltese Islands, India, Cuba, Eastern part of African subcontinent, China, European countries, middle east, mediterranean and other countries (Odebiyi and Sofowora, 1978; Lanfranco, 1992; Vlietinck *et al*., 1995; Fabry *et al*., 1998; Barrett *et al*., 1999; Bhatt *et al*., 2002; Cano and Volpato, 2004; Arora and Kaur, 2007; Basha and Sudarshanam, 2011; Mizaei-Aghsaghali, 2012; Mahima *et al*., 2012; Midrarullah *et al*., 2014).

Improper diagnosis of any microbial infection leads to untargeted therapy and injudicious use of allopathic drugs, giving way to the emergence of antimicrobial drug resistant pathogens (Kumar *et al*., 2010; Tiwari *et al*., 2013a). Thus, due to exhaustive and indiscriminate use of antibacterials the phenomena of antibacterial therapy failure or ineffectiveness has evolved many drug resistant

pathogens. Amongst these, multidrug resistant pathogenic microorganisms are the concealed enemies to the mankind and animals (Tiwari *et al*., 2013a). The development of antimicrobial resistance among the bacteria is an important issue for treatment of infectious diseases in man as well as animals. Although, there is progress in research and development of new and improved salts of antimicrobial agents but the bacteria are developing resistances to these antibiotics at a higher pace from it. Antibiotic sensitivity testing of the currently available bacterial agents, isolated from different cases of infections, revealed resistant strains even against multiple drugs (Okeke *et al*., 1999; Levy, 2002; Alp, 2007; Tiwari *et al*., 2013a).

Nowadays, various risks factors have been identified which interfere in maintaing a sound health and predispose to several diseases and disorders/ailments, thus increasing the sufferings of both humans and animanls. Some of thes comprise of various stresses, immune pressures, environmental changes especially the global warming effects; increasing population, changing life styles and food habbits and biodiversity changes. Common health problems being flared up due to these predisposing factors in humans are diabetes, blood pressure, heart ailments, arthritis, organ failures, increased incidences of tumors/cancers, immunodepression and obesity. Apart from these, both infectious and non-infectious diseases/disorders are showing an ever increasing trend both in humans and their companion animals alongwith threats of zoonotic pathogens and even pandemics (Taylor *et al*., 2001; Jones *et al*., 2008; Myers and Patz, 2009; Dhama *et al*., 2013a, b; Tiwari *et al*., 2013a; Dhama *et al*., 2014; Verma *et al*., 2014a, b).

In the present scenario of increasing emergence of drug resistance on behalf of continuously evolving resistant microbial pathogens; injudicious use of antimicrobials especially the antibiotics, residual toxic effects of drugs in food and in lieu of emerging and re-emerging pathogenic strains, many novel and safer therapeutic modalities are being explored. These approaches include a combination of immunological, biotechnological and molecular methods. Some of these comprise of bacteriophages, enzybiotics, virophages, mycophage, apoptins, cytokines, monoclonal antibodies, egg yolk antibodies, stem cells, si-RNA, nanomedicines, nutritional immunomdulation, probiotics, antioxidants, panchgavya elements, phytonutrients, fruits and vegetables and herbal remedies; which altogether could be of great help in curbing emerging and evolving pathogenic threats and zoonotic concerns (Natesan *et al*., 2006; Chah *et al*., 2006; Chakravarthi and Balaji, 2010; Shirley *et al*., 2011; Gokulakrishnan *et al*., 2012; Dhama *et al*., 2008, 2013c, d, e, f, 2014; Amarpal *et al*., 2013; Mahima *et al*., 2012, 2013a, b; Tiwari *et al*., 2012, 2013b, 2014a, b, c; Karthik *et al*., 2014; Rahal *et al*., 2014b). Out of all these alternative and novel therapies, traditional homeopathic and ayurvedic/herbal therapies are again gaining much momentum and particularly the herbal therapy is attaining wide popularity and speeding up with a good pace (Mahima *et al*., 2012; Dhama *et al*., 2013b).

Medicinal plants and herbs, the ancient period magical chemotherapeutic drugs and natural treasure to prevent or cure various diseases and ailments are very interesting and play crucial role in safeguarding various health related issues (Farnsworth *et al*., 1985; Ernst, 2000; Krishnan, 2006; Zampini *et al*., 2009; Umashanker and Shruti, 2011; Mizaei-Aghsaghali, 2012; Mahima *et al*., 2012; Dhama *et al*., 2013c, f; Kumar *et al*., 2013a; Tiwari *et al*., 2012, 2013b, 2014d, e). Nowadays, herbal remedies are also getting popularity in providing a viable and safer alternative to prevent and treat cancers (Wargovich *et al*., 2001; Agarwal *et al*., 2011; Mahima *et al*., 2012; Tiwari *et al*., 2012; Dhama *et al*., 2013f; Yarney *et al*., 2013). Being a valuable treasure of natural medicines, these are gaining much attention with their demand increasing day by day; owing to having several advantages over other medicinal sytems including of allopathy. These possess multi-dimensional health benefits and show high utility in alternative and complementary medicinal systems as effective prophylactic and therapeutic regimens. Herbs also help in maintenance and boosting of general health condition, serve as general tonics and have wider practical applications at global level. Though variations in morphology, phytoconstituents, active principles and genetic make occur but altogether the wonder world of herbs forms a bunch of safer (show lesser or no side effects), cheaper/cost-effective and easily available nature's medicines (Dhar *et al*., 2006; Kumar *et al*., 2007; Mahima *et al*., 2012). Such valuable therapeutic alternatives need to be explored fully, tested, standardized, validated and finally be used optimally for the cause of mankind.

Many studies have been performed at various places to know the exact therapeutic mechanisms and sensitivity patterns of herbal products against specific food-borne pathogens and bacterial agent of various infections/ailments in different species of animals (cattle, buffalo, goat, horse, camel, dog and avian species) (Rota *et al*., 2004; Kumar *et al*., 2010, 2011, 2013a; Adetutu *et al*., 2011; Mahima *et al*., 2012; Vashney *et al*., 2012; Bhatia *et al*., 2013a; Sharma *et al*., 2014). Many developed as well as developing nations including India are rich source of plants used for medicinal purposes

(2500 species of plants found) and exponential growth has been observed in the application of herbal medicines while treating bacterial infection. In India, a long list of medicinal plants and herbs have been reported to possess high utility against several diseases and disorders including of cancers and tumours and act as potent antimicrobial agents. These medicinal plants are available in the treasures of herbal medicines such as Ashwagandha, Amla, Tulsi, Heeng, Arjuna, Aloe vera, Garlic, Turmeric, Ginger, Giloy, Shatavari, Neem, Guduchi, Pipali, Kiwifruit, Tut, Kamala, Tea tree, Palashlata, Kokilaksha etc., (Archana *et al*., 2011; Umashanker and Shruti, 2011; Mizaei-Aghsaghali, 2012; Mahima *et al*., 2012; Dhama *et al*., 2013f; Kumar *et al*., 2013b, 2013c; Yakout *et al*., 2013; Midrarullah *et al*., 2014; Tiwari *et al*., 2012, 2013b, 2014d, e). These are being used for human and animal health benefits since long back and are reported to have a therapeutic role in curing superficial wounds and other disease conditions due to bacteria (Faoagali *et al*., 1997; Parekh and Chanda, 2007a, b; Mahima *et al*., 2012; Tiwari *et al*., 2013b; Rahal *et al*., 2014b). Moreover, an array of herbal remedies is in constant use as folk medicines used by the various tribal communities of India and other countries both orally and topically against various bacterial agents including of multi-drug resistant bacteria. Some of the best known examples of such plants/herbs are *Calotropis procera*, *Acacia nilotica*, *Cassia fistula*, *Tridax procumbens*, *Hypericum japonicum*, *Trigonella foenum-graecum*, *Heliotropium indicum*, *Argemone maxicana*, *Terminellia chebulla*, *Terminellia balarica*, *Plumbago zeylanicia*, *Chlorophytum borivialum*, *Moringa olifera*, *Acalypha indica*, *Hypericum papuanum*, *Hypericum perforatum*, *Cissus quadrangularis*, *Ocimum gratissimum*, *Ocimum sanctum*, *Ageratum conyzoides*, *Soncus asper* and many others (Shafiqur *et al*., 2007; Kumar *et al*., 2011; Mahima *et al*., 2012; Vashney *et al*., 2012; Bhatia *et al*., 2013a, b; Upadhyay *et al*., 2013; Sharma *et al*., 2014).

The traditional system of medicines is supposed to evolve around 60,000 years ago, incorporating usage of plants and herbs for therapeutic purposes. However, lacking of proper documentation has restricted the use of herbal healers in the urban society even though their ethnobotanical prospection and ethnopharmacological aspects are well proven (Rigat *et al*., 2009; Chakraborty and Pal, 2012; Rahal *et al*., 2014b). The emergence of drug resistance as well as modern developments in therapeutic field have revived the use of traditional medicines and the plant-based remedies as potential source of therapeutic aids in health systems all over the world for both humans and animals (Macfoy and Cline, 1990; Rios and Recio, 2005; Mahima *et al*., 2012). Apart from treating infectious and systemic diseases, topical botanical/herbal application is equally effective against specific conditions of ear infections, wounds, burns and skin irritations. Topical applications like pultis/bandages of herbs and various sprays have advantage of being easy to apply; these gives soothing effects and immediate relief from superficial infections, burns, skin irritations and wounds due to bacterial etiology (Bowler *et al*., 2001; Tiwari *et al*., 2013b; Arun *et al*., 2013). Interestingly, 65% of the population of the world has incorporated methodology of medicinal agents involving plants into their primary health care modality as per the World Health Organization (WHO) and today, the plants/herbs constitute 25% of all the drugs prescribed (Farnsworth *et al*., 1985; Raskin and Ripoll, 2004; Mahima *et al*., 2012; Rahal *et al*., 2014b). The use of herbal medicine has proved positive upshot, being very encouraging and has a strong potential to be widely used in traditional health care around the globe (Farnsworth and Bingel, 1977; Newall *et al*., 1996; Ramalivhana *et al*., 2010).

The present mansuscript is a very exhaustive and comprehensive compilation well supported with evidence based updated information narrating the potential role and useful applications of several medicinal plants and herbs in treating and combating important bacterial pathogens and various types of bacterial diseases. It systematically covers most of the salient beneficial antibacterial applications of traditional herbs and novel phytomedicines, from ancient periods to modern usages. A special focus has also been given to various important phytoconstituents present in various herbs, their biological activities and pharmacological principles, mechanism of actions along with useful antibacterial effects with classical examples. Due emphasis has been made regarding current scientific approaches and advancements along with future perspectives of herbal remedies with a vision to counter the emerging problem of antimicrobial resistance by exploring rich heritage of medicinal herbs found in nature. The review will certainly help in promoting and popularizing medicinal plants and herbs as potent alternatives to conventional antimicrobials, particularly in the event of emerging MDR bacterial infections. It will be highly useful for researchers, biologists, pharamacists, medical and veterinary professionals, drug and pharmaceutical industries, animal sector (livestock and poultry industry), medicinal practioners and the common man too. Global usages of herbs as alternative and complementary medicines to various antimicrobials could also help obtain optimum production from animals apart from protecting health of

both animals and humans. It can also take care of various public health concerns associated with food safety issues viz., antibiotic residual effects in animal products (milk, meat) and zoonotic threats which would altogether help in safeguarding health of humans and their companion animals in a holistic way.

IMPORTANT BACTERIAL PATHOGENS AND EMERGING ANTIBIOTIC RESISTANCE

Important bacterial diseases affecting animals and thereby affecting the socio-economic status of any country include anthrax (*Bacillus anthracis*); haemorrhagic septicaemia (*Pasteurella multocida*); Brucellosis (*Brucella abortus*, *B. mellitensis*); tuberculosis (*Mycobacterium bovis*); Johne's disease (*Mycobacterium avium* subsp. *paratuberculosis*); listeriosis (*Listeria monocytogenes*); leptospirosis (Leptospires); campylobacteriosis (*Campylobacter* spp.); glanders (*Burkholderia mallei*); swine erysipelas (*Erysipelothrix rhusiopathiae*); actinomycosis (*Actinomyces bovis*); actinobacillosis (*Actinobacillus lignieresii*), black quarter, mastitis and others (Jones *et al*., 2008; Deb *et al*., 2013; Dhama *et al*., 2013b, 2014; Singh *et al*., 2014; Verma *et al*., 2014a, b). Important bacterial diseases of poultry are bacillary white diarrhea (*Salmonella pullorum*); fowl typhoid (*Salmonella gallinarum*); fowl cholera (*Pasteurella multocida*); *Escherichia coli* infections; infectious coryza (*Haemophillus paragallinarum*), tuberculosis (*M. avium* complex); chronic respiratory disease (*Mycoplasma gallisepticum*); avian spirochaetosis (*Borrelia anserina*) and psittacosis (*Chlamydophilla psittaci*) (Saif *et al*., 2003; Kataria *et al*., 2005; Kabir, 2010; Dhama *et al*., 2011; 2013b, 2014). Important infectious diseases affecting humans include tuberculosis (*M. tuberculosis*); Plague (*Yersinia pestis*); campylobacteriosis; salmonellosis; *E. coli* infections; mud fever (Leptospires); whooping cough (*Bordetella partusis*); Ornithosis (*Chlamydia psittaci*); sore throat (*Streptococcus* sp.); Staphylococcosis (*Staphylococcus aureus*), tetanus (*Clostridium tetani*) and others. Apart from these, several zoonotic bacterial diseases pose significant public health concerns viz., anthrax (*Bacillus anthracis*); plague (*Yersinia pestis*); glanders (*B. mallei*); Lyme disease (*Borellia burgdoferi*); tuberculosis (*M. bovis*); salmonellosis (*Salmonella* sp.); campylobacteriosis (*Campylobacter jejuni*); colibacillosis (*E. coli*); leprospirosis (Leptospires), listeriosis (*Listeria monocytogenes*), chlamydiosis/psittacosis (*Chlamydophila psittaci*); Q fever (*Coxiella burnetti*); tularaemia (*Francisella tularensis*) and botulism (*Clostridium botulinum*) (King, 2004; Kahn *et al*., 2007; Wolfe *et al*., 2007; Myers and Patz, 2009; Cascio *et al*., 2011; Verma *et al*., 2012, 2014a, b; Dhama *et al*., 2013b, g, h, i, j, k, 2014).

Interaction of bacterial pathogens and human or animal host is a continuous process. A series of events including the interactions of virulence attributes of bacterial pathogens and protective mechanism of host cellular system occur before the onset of any infection or disease. Proper balance of both is thus essentially required to keep host healthy and free from infections. Pathogenic microorganisms (viruses, bacteria, fungi) are the concealed enemies of animals and mankind and can enter through various routes including air, water and food and are well known for their zoonotic concerns (Dhama *et al*., 2013g, 2014; Verma *et al*., 2014a). Among these, bacterial agents are very prevalent viz., *Staphylococcus* species (*S. aureus*, *S. albus*, *S. citras*, *S. intermedius*), *Streptococcus* sp., *Bacillus coli*, *B. pyocyaneus*, *E. coli*, *Salmonella* sp., *Pseudomonas*, *Klebsiella*, *Aeromonas*, *Proteus* sp., multi-drug resistant *Acinetobacter* and *Proteus* sp. and many others as narrated above (Miyasaki *et al*., 2010; Pratheepa *et al*., 2010; Tiwari *et al.,* 2013a; Verma *et al*., 2014a). Bacterial infections are typically caused by colonizing normal flora under certain circumstances and also by antibiotic resistant bacteria such as MRSA (Methicillin Resistant *S. aureus*), CA-MRSA (Community Acquired Methicillin Resistant *S. aureus*), VREF (Vancomycin Resistant *Enterococcus faecalis*) and other drug resistance bacteria. Superficial infections are primarily caused by aerobic micro-organism such as *Staphylococcus, Streptococcus* (Flesh eating bacteria), *Vibrio* or *Aeromonas* species, *Corynebacteria* sp., *Pseudomonas aeruginosa*, *Pasteurella multocida, Erysipelothrix species* but deeper areas may also be infected with anaerobic pathogens such as *Bacteroides* and *Clostridium* species. Bacterial skin infections which are common in small animal and veterinary practice, most frequently involve *Staphylococcus intermedius* apart from *E. coli* and *Proteus* sp., *S. intermedius* which is a normal resident in the nasal cavity, oropharynx and the perianal region of animals. It can be a transient resident in other sites especially during trauma and is probably transferred to these sites from the oral and anal mucosa during grooming. *P. multocida* is another principal microbial agent especially found in subcutaneous abscesses in cats. Many other pathogens play crucial role in different disease initiations and applications of herbal preparations not only help in preventing their ill effects but also cure animals from many of such ailments (Mahima *et al*., 2012; Tiwari *et al*., 2012; Mizaei-Aghsaghali, 2012;

Midrarullah *et al*., 2014). Gram negative bacteria are generally the secondary invaders which are controlled by therapy effective against *Staphylococcus*. *Pseudomonas* is difficult to eliminate and requires specific therapy (Yah *et al*., 2004). Enteric or diarrheal infections are another quandary of major public health concerns in developing countries adding to the death toll of many million patients and other economic losses annually. Enteric bacteria mainly of *Salmonella* sp., *E. coli*, *Campylobacter* sp., *Shigella* sp., *Proteus* sp., *Klebsiella* sp., *Arcobacter* sp., *L. monocytogenes*, *Clostridium perfringens*, *Cl. botulinum*, *Yersinia enterocolitica*, *Pseudomonas* sp., *S. pneumoniae*, *S. agalactiae*, *Mycoplasma* sp., *Vibrio cholerae*, *Bacillus cereus* and *S. aureus* act as major etiological agents of sporadic as well as epidemic diarrhea (Rani and Khullar, 2004; Akins, 2005; Anbumani *et al*., 2006; Miyasaki *et al*., 2010; Pratheepa *et al*., 2010; Dhama *et al*., 2013g).

Due to emerging drug resistant bacterial strains, nowadays many bacterial diseases do not resposnd to prescribed antibiotic treatments options and thus infectious diseases caused by various bacterial pathogens are flaring up and becoming uncontrollable (Tiwari *et al*., 2013a). The most common antibiotic-resistant organisms include *E. coli*, *Salmonella*, *Shigella*, *Klebsiella, Proteus*, *Vibrio cholarae Campylobacter* sp., *Enterococci* and others. Of these, few pathogens have become Multidrug Resistant (MDR) in nature viz., Methicillin-Resistant *Staphylococcus aureus* (MRSA), Vancomycin-Resistant Enterococci (VRE) among Gram positive bacteria; *Klebsiella pneumoniae* Carbapenemase (KPC), Extended-spectrum β-lactamase (ESBLs) producing Gram-negative bacteria; *S. enteritica* serovar Typhimurium DT 104 (ACSSuT-phenotype); Imipenem-resistant or MDR organisms *Acinetobacter baumannii*, *A. baylyi*, *Pseudomonas aeruginosa*, *Bacteroides* sp.; Clindamycin-resistant *Clostridium difficile*, Streptomycin-resistant *Thermus thermophilus*; *E. coli* resistant to multiple fluoroquinolone; *Mycobacterium tuberculosis* revealing resistance to isoniazid, rifampin (Levy and Marshall, 2004; Tiwari *et al*., 2013a; WHO, 2013). MDR, Extremely drug-resistant (XDR) strains and/or Totally Drug Resistant (TDR) strains include *Staphylococcus aureus*, tuberculosis bacterium and *Pseudomonas aeruginosa*. Thus many antibiotics like penicillin, methicillin, tetracycline, erythromycin, fluoroquinolone, kanamycin, chloramphenicol, cefatoxime, isoniazid, rifampin etc., are not having much values in treating bacterial diseases effectively as they were of high use in earlier times (Tiwari *et al*., 2013a). Some specific drugs/antibiotics viz., DDT, diclofenac, paracetamol, aspirin, analgin, furazolidone, piperazine, nitrofurazone, penicillin as skin or eye ointments, tetracycline as liquid oral preparation of drug and many other drug combinations have been banned in many countries. It is because of their side effects, residual toxicity and related food safety concerns. Also, the use of penicillin, sulphonamides and many other drugs has raised public health and industrial issues. The resistant bacteria in animals can be transmitted to humans via consumption of improper/undercooked contaminated meat, milk or eggs, close or direct contact with animals or through the environment and thus poses significant food safety concerns and public health issues. Altogether, the ever emerging issue of antibiotic resistance has posed an alarming public health threat worldwide and increased the global worries, for which purpose solutions are being thought of including of finding alternative and complemenray therapeutic modalities (Byarugaba, 2004; Levy and Marshall, 2004; Zhang *et al*., 2006; Aminov, 2009; Yeh *et al*., 2009; Mahima *et al*., 2012; Dhama *et al*., 2013c; Tiwari *et al*., 2013a; WHO, 2013).

HERBAL REMEDIES TO COUNTER BACTERIAL INFECTIONS

The plant world is an immense store of pharmacologically active chemical compounds which exist as secondary phytoconstituents. The beneficial medicinal effects of plant materials typically result from the combinations of secondary products present in the plant. The medicinal actions of plants are unique to particular plant species or a related group (Archana *et al*., 2011; Umashanker and Shruti, 2011; Mahima *et al*., 2012; Midrarullah *et al*., 2014; Rahal *et al*., 2014b). This concept is consistent with the fact that the combinations of secondary products in a particular plant are often taxonomically distinct. The secondary products can have a variety of functions in plants at the cellular level as plant growth regulators, modulators of gene expression, in signal transduction and also have protective actions in relation to abiotic stresses (Rahal *et al*., 2014c). So, it is likely that their ecological function may have some bearing on potential medicinal effects for humans and animals as well. Since, ancient times, antimicrobial activity of indigenous herbs and their essential oils have been exploited to promote human and animal health (Shelef, 1983; Zaika, 1988; Beuchat and Golden, 1989; Juven *et al*., 1994; Chang, 1995; Archana *et al*., 2011; Sant'Ana, 2011; Mizaei-Aghsaghali, 2012; Midrarullah *et al*., 2014). For the last one decade, many a medicinal plant extracts have

been developed and proposed for use in human and animal food as natural antimicrobials (Del Campo *et al*., 2000; Hsieh, 2000; Hsieh *et al*., 2001; Mahima *et al*., 2012; Rahal *et al*., 2014b).

In the role of secondary products as defense chemicals, many phytoconstituents remain as a mixture of chemicals having additive or synergistic effects at multiple target sites. These phytoconstituents not only ensure effectiveness against a wide range of pathogens but also decrease the chances of these micro-organisms to develop resistance or immune evasion mechanisms (Rahal *et al*., 2014c). Such non-nutrient phytochemicals today form an important component of our routine feeding menu as vegetable or fruits and yet go unnoticed (Mahima *et al*., 2013a, b; Rahal *et al*., 2014b). With an increasing focus on the health care management using natural products, these plants and their constituents are increasingly being recognized as potential health promoters. These have been found useful in reducing the risks of various infectious and systemic diseases including of cardiovascular diseases, blood pressure problems, atherosclerosis; ameliorating various streses and help maintain a sound health (Mahima *et al*., 2012; Rahal and Kumar, 2014).

Antibacterial mechanisms of medicinal plants and herbs: The antibacterial activities of herbs are multi fold and depend upon the phytoconstituents, concentration of phytoconstituents/phytochemicals and bioactive principles and their synergistic as well as antagonistic actions (Archana *et al*., 2011; Umashanker and Shruti, 2011; Mizaei-Aghsaghali, 2012; Mahima *et al*., 2012; Midrarullah *et al*., 2014). These phtochemicals include flavonoids, steroids, β-carotene, anthocyanins, anthraquinones, glycosides, coumarins, alkaloids, saponins, tannins, phenolic acids alkaloids, gallic acid and others (Kwon *et al*., 2000; Miyazaki *et al*., 2005; Islam, 2008; Pochapski *et al*., 2011; Sandhya *et al*., 2011; Mahima *et al*., 2012; Bhatia *et al*., 2013b; Kumar *et al*., 2013c; Sharma *et al*., 2014). Various mechanisms of action and antibacterial abilities of herbal remedies relies on their several beneficial properties viz., immunomodulatory nature with enhancement of both humoral and cell mediated immunity as well ameliorating stress and immunosuppression; cytokine regulation; anti-inflammatory, antioxidative and inhibiting pathogens by a variety of pathways (Archana *et al*., 2011; Mizaei-Aghsaghali, 2012; Mahima *et al*., 2012; Midrarullah *et al*., 2014; Rahal *et al*., 2014b). Many herbs have anti-oxidative potential by counteracting free radicals or metaboloites produced during various biochemical pathways (Barreto *et al*., 2007; Morais *et al*., 2010; Rufino *et al*., 2009, 2010; Rahal *et al*., 2014c). A vast number of herbal plants show anti-inflammatory action by selective inhibition of cyclooxygenase-2, 5-lipoxygenase, glutathione S-transferase and thus inhibiting the prostaglandin biosynthesis. Several herbs decreases the production of of inflammatory agents (histamine, bradykinin, serotonin), enhance activity of cortisol and augments bllod circulation which help removing bacterial toxins out of the body (Nahrstedt *et al*., 2006; Rahal *et al*., 2014c). Certain plants contain vitamin C and carotenoids which have been found to augment both humoral and cell-mediated immune function, thereby reducing risk of infectious by enhancing the antigenic surveillance of the immune system (Bendich, 1989; Henson *et al*., 1991; Ringer *et al*., 1991; Mahima *et al*., 2012). Immunomodulation of most of herbal extracts are governed by cytokine regulation as well as anti-inflammatory properties (Wildfeuer and Mayerhofer, 1994; Bhatia *et al*., 2013b; Kumar *et al*., 2013c; Dhama *et al*., 2013e; Sharma *et al*., 2014). Certain plants facilitate proliferation of $CD4^+$ T-helper and B type immune cells. Others have been found beneficial in blocking bacterial adherence to different body cells thus help preventing the infection; blocking NF-êB pathway and the motogenic responses in infected cells; causing damage to cell membrane with loss of electrolytes and intracellular contents leading to bacteria death; downregulating the synthesis of LasA protease, LasB elastase and AHL molecules which inhibits the bacterial pathogenesis phenomenon by quorum sensing (Ruberto *et al*., 2000; Joe *et al*., 2004; Lee *et al*., 2006; Choi, 2008; Akram *et al*., 2010; Kang and Min, 2012; Yoo *et al*., 2012; Diao *et al*., 2014). Steroidal alkaloids and steroidal lactones present in herbs enhance engulfing activity of macrophages, increases the activity of white blood cells and other immune cells which in turn enhances their antimicrobial potentials (Gunning, 1999; Govindarajan *et al*., 2005; Owais *et al*., 2005; Tiwari *et al*., 2014d). All these factors decide the ultimate effect on host and pathogens and remedial effects of various herbs. Such mechanisms of actions, nature of phytoconstituents and potential antibacterial role/applications of many well established herbs and medicinal plants have been briefly enlisted in Table 1 and depicted in Fig. 1.

Alternative/traditional medicines are becoming progressively more popular and worth to overcome many multi-resistant organisms like as seen with potent efficacy of herbal extracts against multi-drug resistant *Acinetobacter baumannii* (Miyasaki *et al*., 2010; Vashney *et al*., 2012; Sharma *et al*., 2014). Such activities of plant extracts are mainly observed due to the presence of saponin, tannins, alkaloids, anthraquinone and cardiac

Table 1: Plants/herbs, common name, type of extract, pharmacological active components and their antibacterial activity

Scientific name	Common name	Pharmacologically Active phytoconstituents	Biochemical class	Type of extracts	Antibacterial activity against	References
Acorus calamus	Bach, sweet flag, calamus, vasambu	Beta-asarone, eugenol	Phenylpropanoids	Crude methanolic extracts from rhizomes	*S. albus*, *B. subtilis*, *S. typhimurium*, *S. dysenteriae*, *E. coli*	Phongpaichit *et al.* (2005)
Actinidia macrosperma	Kiwi fruit	1,2-dimethyl-lindoline, linalool, linolenic acid methylester, (E)-phytol, polysaccharides, alkaloids, saponins, organic acid,	Naturally occurring terpene alcohol	Leaf oil extracted by hydrodistillation	*S. aureus*, *Bacillus subtilis*, *E. coli*	Lu *et al.* (2007), Lu *et al.* (2012)
Allium sativum	Garlic, lasun, dasuan, vellai Poondu	Allin, allicin, allyl sulfides	Organosulfur compound	Methanolic and aqueous extracts	*C. jejuni*, *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *S. typhi*, *S. paratyphi* A2	Venugopal and Venugopal (1995), Agarwal (1996); Karuppiah and Rajaram (2012)
Aloe vera	Guarpatha, Ghrita kumara, Star cactus, Barbados, Katraazhai	Latex, Glucomannan, acemannan, mannose derivatives, hemicellulose, carboxypeptidase, salicylate Aloin, ρ-coumaric acid, aldopentose, calcium oxalate	Complex mixture Polysaccharides Hydroxycinnamic acid/Phenolic acid	Aqueous, ethanol and methanolic extracts	*Corynebacterium*, *Salmonella*, *Streptococcus*, *S. aureus*	Martinez and Baquero (2002); Grace *et al.* (2008), Alemdar and Agaoglu, (2009), Athiban *et al.* (2012)
Andrographis paniculata	Charita, kalmegh	Andrographolide, deoxy andrographolide, tannins, andrographolide, flavonoids and saponins	Diterpene lactones	Aqueous, ethanolic and methanolic extracts	*Bacillus cereus*, *Staphylococcus aureus*	Mishra *et al.* (2009); Malahubban *et al.* (2013); Vidyalakshmi and Ananthi (2013)
Annona squamosa	Sitaphal, custard apple, sugar apple	Squamosamide, acetogenin	Polyketide natural products	Acetone, boiling water, methanol and ethanolic extracts from the leaves	*B. cereus*, *B. subtilis*, *S.aureus*, *P. aeruginosa*, *E. coli*	El-Chaghaby *et al.* (2011)
Astragalus membranaceus	Astragalus	Astragalosides Liquiritigenin, calycosin, calycosin 7-O-β-D-glucoside, formononetin, formononetin 7-O-β-D-glucoside (6), daidzein, daidzein 7-O-β-D-glucoside, methylnissolin, isomucronulatol	Triterpenoid, saponins flavonoids	Methanolic and ethanolic extracts from dried root and leaves	*E. coli*, *S. enteritidis*, *Shigella* sp.,	Balachandar *et al.* (2012), Teyeb *et al.* (2012)
Azadirachta indica	Neem, holy tree, vembu	Azadirachtin, nimbin, gedunin, gallic acid, catechin, NB-II peptidoglycan	Limonoid group, Phenolic acid, tannins	Aqueous, methanolic and ethanolic extracts from seed, neem oil, dried root and leaves	*Campylobacter jejuni*, *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *S.typhi*	Jahan *et al.* (2007), El-Mahmood *et al.* (2010), Koona and Budida (2011), Tiwari *et al.* (2014e)
Brassica campestris	Mustard, sarsaun	Glucosinolates and sterols	Goitrogenic glycosides	Ethanol, petroleum ether, methanolic, ethyl acetate extracts from root, stem and leaves	*S. aureus*, *B. cereus*, *P. aeruginosa*, *E. Coli*, *Staphylococcus epidermidis*	Agrawal *et al.* (2013)
Calotropis gigantea	Akanda	Calatropin, gigantin, 2,4-bis(1,1-dimethylethyl)-, Methyl tetradecanoate, Bicyclo[3.1.1] heptane,2,6,6-trimethyl-, (1á,2β,5á)-, Hexadecanoic acid	Cardiac glycoside, phenols, alkaloids, tannin, quinines	Methanolic extract and its chloroform and petroleum ether fraction from the root bark	*Sarcina lutea*, *Bacillus megaterium*, *P. aeruginosa*, *subtilis* and *Shigella sonnei*	Alam *et al.* (2008), Anitha *et al.* (2014)

Table 1: Continue

Scientific name	Common name	Pharmacologically Active phytoconstituents	Biochemical class	Type of extracts	Antibacterial activity against	References
Camellia sinensis	Green tea	Catechin	Flavonoid	Methanolic and aqueous extracts	*Shigella* sp., *Vibrio* sp., *S. mutans*	Matsubara *et al.* (2003)
Cassia angustifolia	Senna	Rhein	Anthraquinone	Aqueous extracts from seeds and leaves	*S. aureus*	Roopashree *et al.* (2008)
Catharanthus roseus	Periwinkle, nityakalyani, sadabahar, baramassi, ushamalari	Vinblastine, vincristine, raubasine, reserpine, serpentine	Alkaloids	Ethanolic, methanolic extracts from leaf, stem, flower and root	*B. subtilis*, *E. coli*, *S. aureus*, *S. thyphi*, *P. aeuroginosa*	Goyal *et al.* (2008), Govindasamy and Srinivasan (2012)
Centella asiatica	Gotu kola	Asiatocoside, α-Humulene, β-caryophyllene, bicyclogermacrene, germacrene B, myrcene	Terpenoid	Methanolic and aqueous extracts	*M. leprae*, *S. aureus*	Zheng and Qin (2007), Dash *et al.* (2011)
Curcuma longa	Turmeric, haldi, Indian saffron, yellow ginger	Zingiberene, curcumin, α and β-turmerone	Monocyclic sesquiterpene	Ethyl acetate, methanol and water extracts	Methicillin resistant *S. aureus* (MRSA) *Listeria monocytogenes*, *Salmonella* sp, *Shigella* sp.	Kim *et al.* (2005), Fazreen (2012)
Datura alba	Vellummattai, kaladhatura	Hyoscyamine, hyoscine, meteloidine	Tropane alkaloid	Ethanolic extract from leaves	*Staphylococcus* sp., *Klebsiella* sp., *E.coli*, *Streptococcus* sp., *Pseudomonas* sp., *Salmonella* sp., *Vibrio* sp.	Qureshi *et al.* (2011)
Echinacea purpurea	Indian comb, purple coneflower	Alkamides, echinacoside, arabinogalactan, caffeic acid, chicoric acid	Natural phenols	Aqueous and ethanolic extracts of leaves	*S. typhimurium*, *P. syringae*, *B. sphaericus*	Gunning (1999)
Emblica officinalis	Amla, Indian Gooseberry	Kaempferol, ellagic acid, gallic acid	Flavonoids	Methanolic and aqueous extracts of fresh leaves and fruits	*E. coli*, *K. pneumoniae*, *K. ozaenae*, *P. aeruginosa*, *S.typhi*, *S. paratyphi* A 2 and B, *S. marcescens*	Saeed and Tariq (2007), Vijayalakshmi *et al.* (2007)
Foeniculum vulgare	Fennel, finocchio, saunf	Anethole, essential oils, trans-anethole, estragole	Phenylpropene	Essential oil obtained from seeds	*Staphylococcus albus*, *B. subtilis*, *S. Typhimurium*, *Shigella dysenteriae*, *E. coli*	Ruberto *et al.* (2000), Diao *et al.* (2014)
Glycyrrhiza glabra	Liquorice	Glycyrrhizic acid, glabridin, sterine	Isoflavonoid	Ethanolic and aqueous extracts from leaves and root extracts	*B. subtilis*, *Enterococcus faecalis*, *K. pneumoniae*, *P. aeruginosa*, *S. aureus*, *E. coli*	Irani *et al.* (2010), Sedighinia *et al.* (2012)
Hydrastis canadensis	Goldenseal	Berberine, Hydrastine	Alkaloids	Methanolic and aqueous extracts	*M. tuberculosis*,	Gentry *et al.* (1998)
Mentha piperita	Peppermint	Menthol	Terpenoid	Ethanol, methanol, ethyl acetate, chloroform, hexane and petroleum ether extracts from the leaves	*B. subtilis*, *Streptococcus pneumoniae*, *S. aureus*, *E. coli*, *Proteus vulgaris*, *K. pneumoniae*	Sujana *et al.* (2013)

Table 1: Continue

Scientific name	Common name	Pharmacologically Active phytoconstituents	Biochemical class	Type of extracts	Antibacterial activity against	References
Morinda citrifolia	Great morinda, Indian mulberry, nunaakai, noni, Ba Jitianin, dog dumpling, mengkudu, painkiller bush, cheese fruit, beach mulberry	*L*-asperuloside, acubin, alizarin Kaempferol, Rutin Scopoletin, Isoscopoletin Octanoic acid, ascorbic acid, Ursolic acid, Ricinoleic acid Damnacanthal, morindone	Iridoid glycoside Flavonoid Coumarin Acids Anthraquinone Triterpenoids and sterols	Aqueous, ethanol, methanol, chloroform, petroleum ether extracts from the root bark, leaves, fruits and seeds	*S. aureus*, *P. aeruginosa*, *B. subtilis*, *Vibrio alginolyticus*, *E. coli*, *Proteus morgaii*, *Salmonella typhosa*, *S. Montevideo*, *Lactobacillus lactis*, *Streptococcus thermophilus*	Dittmar (1993), Saludes *et al.* (2002), Murray *et al.* (2008), Selvam *et al.* (2009), Usha *et al.* (2010); Natheer *et al.* (2012), West *et al.* (2012)
Ocimum sanctum	Tulsi, holy Basil	Oleanolic acid, ursolic acid, rosmarinic acid, carvacrol, eugenol, β-caryophyllene	Triterpenoid	Methanolic and aqueous extracts of fresh leaves and stems	*E. coli*, *S. aureus*, *K. pneumoniae*, *K. ozaenae*, *P. aeruginosa*, *S. typhi*, *S. paratyphi* A 2	Vijayalakshmi *et al.* (2007), Kumar *et al.* (2011); Kumar *et al.* (2013c)
Olea europaea	Olive oil	Hexanal, caffeic acid, verbascoside, oleuropein, luteolin 7-O-glucoside, rutin, apigenin 7-O-glucoside, luteolin 4′-O-glucoside	Aldehyde	Methanolic, ethanolic and aqueous extracts	*B.cereus*, *B. Subtilis*, *S. aureus*, *P. aeruginosa*, *E. coli*, *K. pneumonia*	Pereira *et al.* (2007)
Panax ginseng	Ginseng	Ginsenosides Panaxadiol, panaxatriols Ginsan	Steroid glycosides Saponins Acidic polysaccharide	Aqueous, ethanolic and chloroform extracts from the roots	*Porphyromonas gingivalis*, *Actinobacillus actinomycetemcomitans*, *Propionibacterium acnes*, methicillin-resistant *S. aureus*, *B.subtilis*, *E. coli*, *S. marcescens*	Lee *et al.* (2006), Choi (2008),
Picrorhiza kurroa	Kutakai, kuru	Kutkin, picroside I, kutkoside, picroside, vanillic acid, D-mannitol, androsin, apocynin. phenolic compounds, sterols, cucurbitacins	Triterpenoids and iridoid glycosides	Methanolic and aqueous extracts from rhizomes	*P. aeruginosa*, *S. aureus*, *B. subtilis*, *Micrococcus luteus*, *E. coli*	Rathee *et al.* (2012), Usman *et al.* (2012)
Piper longum	Pipali, Indian long pepper	Piperine, piperlonguminine, pellitorine	Alkaloid	Ethyl acetate fraction	*Mycobacterium tuberculosis*, *Bacillus sphaericus*, *S. aureus*	Reddy *et al.* (2001), Singh *et al.* (2011)
Podocarpus nagi	Tree bard	Totarol	Flavonol	Ethanolic extracts of leaves	*S. Typhimurium*, *P. syringae*, *B. sphaericus*	Kubo *et al.* (1994)
Rosmarinus officinalis	Rosemary	Essential oil, rosmarinic acid, carnosic acid, carnosol, 12-methoxy-trans-carnosic acid, ursolic acid, oleanolic acid	Abietane, diterpenes	Ethanol, methanol and aqueous extracts from leaves	*Streptococcus mutans*, *S. salivarius*, *S. sobrinus*, *S. mitis*, *S. sanguinis*, *E. faecalis*	Bernardes *et al.* (2010)
Satureja Montana	Savory	Carvacrol	Terpenoid	Aqueous, ethanolic extracts and essential oil	*Salmonella Typhimurium*	Serrano *et al.* (2011)
Solanum nigrum	Black nightshade, wonderberry, manathakali	Solasodine	Glyco-alkoloids	Ethanolic and methanolic extracts of stem, berries and whole plant	*P. multocida*, *E. coli*, *B. subtilis*, *S. aureus*	Zubair *et al.* (2011), Parameswari *et al.* (2012)

Table 1: Continue

Scientific name	Common name	Pharmacologically Active phytoconstituents	Biochemical class	Type of extracts	Antibacterial activity against	References
Syzygium aromaticum	Caryophyllus, kiraambu	Eugenol, eugenol acetate, á and β-caryophyllene	Phenylpropanoids	Aqueous, ethanolic and methanolic extracts from whole clove	*S. aureus*, *P. aeruginosa*, *E. coli*	Pandey and Singh (2011)
Taxus baccata	Yew	(--)-rhododendrol, 4-(4'-hydroxyphenyl)-butan-2-one, 4-(4'-hydroxyphenyl)-trans-but-3-en-2-one	Complex mixture	Ethanolic extracts of heartwood and leaves	*S. typhimurium*, *P. syringae*, *B. sphaericus*	Reddy *et al.* (2001), Erdemoglu and Sener (2001)
Terminalis arjuna	Arjun tree, neer marunthu, koha, white Marudah	Arjunic acid, arjunantin, β-stilbesterol, tannins	Triterpenoids	Methanolic and aqueous extracts stem bark and leaves	Methicilin-resistant *Staphylococcus aureus*	Sato *et al.* (1997), Chaudhari and Mengi (2006)
Tinospora cardifolia	Giloy, guduchi, amrita	Tinosporone, tinosporic acid, berberine, giloin.	Alkaloids, diterpenoids, flavonoid, lignins	Aqueous, ethanol and chloroform extracts from the stems	*S. aureus*, *Enterobacter faecalis*, *Serratia marcesenses*, *E. coil*, *P. vulgaris*, *S. typhi*	Jeyachandran *et al.* (2003), Nagaprashanthi *et al.* (2012)
Uncaria tomentosa	Cats claw	Ochamin C, 5'-hydroxycudraflavone A, dihydrocudraf lavone B, pentacyclic and tetracyclic oxindoles	Flavonoids	Ethanolic and aqueous extracts from leaves and root extracts	*E. faecalis*, *S. aureus*, *Candida albicans*	Ccahuana-Vasquez *et al.* (2007), Herrera *et al.* (2010)
Vaccinium spp.	Blueberry	Fructose	Monosaccharide	Aqueous, ethanolic extracts	*E. coli*	Ofek *et al.* (1996)
Withania somnifera	Ashwagandha, winter cherry, Indian Ginseng	Withanolides, Withaferin A	Steroidal alkaloids and lactones	Methanolic and ethanolic extracts from dried root and leaves	*E. coli*, *S. enteritidis*, *Shigella*, Campylobacter, *P. aeruginosa*, *S. typhimurium*	Owais *et al.* (2005), Tiwari *et al.* (2014d)
Zingiber officinale	Ginger, adarak	Citral, curcumin Dehydrozingerone	Sesquiterpene	Ethanolic and aqueous extracts from rhizomes	Multi-drug resistant bacteria such as *S. aureus*, *P. aeruginosa*	Azu *et al.* (2007),

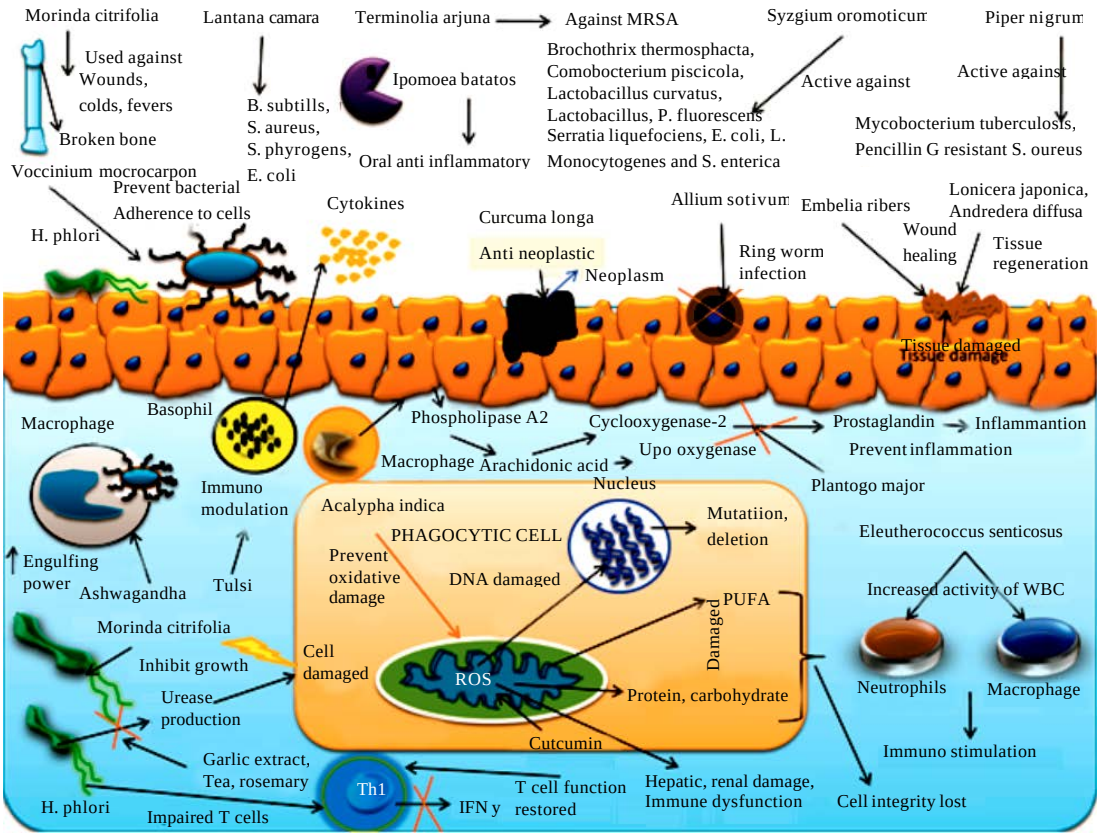

Fig. 1: Overview of the mechanism of actions and potential antibacterial role/applications of herbs

glycosides; suggesting possible antimicrobial effects with marked bacteriostatic but not bacteriocidal effect (Azu *et al*., 2007; Sharma *et al*., 2014). Similarly, many plant and herb species have been analyzed for phytochemical substances and their antibacterial activities (Mahima *et al*., 2012; Tiwari *et al*., 2012, 2014d, e). Berberine, a natural isoquinoline present in a number of plants viz., *Coptis chinensis*, *Berberis vulgaris*, *Berberis lyseum* and *Hydrastis canadensis* has been found to be active against *S. aureus in vitro* with Minimum Inhibitory Concentration (MIC) of 25.0 mg mL^{-1}; which can be further potentiated by bioflavones. This antibacterial effect appears to be due to inhibition of a Multidrug Resistance (MDR) pump of *S. aureus* (Chi *et al*., 1991; Gentry *et al*., 1998; Haq *et al*., 1999; Stermitz *et al*., 2002). Another well known medicinal herb, *Artemisia annua* has been employed for assessing the presence of inhibitors of bacterial MDR resistance pumps. Flavones (chrysoplenol-D and chrysoplenetin) from the plant possess weak growth inhibitory action which can be enhanced along with berberine (Stermitz *et al*., 2000). A petroleum ether extract of the aerial parts of *Hypericum perforatum* (St. John's wort) has been found to be active against Gram positive bacteria especially MRSA. Hyperforin, a phloroglucin derivative, has got an excellent antimicrobial activity with a MIC value of 1.0 μg mL^{-1} against MRSA hyperforin (Reichling *et al*., 2001). Plants such as *Aloe arborescens*, *A. striatula* and *Psidium guajava* possess significant antibacterial activities against strains of *Salmonella*, *Shigella*, *Escherichia*, *Staphylococcus*, *Pseudomonas* and *Enterococcus*. This reflect credence of their use in ethnomedicine against Multidrug Resistance (MDR) enteric pathogens; especially against *S. enterica* serotype Typhi followed by *S. enterica* serotype Typhimurium strains exhibiting Extended-Spectrum Beta-Lactamases (ESBLs) (Parekh and Chanda, 2007a; Bisi-Johnson *et al*., 2012). Similarly, different herbal and plant preparations play vital role in the prevention and cure of disease development mechanism (Mahima *et al*., 2012). The role and useful applications of herbal constituents against bacterial pathogens is multifaceted. The herbs may either influence the pathogenicity of the pathogen, improve the immune status of the host or may even modulate the micromilieu of the disease production site.

Herbs affecting virulence of bacterial pathogens: Thymol and carvacrol (active ingredients that are present in thyme) produce their antibacterial action by penetration into the Gram negative bacteria (Helander *et al*., 1998). Juven *et al*. (1994) postulated that the ingredients which are actively present in thyme bind to the amine as well as hydroxylamine groups of the membrane protein of bacteria resulting in lysis of bacterial cell. Examples of medicinal plants having activity against *E. coli* include essential oils extracted from anise (*Pimpinella anisum*), angelica (*Angelica sinensis*), basil (*Ocimum basilicum*), carrot (*Daucus carota*); celery (*Apium graveolens*), cardamom (*Elettaria cardamomum*), coriander (*Coriandrum sativum*), dill weed (*Anethum graveolens*), fennel (*Foeniculum vulgare*), oregano (*Origanum vulgare*), parsley (*Petroselinum crispum*) and rosemary (*Rosmarinus officinalis*); as tested during *in vitro* studies (Elgayyar *et al*., 2001; Mahady, 2005; Sharma *et al*., 2014).

In Asia, plants like *Cassia tora*, *Calendula officinalis* as well as *Momordica charantia* are well known for their wide range of antibacterial activities. In India, they have been used as folk remedy as decoctions as well as infusions. These herbs have been subjected to successive extraction using various solvents in order to evaluate their antibacterial activity against both Gram positive as well as Gram negative organisms (Bhatia *et al*., 2013a; Upadhyay *et al*., 2013; Sharma *et al*., 2014). *S. aureus* has shown an increasing pattern of development of resistance against the common antibacterial agents that are available at present (Upadhyay *et al*., 2013). The aqueous extracts of the seeds of *Cassia tora* as well as *M. charantia* and flowers of *C. officinalis* have been found to possess better antibacterial activity against bacteria in comparison to the petroleum ether/methanolic or ethanolic extracts (Christopher, 2005; Roopashree *et al*., 2008).

Herbs modulating the host factors: Any impairment in antioxidant defence mechanism of the host facilitates the instigation and growth of the micro-organisms (Nathan and Shiloh, 2000). The phagocytic killing, the primary defence system of the host, indicates a microbicidal role of Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) (Halliwell and Gutteridge, 2007). These free radicals are produced from macrophages and neutrophils to combat the invading microbes. However, reactive species can also injure the host tissues (immunopathological changes) as well as observed during chronic inflammationc leading to extensive tissue damage with a subsequent burst in oxidative stress (Sorci and Faivre, 2009; Rahal *et al*., 2014c). The multicomponent flavoprotein NADPH oxidase which play vital role in inflammatory processes by catalyzing the production of superoxide anion radical (O^{2-}) and ROS, leads to cellular damage. This cellular damage in general leads to altered immune response to microbes and ultimately altered susceptibility to bacterial, viral and parasitic infections (Puertollano *et al*., 2011). There are many herbs which have counter active metaboloites to act againest free radicals directly or by modifying many biochemical pathways, indirectly. Like certain photochemicals have been found to augment both humoral and cell-mediated immune function. Vitamin C and carotenoids have beneficial effects on immune function, thereby reducing risk of infectious by enhancing the antigenic surveillance of the immune system (Bendich, 1989; Henson *et al*., 1991; Ringer *et al*., 1991). Steroidal alkaloids and steroidal lactones of Ashwagandha root, the Indian ginseng, have been found to enhance engulfing power of macrophages and other immune cells which in turn enhances the antimicrobial properties of this plant against organism like *Salmonella* (Govindarajan *et al*., 2005; Owais *et al*., 2005; Tiwari *et al*., 2014d). *Vaccinium macrocarpon* (Cranberry) when taken as a juice or administered as a concentrated tablet form helps interfere with adherence of bacteria to the lining of bladder and thus can prevent the infection. At a dose of 4-32 ounces a day of *V. macrocarpon* juice, prevention of bacterial adherence has been reported (www.herbco.com). *Centella asiatica*, a very important medicinal herb belonging to the family *Umbellifere* (*Apiceae*) and commonly known as M*andukparni* or Indian pennywort or *Jalbrahmi*, has been used in Indian Ayurvedic medicine system for several years; being listed in the historic '*Sushruta Samhita*'. The herb is also known as "miracle elixirs of life" and its extracts are recommended in the treatment of various skin conditions such as leprosy, lupus, varicose ulcers, eczema, psoriasis along with its wound healing properties (Chandra and Purohit, 1980; Zheng and Qin, 2007; Dash *et al*., 2011; Upadhyay *et al*., 2013).

Herbs affecting macro and microenvironment of disease: The inception of a bacterial disease in a tissue depends on several factors of both bacteria and host. Oxidative stress is a normal biochemical and physiological phenomenon. Under normal conditions, the physiologically important intracellular levels of ROS are maintained at low levels by various enzyme systems participating in the *in vivo* redox homeostasis. Increased oxidative stress is a prerequisite for the production of a disease (Rahal *et al*., 2014c). Oxidative stress is also a

biomarker for the stress in a tissue. The ROS produced in the tissues cause direct damage to macromolecules of the cell, such as lipids, nucleic acids and proteins (Pechan *et al*., 2003), with polyunsaturated fatty acids as one of the favored oxidation targets. DNA bases may also undergo oxidation and cause mutations and deletions in both nuclear and mitochondrial DNA. Mitochondrial DNA is equally prone to oxidative damage due to its close proximity to a ROS origin and deficient repair capacity. These oxidative modifications thus lead to functional changes in both enzymatic as well as structural proteins, thereby producing a substantial physiological impact. Similarly, redox modulation of transcription factors may modify the gene expression (Rahal *et al*., 2014c).

Herbs in wound healing process: Application of herbs and herbal preparations on wounds and other skin ailments is commonly used all over the world and these are supposed to be boon for the cure of skin and wound conditions (Pawar and Toppo, 2012; Tiwari *et al*., 2013a, b, 2014e). *Elaeis guineensis* of Arecaceae family is widely used in conventional medicine in African countries and in other parts of globe. Leaf extract of *E. guineensis* has potent wound healing capacity and is famous for its antioxidant, antibacterial and antifungal properties which help in preparation of a potent antimicrobial natural ointment (Chong *et al*., 2008). Similarly, oleanolic acid obtained from *Andredera diffusa* has wound healing potentials (Moura-Letts *et al*., 2006). *Lonicera japonica*, a widely used traditional Chinese medicinal plant, also possess wound healing capacity as evidenced by its greater tissue regeneration effects on fibroblasts and angiogenesis and wound contraction; thus help to accelerate wound repair by anti-inflammatory properties of the medicinal plant.

Similarly, *Acalypha indica* extract has shown to affect the process of dermal wound healing by its antioxidative potential. *A. indica* contains four glycosides namely mauritianin, clitorin, nicotiflorin, biorobin and many other phytochemical constituents like flavonoids, acalyphamide, alkaloids and glycosides (Nahrstedt *et al*., 2006). Furthermore, *L. japonica* has significant antimicrobial activity against *S. aureus*, *S. epidermidis*, *E. coli*, *Candida albicans* and *C. tropicalis*. Other prominent herbs identified for reducing the inflammatory processes include *Achillea millefolium* (yarrow), *Allium sativum* (garlic), *Convallaria majalis* (lily of the valley), *Cratageus laevigata* (hawthorn), *Cynara scolymus* (globe artichoke), *Gingko biloba* (gingko) and *Viburnum opulus* (cramp bark). *Drymis brasiliensis* Miers (Casca-d'anta) is an antinflamatory spice (Lago *et al*., 2010). *Echinacea angustifolia* and *E. pallida* have antiseptic properties due to complex mixtures of secondary plant metabolites like phenylpropenes and terpenes which have made these plants as most widely used herb. *E. pallida* as well as *Eleutherococcus senticosus* (Siberian Ginseng) show immunostimulatory property and increases the activity of the white blood cells. Hence, they are used for prevention as well as for treatment of viral, bacterial and fungal infections particularly and have been found useful in treating cases of chronic arthritis and upper respiratory tract infections (Gunning, 1999).

One of the most extensively researched medicinal plants is garlic (*Zingiber officinale*) which has potent antibacterial action due to allicin that has inhibitory effects (multiple) on various enzyme systems that are thiol dependent. A range of potencies have been shown by individual constituents like garlic oil and garlic powder during *in vitro* studies against enteric bacteria in human including *Helicobacter pylori*. It has been found that against certain strains of *H. pylori,* garlic and omeprazole have synergistic effects but their concurrent administration is not much effective (Boon and Smith, 1999; McNulty *et al*., 2001; Ross *et al*., 2001). Garlic contains ajoene which exhibit antifungal and antidermatophytic activity. Aqueous extract of garlic is effectual against 90% of the dermatophytes and is capable of inhibiting a wide range of fungi in cases of ringworm infections (Agarwal, 1996).

Extracts of cinnamon *in vitro* have been found to have inhibitory effect on the growth as well as urease activity of a number of strains of *H. pylori* and thus have encouraged a number of researchers for conducting clinical trials. It has been suggested that the eradication of this particular organism can be achieved by the use of higher concentrations of cinnamon on a regimen by combined use of antibiotic as well as herbal therapy along with it (Tabak *et al*., 1999; Nir *et al*., 2000). Gosyuyu is a crude extract from the fruit of *Evodia rutaecarpa* (a Chinese herbal medicine) which is having antibacterial activity *in vitro* against *H. pylori.* The two active components in this herb include 1-methyl-2-[(Z)-8-tridecenyl]-4-(1H)-quinolone and 1-methyl-2-[(Z)-7-tridecenyl]-4-(1H)-quinolones. The Minimum Inhibitory Concentration (MIC) of these compounds against reference strains as well as *H. pylori* clinically isolated has been found to be similar to the MIC of amoxicillin as well as clarithromycin. Similarly, the urease activity of *H. pylori* is inhibited by the tea (*Camellia* sp.) as well as rosemary (*Rosmarinus officinales*) (Matsubara *et al*., 2003).

Ipomoea batatas, popularly known as Sweet Potato (SP), has been effectively used in herbal medicine to treat

inflammatory as well as infectious oral, viral and microbial diseases. It contains different effective active principles like flavonoids, triterpenes/steroids, β-carotene, anthocyanins, caffeoyl quinic acid derivatives, anthraquinones, coumarins, alkaloids, saponins, tannins and phenolic acids that promote the process of curing the infection (Kwon *et al*., 2000; Miyazaki *et al*., 2005; Islam, 2008; Pochapski *et al*., 2011; Sandhya *et al*., 2011).

The bark of plant *Carallia brachiata* Merrill, belonging to *Rhizophoracea* family, has been found effective in the treatment of itching, cuts and wounds, oral ulcers. *Elephantopus scaber*, belonging to family *Asteraceae*, contains sesquiterpene, lactones, deoxyelephantopin, isodeoxyelephantopin, scabertopin, epifriedelinol, lupeol and stigmasterol. These plant extract promotes the wound healing when applied over the surfaces of wounds. Leaf paste of *Myrsinaceae* member *Embelia ribes* cures the wounds due to cation of quinone derivative embelin, an alkaloid christembine and a volatile oil vilangin. *Hibiscus rosa sinensis* (*Malvaceae*) is a herb used to rejuvenate the inflamed skin and in the treatment of wounds. *Jasminum auriculatum* and *Jasminum grandflorum*, member of *Oleaceae*, contains *lupeol and jasminol* which has remarkable effects on wounds (Deshpande and Upadyaya, 1967; Kumari *et al*., 2013). When extract of leaves of *J. auriculatum* is applied over the wounds in the form of jelly, beneficial effects have been observed in the form of endorse wound healing. *Lycopodium serratum*, member of family *Lycopodiaceae*, is the plant especially useful in the treatment of burns, sores, cuts and wounds. A thick paste of this plant prepared by boiling in water has widely been used by the tribes for treating wounds. *Rafflesia hasseltii* buds and flowers extracts are very effective in accelerating the wound healing process (Chandra and Purohit, 1980; Chopra *et al*., 1981; Kumari *et al*., 2013). Honey in combination with *Azadirachata indica* (neem) bark decoction can be used for the treatment of chronic wounds (Chandra and Purohit, 1980; Kelmanson *et al*., 2000; Srinivasan *et al*., 2001; Abu-Shanab *et al*., 2004; Mohanasundari *et al*., 2007; Vasu and Singaracharya, 2008; Kwakman *et al*., 2008; Raja *et al*., 2011; Dorai, 2012; Gokulakrishnan *et al*., 2012, Kumari *et al*., 2013; Tiwari *et al*., 2013b, 2014e).

There are certain other plants that contain several active components like saponin and alkaloids; fatty acids and sterols; amino acids and amino glycosides which are essentially effective in the treatment of various bacterial infections. *Melaleuca alternifolia* oil, popularly known as tea tree oil, is used topically for treatment of bacterial and fungal infections. Tea tree oil has shown *in vitro* activity against microorganisms such as *Propionibacterium acnes*, *S. aureus*, MRSA, *E. coli*, *C. albicans*, *Trichophyton mentagrophytes* and *T. rubrum*. Extracts from *Derris elliptica*, *D. indica* and *D. trifoliate*, Cinnamon, *Citrus aurantifolia* and *C. aurantium* (Rutaceae); *Punica granatum* (Punicaceae); *Phyllanthus acidus* (Euphorbiaceae); *Crescentia cujete* (Bignoniaceae); *Rosmarinus officinalis* (Lamiaceae); *Urena lobata* (Malvaceae); *Cimicifuga* sp.; *Terminalia chebula*, *T. bellerica*; *Ocimum sanctum*; *Acacia nilotica* and *Tamarindus indica* (Caesalpiniaceae) possess strong *in vitro* antibacterial activity against many bacteria agents. These plant extracts have shown activity against *Helicobacter pylori*, *E. coli*, *Pseudomonas* sp., *Proteus* sp., *Bacillus* sp., *Streptococcus* sp., *Klebsiella* sp. and *S. aureus* (Binutu and Lajubutu, 1994; Takenaka *et al*., 1997; Nir *et al*., 2000; Mazumder *et al*., 2001; Khan *et al*., 2006; Melendez and Capriles, 2006, Kumar *et al*., 2011; Vashney *et al*., 2012; Bhatia *et al*., 2013a; Sharma *et al*., 2014).

Leaf extract of *Aegle marmelos*, member of family Rutaceae, exerts immune response in freshwater fish, *Cyprinus carpio* (Cyprinidae), to enhance the disease resistance against *Aeromonas hydrophila* infection (Pratheepa *et al*., 2010; Laphookhieo *et al*., 2011). Leaves of Siam weed (*Chromolaena odorata*) possess antibacterial properties against aerobic bacterial isolates of wound infections as these contain phenolic compounds (Phan *et al*., 2001; Oyetayo and Oyetayo, 2006). Examples include: *Aegle marmelos*, *Allamanda catharica*, *Allium sativum*, *Datura alba* (Qureshi *et al*., 2011), *Dendrophthoe falcata*, *Flabellaria paniculata*, *Flaveria trinervia*, *Mimosa pudica* (Zhang *et al*., 2011), *Morinda citrofolia* and *Moringa oleifera* (Sharma, 2010).

Oxidative stress and altered immune function: The correlation between oxidative stress and immune function of the body is beyond doubts. The skilled phagocytic cells (macrophages, neutrophils, eosinophils) possess an enzyme, the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (Hampton *et al*., 1998; Babior, 1999); which is responsible for the production of ROS following an immune challenge. The host defense mechanism uses the lethal effects of ROS and RNS in the killing pathogens. At the commencement of an immune response, phagocytes increase their oxygen demand by 10-20 folds via., process of respiratory burst. The nascent oxygen generated by this enzyme serves as the starting material for the production of an array of reactive species. Production of other powerful pro-oxidants, such as hydrogen peroxide (H_2O_2), hypochlorous acid (HOCl), peroxynitrite ($ONOO^-$) and possibly hydroxyl (OH●) and

ozone (O_3) by these cells have also been reported. Although, these highly reactive endogenous metabolites damage all the the bacterial cells non-specifically, they can also injure the host tissues (Rice-Evans and Gopinathan, 1995). Cashewnut, (*Anacardium occidentale*) is an antioxidant and is used in indigenous system for immunomodulation purposes (Barreto *et al*., 2007; Morais *et al*., 2010; Rufino *et al*., 2009, 2010).

Increased production of Nitric Oxide (NO) has been documented in dengue and in monocyte cultures infected with different types of viral infections and has role in inflammation and in the relationship between oxidative stress and immunomodulation (Valero *et al*., 2013). Increased level of stress leads to activation of hypothamic-pituitary-adrenal axis and indirectly the release of endogenous antistress hormone, cortisol. The herb may act by its anti-inflammatory activity thus reduces the oxidative stress in the target tissue and ultimately facilitates the system against the pathogenic bacteria. Immunomodulation of most of herbal extracts are governed by cytokine regulation. Up and down regulation of cytokine governs immunomodulation as well as anti-inflammatory activities (Wildfeuer and Mayerhofer, 1994; Dhama *et al*., 2013e; Bhatia *et al*., 2013a; Sharma *et al*., 2014).

IMPORTANT HERBS AND THEIR VITAL ROLES/APPLICATIONS AGAINST BACTERIAL PATHOGENS

Tulsi (*Ocimum sanctum* or Holy Basil): Ocimum is a household remedy throughout tropical and semitropical region of India and other Asian countries. Different parts of tulsi are traditionally utilized in the Ayurveda and Siddha systems of medicine for treatment of several aliments (Kumar *et al*., 2013c). The phytoconstituents of *Ocimum sanctum* is complex and include: Eugenol and urosolic acid; alkaloids and flavonoids; tannins and carbohydrates. The antibacterial activities of the plant is well proven against a wide variety of Gram positive and Gram negative bacteria including enteric organisms viz., *E. coli*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Klebsiella aerogens*, *Shigella dysentriae*, *Salmonella* Typhimurium, *Vibrio cholera* and *S. aureus* (Bhatia *et al*., 2013a; Kumar *et al*., 2011, 2013c). Equally are susceptible the fungi and viruses (including fish pathogens) indicating versatility of its anti-infective properties. Methanolic extracts and aqueous suspension of leaves and seeds oil of tulsi, all bear immunomodulatory properties. The leaves of the plant can induce cytokine secretion. The fixed oil and linolenic acid of tulsi possess good analgesic, antipyretic as well as anti-inflammatory activities (Bhatia *et al*., 2013b; Kumar *et al*., 2013c).

Black cohosh (*Cimicifuga racemosa*): Black cohosh has a long history of use in traditional medicine since 18th century (Rahal *et al*., 2013). It has been used to relieve pre-menstrual symptoms, dysmenorrhea and discomfort of menopause. In homeopathy, preparations of *C. racemosa* have been used for treating discomfort in late pregnancy, labor pains, headache and depression. It is an effective ecofriendly drug for the management of abortions, prolapse as well as post-parturient care in large animals. The black roots of *C. racemosa* contain 15-20% amorphous resinous substance, cimicifugin and racemosin. Also the herb contains triterpene constituents, actein, cimigenol, cimicifugioside and 27-deoxyacetylacetol and the glycoside, 27-deoxyactein (27-deoxyacetylacetol-O-D-xylopyranoside). The anti-inflammatory potential of the alcoholic extract of C. *racemosa* has been scientifically proven (Rathore *et al*., 2012). The constituents, actaealactone, cimicifugic acid and fukinolic acid display an antioxidant activity (Nuntanakorn *et al*., 2006, 2007).

Cinnamon (*Cinnamomum cassia*): Essential oils of *Cinnamon* have been found to possess antimicrobial properties against *B. cereus* (Kalemba and Kunicka, 2003; Valero and Salmeron, 2003) and *H. Pylori* (Tabak *et al*., 1999). A blend of cinnamon and nisin accelerated the death of *S. typhimurium* and *E. coli* O157:H7 in apple juice, thereby increasing its safety and shelf life (Yuste and Fung, 2004). An equal volume mixture of extracts of chive (*Allium tuberosum*), cinnamon and corni fructus (*Cornus officinalis*) has been found to possess a good antimicrobial spectrum in orange juice, pork and milk against common foodborne microorganisms; thereby increases their stability to heat, pH and storage (Mau *et al*., 2001). The cinnamon extract was well tolerated and side effects were minimal (Nir *et al*., 2000). A hydroethanolic extract of cinnamon bark inhibits the activity of bacterial endotoxin (Azumi *et al*., 1997) and growth of fluconazole resistant *Candida* sp. which cause an emerging illness. Cinnamaldehyde (CNA, 1), 2-hydroxycinnamaldehyde (2-CNA), coumarin (2) and cinnamyl acetate have been identified as chief antibacterial pytocinstituents of the essential oil of cinnamon (Choi *et al*., 2001; Sharma, 2010).

***Curcuma longa* (Turmeric):** *Curcuma longa*, a perennial herb, is a member of the Zingiberaceae family. The roots form an important ingredient of Chinese and Ayurvedic

systems of medicine. The rhizomes of *C. longa* possess a large inventory of moniterpenoids, sesquiterpenoids and curcuminoids (Tang and Eisenbrand, 1992; Fang *et al*., 2003), which show antibacterial, anti-inflammatory as well as antineoplastic activities. Curcuminoids, which are basically bioflavonoid compounds, exhibit a variety of beneficial therapeutic and preventive health effects (Joe *et al*., 2004). Curcumin is the principal curcuminoid along with desmethoxycurcumin and bis-desmethoxycurcumin, the other two curcuminoids (Akram *et al*., 2010). Insecticidal activity of the turmeric rhizome has also been reported (Chander *et al*., 1991, 1992). Curcumin has antioxidant, anti-inflammatory, antiviral and antifungal actions (Akram *et al*., 2010). Curcumin blocks NF-κB and the motogenic response in *H. pylori* infected epithelial cells and carries thremendous therapeutic potential. It acts as an inhibitor for cyclooxygenase, 5-lipoxygenase and glutathione S-transferase. In addition to this, turmeric has been found to reduce the release of inflammation-inducing histamine, increase and prolongs the action of cortisol and improves circulation; thus increases the flushing toxins out of the body. Curcumin facilitates proliferation of $CD4^+$ T-helper and B type immune cells.

Turmeric acts as a cholagogue, stimulating bile production, thus increases the digestion of fats and eliminating toxins from the liver. Wound healing and detoxifying properties of turmeric curcumin have also received considerable attention (Joe *et al*., 2004). The ethyl acetate extract of *C. longa* has demonstrated an excellent antibacterial activity against MRSA at a concentration of 0.125-2 mg mL^{-1} (Kim *et al*., 2005). A study by Limtrakul *et al*. (2004) using RT-PCR showed that all three curcuminoids isolated from *C. longa rhizomes* inhibit expression of MDR-1 gene. The oleoresin (second fraction of the turmeric oil) contains ar-turmerone, turmerone and curlone and has been proven antibacterial against *B. cereus*, *B. subtilis*, *B. coagulans*, *E. coli*, *S. aureus* and *P. aeruginosa* (Negi *et al*., 1999).

***Piper nigrum* (Black pepper):** Both aqueous and ethanol extracts of black pepper inhibit the growth of penicillin G resistant strain of *S. aureus* (Dorman and Deans, 2000). The extracts from *Piper longum* contain pharmacological molecules piperlonguminine, piperine and pellitorine which exhibit significant antibacterial activity against Gram positive bacteria and moderate activity against Gram negative bacteria (Reddy *et al*., 2001). Piperine, [1-[5-[1,3-benzodioxol-5-yl]-1-oxo-2,4, pentadienyl piperidine, a pungent alkaloid present in *P. nigrum*, enhances the bioavailability of various structurally and therapeutically diverse drugs. Perhaps, it forms non-polar complexes with drug molecules and increases their permeability across the barriers (Khajuria *et al*., 1998). The *Piper longum* fruit extracts have also shown significant anti-mycobacterial activity against MDR *Mycobacterium tuberculosis* (Singh *et al*., 2011). Along with potent antimicrobial activity, black pepper is used to treat asthma, chronic indigestion, colon toxins, obesity, sinus congestion, fever, intermittent fever, cold extremities, colic, gastric ailments and diarrhea (Khajuria *et al*., 1998; Rahal *et al*., 2014b).

***Syzgium aromaticum* (*Clove*) (*Syn-Caryophyllus aromaticum*, *Eugenia aromatica*, *Eugenia caryophyllus*, *Eugenia caryophyllata*):** The aqueous and methanolic extract from whole clove is being efficiently used as an antimicrobial agent against food spoilage bacteria and food borne pathogens (*S. aureus, P. aeruginosa, E. coli*). The bread with a maximal of 1% clove extract is acceptable for human consumption (Pandey and Singh, 2011; Saeed *et al*., 2013). Essential oils of clove possess antimicrobial properties (Kalemba and Kunicka, 2003) against four Gram positive bacteria such as *Brochothrix thermosphacta*, *Carnobacterium piscicola*, *Lactobacillus curvatus* and *Lactobacillus* and Gram negative bacteria such as *P. fluorescens* and *Serratia liquefaciens*, *E. coli*, *L. monocytogenes* and *S. enterica* (Friedman *et al*., 2002). Its antimicrobial properties are utilized in meat industry. A positive relationship has been established between the inhibitory effect of essential oils and the presence of eugenol and cinnamaldehyde (Ouattara *et al*., 1997). Crude methanolic extract inhibits gram-negative anaerobic pathogens, including *Porphyromonas gingivalis* and *Prevotella intermedia*. Eight pharmacologically active principles (5,7-dihydroxy-2-methylchromone 8-C-beta-D-glucopyranoside, biflorin, kaempferol, rhamnocitrin, myricetin, gallic acid, ellagic acid and oleanolic acid) have been identified following chromatographic fractionation of clove oil. The bioflavonoid, kaempferol and myricetin also show potent growth-inhibitory activity against the periodontal bacteria, *Porphyromous gingivalis* and *P. intermedia* (Cai and Wu, 1996). Clove and clove oils are used in day todays life as potent anti-bacterial, anti-inflammatory and analgesic agents (Rahal *et al*., 2014b).

***Thymus vulgaris* (Thyme):** The oil of thyme is a naturally occurring antibacterial, anticandidal and antioxidant agent when used topically due to which it is gaining popularity (Venugopal and Venugopal, 1995; Naganawa *et al*., 1996; Caelli *et al*., 2000; Dursun *et al*., 2003; Akins, 2005; Carson *et al*., 2006; Shenefelt, 2011). Thyme has a broad antibacterial spectrum against both Gram positive and

Gram negative bacteria with a highly sensitivity against the former group (Nevas *et al*., 2004). Thymol and carvacrol are active constituents of ethanolic extract of thyme. The essential oil of thyme has been found to have strong inhibition activity against *S. sonnei, B. subtilis, L. monocytogenes S. enterica*, *C. jejuni* and *E. coli* O157:H7 (Fan and Chen, 2001; Friedman *et al*., 2002). The aqueous extract of thyme on the other hand was found to have significant inhibitory effects on the growth of *H. pylori* (Tabak *et al*., 1999). Thymol decreases the viable count of *S. typhimurium* and *S. sonnei in vitro* (Juven *et al*., 1994). Carvacrol showed a dose-dependent inhibition of *B. cereus* (Ultee *et al*., 2000). The MIC was as low as 0.03% (v/v) thyme oil against *C. albicans* and *E. coli* (Hammer *et al*., 1999). The activity of thyme was modulated by alterations in pH and sodium chloride concentration of the medium (Bagamboula *et al*., 2003). The bacteriostatic and bactericidal properties of essential oil of thyme were evident against the non-toxigenic strain of *E. coli* O157:H7 in a broad temperature range. Lecithin weakened the antibacterial properties (Burt and Reinders, 2003). Thyme showed greatest inhibitory potenital against *Aeromonas hydrophila* compared to other psycrotrophic food-borne bacteria such as *A. hydrophila*, *L. monocytogenes* and *Y. enterocolitica* in *in vitro* conditions.

***Zingiber officinale* (Ginger):** *Z. officinale* possess antimicrobial action against both Gram positive and Gram negative microorganisms (Martin *et al*., 2001; Srinivasan *et al*., 2001). It has potent anti-inflammatory, analgesic, antipyretic and antimicrobial activities. Methanolic extract of the dried powdered ginger rhizome contains 6-, 8-,10-gingerol and 6-shogoal which inhibited growth of different strains of *H. pylori in vitro* with a MIC of 6.25-50 μg mL^{-1}. Higher antibacterial efficacy has been shown by gingerols of the crude extract against *H. pylori* with an MIC range of 0.78-12.5 μg mL^{-1} showed significant activity against the $CagA^+$ strains (Mahady, 2005). Antibacterial activity has also been reported against the pathogens like *S. aureus*, *S. pyogenes*, *S. pneumoniae* and *H. influenzae*. The MIC and MBC values of various ginger extracts ranged from 0.0003-0.7 μg mL^{-1} and 0.135-2.04 μg mL^{-1}, highlighting its therapeutic value (Akoachere *et al*., 2002).

Aloe vera: Aloe vera is obtained from the mucilaginous part of the centre of the leaf. Worldwide several studies have been suggested that Aloe vera, or Aloe vera gel has wide array of utility against various health-related disorders when applied orally and/or topically. The *Aloe vera* gel contains sugars, amino acids, vitamins A, B, C, E, enzymes, polysaccharides and minerals. Several reports have also shown encouraging role of *Aloe vera* in the management of both acute and chronic infected burn wounds (Raina *et al*., 2008). B-sitosterol, acemannan and glycoprotein constituents of *Aloe vera* have therapeutic potentials. The antimicrobial potential of *Aloe vera* juice has been proved against a range of clinically relevant bacteria during *in vitro* studies. The various Gram positive bacteria (*Mycobacterium smegmatis*, *S. aureus*, MRSA, *Enterobacter cloacae*, *E. bovis*, *E. faecalis*, *Micrococcus luteus* and *Bacillus sphericus*); Gram negative bacteria (*P. aeruginosa*, *K. pneumoniae*, *E. coli*, *Shigella flexneri* and *Salmonella typhimurium*) and fungi (*Candida albicans*) were found susceptible to *Aloe vera* juice. Furthermore, *Aloe vera* extract has antimicrobial activity against *M. smegmatis*, *E. faecalis*, *M. luteus* and *B. sphericus*. *Aloe vera* juice can effectively be used in cosmetics and food industary as it has inhibitory effects against pathogenic bacteria causing food poisoning, especially the Gram-positive bacteria (Habeeb *et al*., 2007; Grace *et al*., 2008; Alemdar and Agaoglu, 2009; Rahal *et al*., 2014b).

***Withania somnifera* (Ashwagandha):** Ashwagandha has been found to show remarkable antibacterial properties, owing to its glycoprotein glycowithanolides, withaferin and withanolides (Tiwari *et al*., 2014d). Antibacterial activities have been demonstrated aginst various bacterial pathogens viz., *Neisseria gonorrhoea*, *E. coli*, *Salmonella*, *Bordetella pertussis*, *Pseudomonas fluorescens*, *P. aeruginosa*, *Bacillus subtilis*, *L. monocytogenes*, *Clvibacter michiganensis* subsp. *Michiganensis* and *Staph. aureus* (Akinyemi *et al*., 2004; Owais *et al*., 2005; Girish *et al*., 2006; Teixeira *et al*., 2006; Kulkarni *et al*., 2007; Kambizi and Afolayan, 2008; Mehrotra *et al*., 2011; Sundaram *et al*., 2011; El-Boshy *et al*., 2013). Ashwagandha has also been found useful to counter even Multidrug Resistant (MDR) strains of few bacteria like of methicillin-resistant *Staph. aureus* (Mehrotra *et al*., 2011).

***Azadirachta indica* (Neem):** Neem leaves and oil possesses proven beneficial effects on several skin conditions and bacterial infections (Drabu *et al*., 2012; Tiwari *et al*., 2014e). The methanol extract from the leaves of *Azadirachta indica* has the highest antibacterial activity followed by the hexane, methanol, chloroform extracts from it (Koona and Budida, 2011). The water and hexane extracts from the seeds of *A. indica* inhibits the growth of Gram positive more strongly than Gram negative bacteria. Neem leaf extracts and oil have been demonstarted to posses wide antibacterial activity

against various pathogens viz., *E. coli*, *Pseudomonas aeruginosa*, *Aeromonas hydrophila*, *B. cerus*, *B. pumilus*, *S. aureus*, *S. typhi*, *K. pneumonae*, *Proteus* sp., *P. vulgaris*, *Vibrio* sp., *S. dysenterae*, *Enterococcus faecalis*, *Streptococcus* sp. (*S. mutans*, *S. mitis*, *S. sanguis*, *S. salivarius*), *M. tuberculosis* and *Yersinia enterocolitica* (SaiRam *et al*., 2000; Biswas *et al*., 2002; Parekh and Chanda, 2007b; Prashant *et al*., 2007; Anyaehie, 2009; Dhayanithi *et al*., 2010; Mehrotra *et al*., 2010; Sarmiento *et al*., 2011; Maragathavalli *et al*., 2012; Vinoth *et al*., 2012; Chava *et al*., 2012; Harjai *et al*., 2013; Rosaline *et al*., 2013; Tiwari *et al*., 2014e). Antibacterial potential of leaf extract of neem has been been proven against methicillin-resistant *S. aureus* (Sarmiento *et al*., 2011). The hexane extracts from the seeds produces larger zones of growth inhibition diameter, lower MIC and MBC values when compared to aqueous extracts (El-Mahmood *et al*., 2010). Moreover, it has been reported that the neem oil has low MIC against *S. aureus*, *S. typhi*, *E. coli* and *P. aeruginosa*. *In vitro* studies have also shown the antibacterial activity of neem oil and which indicated that 92% *S. pyogenes*, *P. aeruginosa*, *Proteus* sp. and *E. coli* are susceptibile to it (Jahan *et al*., 2007). Irodin A, recovered from leaves of neem, acts as a potent anti-malarial agent (WHO, 2008; Anyaehie, 2009). The bark and oil of this plant have anti-tuberculosis (*M. tuberculosis*) and anti-leprotic properties (Subramanian and Lakshmanan, 1996; Tiwari *et al*., 2014e). Neem oil show antiplaque actions while chewing its twigs help control dental tartar and caries (Prashant *et al*., 2007; Elavarasu *et al*., 2012). Recently, Kumar *et al*. (2013b) indicated the utility of neem preparations for treating endometritis in cattle.

***Morinda citrifolia* (Noni plant):** *M. cirifolia* has been used by Polynesians for more than 2000 years for the treatment of various conditions and was commonly known as Noni plant (Chan-Blanco *et al*., 2006; Singh, 2012). Acubin, L-asperuloside and alizarin are the major bioactive molecules isolated from the noni fruit and scopoletin, anthraquinone compounds are obtained chiefly from noni roots. Various extracts from the fruits and leaves have shown potent antibacterial activities against *S. aureus*, *P. aeruginosa*, *B. subtilis*, *Vibrio alginolyticus*, *E. coli*, *P. morgaii*, *Salmonella typhosa*, *S. schottmuelleri*, *S. montevideo*, *Lactobacillus lactis*, *S. thermophilus* and *Shigella paradys*. Noni is mainly used for the treatment of broken bones, bruises, sores and wounds, colds, fevers, skin infections and other bacteria induced ailments (Dittmar, 1993; Selvam *et al*., 2009; Usha *et al*., 2010; Natheer *et al*., 2012). A coumarin compound, scopoletin, has also been isolated from noni plant which inhibits the growth of *E. coli* and also helps to heal stomach ulcer by inhibiting the bacteria *H. pylori*. Murray *et al*. (2008) had observed similar *in vitro* effectiveness of noni juice along with chlorhexidine gluconate and sodium hypochlorite (NaOCl) to remove the smear layer of *E. faecalis* from the canal walls of endodontically instrumented teeth. The antibacterial activity of iridoids (deacetyl asperulosidic acid and asperulosidic acid) in *M. citrifolia* fruits against *C. albicans*, *E. coli* and *S. aureus* has been evaluated recently by West *et al*. (2012). Moreover, *M. citrifolia* leaf extract has shown anti-tubercular activity and can effectively kills 89% of *M. tuberculosis* compared to anti-TB drug rifampcin which kills 97% of bacteria at the similar dose concentrations. Various bioactive components like cycloartenol, E-phytol, beta-sitosterol, stigmasterol, ketosteroids stigmasta-4-en-3-one, campesta-5,7,22-trien-3beta-ol and stigmasta-4-22-dien-3-one were isolated from hexane fraction from noni and which are responsible for the pronounced antitubercular activity of noni (Saludes *et al*., 2002; West *et al*., 2012).

***Areca catechu*:** Leaves, buds, shoots, husks and roots of *Areca catechu* are of medicinal values. Antibacterial and growth inhibitory effects of areca leaves have been seen against *B. cereus*, *P. fluorescens*, *Streptococcus mutans*, *S. salivarius*, *S. mitis*, *Lactobacillus acidophilus*, *C. albicans* and *Prevotella intermedia*. Active principles include alkaloids like arecoline and arecaine, catechin, tannins, gallic acid, fat, gum etc. (Lalithakumari and Sirsi, 1965; Samappito *et al*., 2012).

***Berberis lyceum*:** *Berberis lyceum*, a member of family Berberidaceae is a shrub distributed in the temperate and subtropical parts of Asia, Europe and America. The plant contains flavonoids and alkaloids including berberine, tannins, saponins and triterpenoids. The principal alkaloid, berberine, is present in the rhizomes and used in the preparation of drugs for treating leprosy cholera, diarrhoea, dysentery and eye problems. It is also recommended orally for treating bacterial dysentery. However, its combination with Glycyrrhiza species abolishes its therapeutic effect (Hong *et al*., 2005; Irshad *et al*., 2013).

***Carallia brachiata* (Karalla):** *Carallia brachiata* belongs to family Rhizophoraceae and is an evergreen decorative tree. It has been used against stomatitis, throat inflammation and for treating oral ulcers. The bark of the tree contains steroids, triterpenoids, phenols, carbohydrates, fixed oils, fats, proanthocyanidins

(carallidin, mahuannin A, para-hydroxy benzoic acid, tannins, flavonoids) and glyceroglycolipids. The extract has shown antibacterial efficacy against both Gram positive and Gram negative bacteria like *Micrococcus luteus*, *B. subtilis*, *S. aureus*, *E. coli*, *Proteus vulgaris* and *S. Typhi* (Krishnaveni *et al*., 2009; Neeharika *et al*., 2010; Abraham and Thomas, 2013).

***Centella asiatica*:** *Centella asiatica* is a perennial creeping herb of the family *Umbeliferae* that grows in moist areas of many tropical and subtropical countries. *C. asiatica* is the source of active constituents viz., saponins, asiaticoside, triterpenoids, madecassoide, madecassic acid, asiatic acid, terpenoids, sitosterol, glucose, rhamnose and stigmasterol. Others include fatty oils consisting of glycerides of palmitic acid, linoleic acid, stearic acid, linolenic acid and vitamins like ascorbic acid along with minerals like calcium, iron and phosphate. Different extracts of *C. asiatica* have been found very effective in inhibiting the growth of four pathogenic bacteria viz., *P. vulgaris*, *S. aureus*, *B. subtilis* and *E. coli* and two fungal strains of *A. niger* and *C. albicans*. The plant has a promising scope to be developed as a novel broad spectrum antibacterial and antifungal herbal formulation due to potent fungicidal, antibacterial, antioxidant and anticancerous properties (Chandra and Purohit, 1980; Zheng and Qin, 2007; Gohil *et al*., 2010; Dash *et al*., 2011).

***Pyrostegia venusta* (Ker Gawl):** *Pyrostegia venusta* Miers is member of Bignoniaceae and is an ornamental tree cultivated in tropics of South America. Various parts of this plant show antioxidant, antimicrobial, antiviral, antibacterial, hepatoprotective, anti-inflammatory, spasmolytic, antipruritic, anti-angiogenic, antitumor, antiallergic, immunomodulatory and wound healing potentials. The plant contains phyto-chemicals such as iridoid glucosides, naphthoquinones, alkaloids, flavones, triterpenes, polyphenols, tannins, allo-tannic acid, oleanolic acid, seed oils, glycoside bellericanin, acacetin-7-O-β-glucopyranoside and β-sitosterol. It has been found to be effective against diarrhea, cough, respiratory disorders and skin infections such as leukoderma, vitiligo and many bacterial and fungal pathogens. The various pathogens against which *P. venusta* has been tried include *B. subtilis*, *S. epidermidis*, *S. pyogenes*, *S. aureus*, *Micrococcus luteus*, *Enterobacter aerogenes*, *E. coli*, *S. typhi*, *P. aeruginosa*, *Aspergillus niger*, *C. albicans* and *C. tropicana* (Ferreira *et al*., 2000; Roy *et al*., 2011, 2012; Mostafa *et al*., 2013).

***Peperomia galioides* (Silver bush):** It is commonly called as tuna congona, congona grande or shiny bush. The herb is enriched with ethnomedicinal uses as anti-inflammatory, anti-oxidant, diuretic, antibacterial and analgesic. Plant is enriched with many components of medicinal importance, having the potential be be used in the treatment of several health disorders viz., Parkinson's disease, Alzheimer's disease, headache, cancer, cardiovascular disorders, renal disorders, inflammation, abscesses, acne, boils, colic, fatigue, gout, rheumatic pain; as well as utility against various bacterial and viral infections. It possess various alkaloids, tannins, grifolin, grifolic acid, resins, piperogalin, steroids, essential oils, phenols and carbohydrates responsible for broad spectrum antimicrobial activity against a range of pathogens viz., *S. aureus*, *S. epidermidis*, *B. subtilis*, *E. coli*, *P. aeruginosa*, *K. pneumoniae*, *S. Typhi*, *C. albicanas*, *Penicillum notatum*, *A. niger* and *Rhizopus stolon* (Bojo *et al*., 1994; Mahiou *et al*., 1995; Aziba *et al*., 2001; Oloyede *et al*., 2011).

***Panax ginseng*:** Ginseng contains many phytochemical compounds such as tetracyclic triterpenoid saponins (ginsenosides), polyphenolic compounds, polyacetylenes and acidic polysaccharides. It exhibits anti-bacterial capacity by inhibiting survival mechanisms of pathogens. Ginseng extracts have been found to repress the synthesis of LasA protease, LasB elastase and AHL molecules; hence inhibits the pathogenesis mechanism of *P. aeruginosa* by phenomenon of quorum sensing. Similarly, pectin-type polysaccharides of *P. ginseng* as PG-F2, acidic heteroglycans and PG-HMW act against *Porphyromonas gingivalis*, *Actinobacillus actinomycetemcomitans*, *Propionibacterium acnes*, *S. aureus*, methicillin-resistant *S. aureus*, *B. subtilis*, *E. coli*, *Serratia marcescens*, *H. pylori* and many viruses including of influenza, Human Immunodeficiency Virus (HIV) and rota virus (Lee *et al*., 2006; Choi, 2008; Kang and Min, 2012; Yoo *et al*., 2012).

***Plantago major*:** Popularly known as way bread, *Plantago major* is a perennial herb of the Plantaginacea family which grows abundantly beside paths, roadsides and as a weed in crops. The genus name *Plantago* has been derived from a Latin word "planta", meaning as sole of the foot. The plant has been extensively used in folklore medicine since long back because of its anti-tubercular, anti-malarial, anti-infective, anti-inflammatory, anti-oxidative and anti-tumor activities. The inhibitory effects of the herb have been scientific validated against

Cryptococcus, *Francisella*, *Listeria*, *Mycobacteria*, many herpes and adeno viral infections, influenza and viral hepatitis (Chiang *et al*., 2002; Oto *et al*., 2011). Leaf extract of *P. major* contains phenolic compounds, organic acid groups, essential fatty acids, flavonoids, oleanolic acid, ferulic acid, ursolic acid, carotenes and terpenoids (Samuelsen, 2000; Turel *et al*., 2009; Nazarizadeh *et al*., 2013). Mechanism behind the anti-inflammatory action is the selective inhibition of cyclooxygenase-2 by ursolic acid thus inhibiting the prostaglandin biosynthesis. Acetone extract of *P. major* L. leaves has shown effective actions against *B. cereus*, *B. subtilis*, *S. aureus*, *S. epidermidis*, *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *P. mirabilis*, *S. enteritidis*, *C. albicans* and *C. tropicalis*. Soluble pectin polysaccharide (PMII) of *P. major* leaves showed prophylactically protective effects against systemic *S. pneumoniae* infections (Metiner *et al*., 2012). *Scrophularia nodosa* (Figwort): *Scrophularia nodosa* is a flowering herb belonging to family *Scrophulariaceae*. It contains biologically active compounds like phenylethanoids, acylated iridoid glycosides, phenylpropanoids, flavonoids, iridoids, iridoid glycosides and terpenoids. *S. nodosa* crude extract possess significant antibacterial, antifungal, antiprotozoal, antitumor, anti-inflammatory and diuretic activities and have been used in the treatment of wounds, psychological, nervous and gastrointestinal disorders (Stevenson *et al*., 2002; Ahmad *et al*., 2012).

***Tamarindus indicus* (Tamarind tree):** Tamarind has been known as a medicinal plant due to its antimicrobial, antibacterial, antifungal and antiseptic properties. Tamarind leaves show broad spectrum of antimicrobial activity that can be attributed to its phytoconstituents like flavonoids, xyloglucan, benzyl benzoate, limonene, hexadecanol, pentadecanol and other polyphenols metabolites. Thses phytoconstituents have shown antibacterial and antifungal activities against *B. subtilis*, *E. faecalis*, *S. aureus*, *E. coli*, *S. Typhimurium*, *P. aeruginosa* and *C. albicans* (Pino *et al*., 2004; Muthu *et al*., 2005; Doughari, 2006; Escalona-Arranz *et al*., 2010).

***Vitis vinifera*:** *Vitis* is affluent source of potentially bioactive polyphenols as reseveratrol, flavonoids, flavonols and stilbenes. Leaves of *Vitis* are especially rich in total phenols and their extracts have useful antioxidant and antimicrobial activities. The antibacterial and antifungal activities of the extracts has been tested against *S. aureus*, *B. cereus*, *E. coli*, *Campylobacter jejuni*, *Salmonella infantis*, *P. aeruginosa*, *C. albicans*, *C. parapsilosis* and *C. krusei* (Thimothe *et al*., 2007; Katalinic *et al*., 2013; Oliveira *et al*., 2013).

***Stephania glabra*:** The ethanolic extract of *Stephania glabra* has active principals against both Gram positive and Gram negative bacteria such as *S. mutans*, *S. epidermidis*, *E. coli*, *K. pneumoniae* with MIC of 50 μg mL^{-1} (Semwal *et al*., 2009). By realizing these benefits, *S. glabra* has long been used in folklore medicine for the treatment of pyrexia, inflammatory conditions, hyperglycemia, asthma, tuberculosis, dysentery, intestinal disturbances, cancers and sleep disturbances. The tetrahydroberberine alkaloid called as 8-(4'-methoxybenzyl)-xylopinine has been isolated from the ethanolic extract of its tubers and which showed antibacterial activity against *E. coli*, *P. aeruginosa*, *S. typhi* and *S. aureus* with Inhibition Zone Diameter (IZD) of 8-19 mm at MIC of 25-100 ìg/ml (Semwal *et al*., 2012).

***Calotropis gigantea* (Akanda):** The methanol extract and its chloroform fraction from the root bark of Akanda have demonstrated antibacterial activity against *Sarcina lutea*, *P. aeruginosa* and *Bacillus megaterium*. In addition, its petroleum ether fraction showed inhibitory activity against *Shigella sonnei* and *B. subtilis*. The ethyl acetate fraction of *Calotropis gigantea* also showed antibacterial activity against *E. coli* and *P. aeruginosa* (Alam *et al*., 2008). Anitha *et al*. (2014) also evaluated the antibacterial effect of *C. gigantea* latex extract against wide variety of pathogenic bacteria such as *S. aureus*, *Enterococcus faecalis*, *E. coli*, *K. pneumoniae* and *P. mirabilis*. The methanolic and ethanolic extracts have shown enhanced and wide spectrum of antimicrobial activity as compared to other extracts of the same plant. Hot aqueous and hot hydro methanolic extracts of *C. procera* also revealed mild to moderate dose dependent antibacterial activity against *S. aureus*, *E. coli*, *K. pneumoniae* and *P. mirabilis* (Sharma, 2010).

***Nelumbo nucifera*:** Both the white and pink flowers of *Nelumbo nucifera* extracts have shown significant antibacterial activity in a concentration dependent manner. The flowers showed maximal efficacy against *S. aureus*, *E. coli* and *B. subtilis* and moderate effectiveness against *P. aeruginosa* and *K. pneumoniae*. Variation and concentration in pytoconstituents like flavonoids, tannins and alkaloids alter antimicrobial

activity of individual plant extracts. Such variation might occur within the same species with minor differences. Further, colour variations of flowers revealed differences not only in antibacterial activity but also in the level of activity of *Nelumbo*. The hydro ethanolic extract of white flowers showed significant antibacterial activity as compared to pink flower extracts. The white flower extract exhibited lowest MIC against both Gram positive and Gram negative bacteria as compared to pink flowers. Moreover, Gram negative bacteria were found more amenable to antibacterial activity of these flower extracts than the Gram positive bacteria (Brindha and Arthi, 2010).

***Lantana indica* Roxb and *Lantana camara*:** The methanolic and aqueous extracts of the leaves from *Lantana indica* Roxb exhibit strong antibacterial against Gram positive bacteria such as *B. subtilis*, *S. aureus*, *Streptococcus pyrogens* as well as Gram negative bacteria such as *E. coli*, *P. vulgaris* and *K. pneumoniae*. The ethyl acetate extract showed moderate activity against *S. Typhi* and *P. aeruginosa* (Venkataswamy *et al*., 2010). The chemical constituents of essential oil from the fresh leaves of *Lantana* are davanone, α-humulene, β-caryophyllene, bicyclogermacrene and sabinene. These bioactive compounds showed significant antibacterial activity against *B. cereus*, *S. aureus*, *B. subtilis* and *E. coli* (Saikia and Sahoo, 2011).

***Jatropha curcas*:** The ethanolic and methanolic extracts of *Jatropha curcas* possess broad spectrum antibacterial activities. The extracts have lower potency for *K. pneumoniae* in comparison to other bacteria. The methanolic extract on the other hand showed significant antibacterial activity (MIC 0.5-10 mg mL^{-1}) than the ethanolic extract (MIC 0.5-6.25 mg mL^{-1}). This activity may be due to the presence of soluble phenolic and polyphenolic compounds (Igbinosa *et al*., 2009).

***Psidium guajava* L. (Guava):** The antibacterial compound mainly found in guava are reducing sugar, alkaloids, saponins, tannins, phlobatannins, terpenoids and poly phenols. The crude aqueous and methanol extract from the leaf and bark of guava possess strong antibacterial activity against MDR *Vibrio cholerae*. The *in vitro* MIC for the crude aqueous and methanolic extract is 1,250 and 850 μg mL^{-1}, respectively. These concentrations were bactericidal against 10^7 CFU mL^{-1} of *V. cholera*. The antimicrobial activity of guava has other advantage of being stable at 100°C for 15-20 min, indicating the nonprotein nature of the active component (Rahim *et al*., 2010). The ethanol and hot water extracts possess less antibacterial activity compared to methanolic and ethyl acetate extracts (Pandey and Shweta, 2011).

***Ficus carica* L. (Mulberry tree):** *Ficus carica* belongs to the family Moraceae which is one of the oldest fruits in the world and widely used for various diseases. It has been used as an anti-inflammatory agent ulcers and eruptions as well as digestion promoter. The methanolic extract of *F. carica* leaves have antimicrobial activity against MRSA (MIC 2.5-20 mg mL^{-1}) isolated from clinical samples. The methanolic extract also shows synergistic activity in combination with oxacillin or ampicillin and induces a more rapid decrease in the concentration of bacteria. The antibacterial effect has been suggested to act in a dose dependent manner against common bacterial pathogens (Lee and Cha, 2010; Al-Yousuf, 2012).

***Solanum nigrum*:** The methanolic extract and different fractions (ethyl acetate, n-butanol, chloroform and n-hexane) of *Solanum nigrum* leaves possess antimicrobial activity against *S. aureus*, *Pasteurella multocida*, *E. coli* and *B. subtilis* (Zubair *et al*., 2011). Likewise, the ethanolic and methanolic extracts from stem, berries and whole plant of *S. nigrum* inhibits the growth of *B. subtilis*, *E. coli*, *K. pneumoniae* and *P. aeruginosa*. The methanolic extract generally shows higher antibacterial activity than the ethanolic extracts. Furthermore, the extracts of the whole plant have been reported to possess anti-bacterial activity (Parameswari *et al*., 2012).

***Glycyrrhiza glabra* (Licorice) and *Uncaria tomentosa* (Cat's claw):** *G. glabra* and *U. tomentosa* extract show good antibacterial activity against oral pathogens such as *S. aureus E. faecalis* and *C. albicans,* suggesting their possible role to control dental caries and endodontic infections (Ccahuana-Vasquez *et al*., 2007; Herrera *et al*., 2010; Sedighinia *et al*., 2012). The ethanolic and aqueous extracts from leaves and root extracts of licorice show dose dependent antibacterial activity against *B. subtilis, E. faecalis*, *S. aureus*, *K. pneumoniae*, *P. aeruginosa* and *E. coli*. Moreover, the ethanolic extract of the leaves is better against Gram positive bacteria (Irani *et al*., 2010).

***Brassica campestris*:** The ethanolic, petroleum ether, methanol and ethyl acetate extracts from root, stem and leaves of *B. campestris* plant show excellent antibacterial activity against many Gram positive bacteria such as *S. aureus*, *S. epidermidis*, *B. cereus* and Gram negative

bacteria such as *P. aeruginosa* and *E. coli*. Although, benzene and chloroform extracts have antibacterial potential but these effects are least as compared to other other alcoholoic extracts (Agrawal *et al*., 2013).

***Picrorrhiza kurroa*:** The crude extract of Rhizome of *P. kurroa* has been used for long as traditional medicine to treat various gastrointestinal diseases especially diarrheal infections as well as skin and urinary tract infections. The rhizome contains various bioactive phytochemical constituents which includes phenolic compounds, sterols, cucurbitacins (triterpenoids) and iridoid glycosides (picroside I and kutkoside). Most of these compounds are extracted mainly as methanolic extracts and have significant antibacterial activity against *P. aeruginosa* and *S. aureus* and moderate effects against *Micrococcus luteus*, *E. coli* and *B. subtilis* (Rathee *et al*., 2012; Usman *et al*., 2012).

***Actinidia macrosperma*:** The hydrodistillate of leaf oil from *A. macrosperma* has shown variety of pharmacological activities against leprosy and cancers in cats. Its leaf oil contains high amount of monoterpenes. The major bioactive components include the linalool, linolenic acid methylester, (E)-phytol and 1, 2-dimethyl-lindoline. Studies have shown that the oil has mild antibacterial activity against *S. aureus* and *B. subtilise* and significant activity against Gram-negative bacteria such as *E. coli* (Lu *et al*., 2007, 2012; Lau *et al*., 2012).

***Astragalus membranaceus* and *A. gombiformis*:** *A. membranaceus* belongs to family *Fabaceae* and is commonly used to treat a wide variety of infections. The root contains various alkaloids, saponins, terpenoids, flavonoids and cardiac glycosides. Both the methanolic and ethanolic extracts from dried root show significant *in vitro* antibacterial activity against both Gram positive and Gram negative bacteria especially diarrhea causing pathogens (Balachandar *et al*., 2012). The methanolic extract from the leaves of wild *A. gombiformis* Pomel have been shown to exert antibacterial activity against *S. typhimurium* and *P. aeruginosa* (Teyeb *et al*., 2012).

***Emblica officinalis* (Amla) and *Coriandrum sativum* (Coriander):** The aqueous extract from the fruit pulp of *E. officinalis* and *C. sativum* showed significant level of antibacterial activity against 345 bacterial isolates belonging to 6 different genera of especially those of Gram negative type (Saeed and Tariq, 2007). The methanolic extract of *E. officinalis* revealed higher antibacterial activity in comparison to leaf and stem extracts of *O. sanctum* (Vijayalakshmi *et al*., 2007). Recently, ethanolic and aqueous-ethanolic extracts of Coriander have shown variable antibacterial activity against *B. subtilis*, *S. aureus*, *E. coli*, *P. aeruginosa*, *P. vulgaris*, *K. peunomonia* and *L. monocytogenes* (Yakout *et al*., 2013).

***Catharanthus roseus*:** *C. roseus* contains many phytochemical constituents such as reducing sugar, soluble sugar, amino acids, protein, total chlorophyll, lipids, ortho-dihydroxyphenols and phenol (Govindasamy and Srinivasan, 2012). The ethanolic and methanolic extract showed excellent antibacterial activity against *S. aureus*, *B. subtilis*, *E. coli*, *S. thyphi* and *P. aeuroginosa*. Maximal antibacterial activity has been observed against *S. aureus* at a concentration of 100 mg mL^{-1} from its leaf extract (Goyal *et al*., 2008).

***Foeniculum vulgare* (Common fennel) and *Crithmum maritimum* (Marine fennel):** Fennel is commonly used as a culinary spice for preservation of food spoilage. The main antioxidant compounds isolated from fennel are the essential oils which have significant antibacterial activity. Trans-anethole and estragole are the major components which show the antibacterial activity against the food-borne pathogens. These compounds inhibit the growth of the Gram positive bacteria such as *B. subtilis* and *S. albus*. They also exhibit antibacterial activity against Gram negative bacteria such as *S. typhimurium*, *Shigella dysenteriae* and *E. coli*. The essential oils are more active againest *S. dysenteriae* as compared to other bacteria. The possible mechanism of action of the essential oil is by causing damage to cell membranes, resulting in leakage of electrolytes and losses of intracellular contents (Ruberto *et al.,* 2000; Diao *et al.,* 2014).

***Alternanthera sessilis*:** *A. sessilis*, a member of family Amaranthaceae, is known for its antioxidant, hepatoprotective properties and antimicrobial activities along with wound healing potentials. The plant leaves contain active molecules such as A- and β-spinasterols, β-sitosterol and stigmasterol and have been used effectively in the treatment of cuts, wounds and skin diseases. The methanol extracts of *A. sessilis* leaves revealed antimicrobial potential against *E. coli* (Ryan, 1992; Shyamala *et al*., 2005; Lin *et al*., 1994; Jalalpure *et al*., 2008).

***Andrographis paniculata*:** *A. paniculata* belongs to family Acanthaceae, is an annual herb distributed in Sri Lanka and many parts of India. It is enriched with medicinal properties of antimalarial, antidiarrhoeal, antihypertensive, antipyretic, antithrombotic, choleretic, immunostimulant and anti-inflammatory activities. The ethanol extract of plant is a potent growth inhibitor of both Gram negative and Gram positive bacteria especially *B. cereus* and *S. aureus*. The antibacterial properties of the plant may be attributed to the actions of tannins, andrographolide, flavonoids and saponins (Mishra *et al*., 2009; Malahubban *et al*., 2013; Vidyalakshmi and Ananthi, 2013).

***Angelica acutiloba* (Japanese Dong Quai):** *A. acutiloba* is used maily for treating gynecological disorders. Also, Arabinogalactans obtained from *Angelica acutiloba* plant, have immunomodulatory and antiviral effect in animals (Kiyohara *et al*., 1981; Kumazawa *et al*., 1982; Enriquez *et al*., 1995; Liu *et al*., 2011).

***Taxus baccata* (Yew):** The active compound isolated from *Taxus baccata,* (--)-rhododendrol, is active against *Pseudomonas syringae* and *S. Typhimurium.* The other two compounds obtained from thesame plant include 4-(4'-hydroxyphenyl)-butan-2-one and 4-(4'-hydroxyphenyl)-trans-but-3-en-2-one which exhibit antibacterial activity against *P. syringae* and *B. sphaericus* (Erdemoglu and Sener, 2001; Reddy *et al*., 2001).

***Allium cepa* (Onions) and *A. sativum* (Garlic):** The ethanolic extracts from the cloves of *A. sativum* show antibacterial activity against MDR pathogens responsible for nosocomial infection (Karuppiah and Rajaram, 2012). The ethanolic and aqueous extracts from the bulbs of *A. cepa* have been found to have antibacterial action against the common causes of urinary tract infections, *P. aeruginosa* and *S. aureus,* especially those isolated from high vaginal swabs (Azu *et al*., 2007).

***Annona squamosa*:** The bacterial inhibition of the extracts from the leaves of *A. squamosa* is positively correlated with their phenolic contents. The acetone, boiling water, methanol and ethanolic extracts of *A. squamosa* showed low to moderate antibacterial activity in comparison to standard antibacterial drugs (El-Chaghaby *et al*., 2011).

***Acorus calamus*:** The crude methanol extracts from rhizomes of *A. calamus* have significant antimicrobial activities against filamentous fungi and a low degree of activity against bacteria (MIC 5-10 mg mL^{-1}) (Phongpaichit *et al*., 2005).

***Tinospora cordifolia* (Guduchi/Amrita):** It is an extensively used herbal plant in folk Ayurvedic medicine and rasayanas to enhance the immune system and body resistance against infections. The ethanolic extract has been found to show significant antibacterial activity against Gram positive bacteria such as *S. aureus*, *E. faecalis*, *Serratia marcesenses* and Gram negative bacteria such as *E. coil*, *P. vulgaris* and *S. typhi* (Jeyachandran *et al*., 2003; Nagaprashanthi *et al*., 2012).

***Woodfordia fruticosa*:** The methanolic and ethanolic extract from dried leaves of *W. fruticosa* exibit excellent antibacterial activity against both Gram positive and Gram negative bacteria including *E. coli*, *Bacillus subtilis P. aeroginosa*, *Salmonella paratyphi*, *Salmonella typhimurium*, *Shigella sonnei*, *K. pneumoniae*, *S. aureus* and *P. vulgaris* (Chougale *et al*., 2009; Kumar *et al*., 2013d).

***Betula utilis*:** The methanol extract of *Betula utilis* possess significant antibacterial activity against both Gram positive and Gram negative bacteria as compared to its aqueous and ethanolic extracts. However, its petroleum ether and chloroform extracts did not have any significant antibacterial activity (Kumaraswamy *et al*., 2008).

***Terminalia arjuna*, *T. Bellerica* and *T. chebula*:** These are commonly used herbal preparations in traditional medicinal system of India. Different preparations of their leaves, stem, bark and seeds are used either as aqueous, ethanolic, methanolic or hydromethanolic extracts. These have been proven antibacterial activities. Tannins as antimicrobial constituents have been purified from *T. chebula* Retz which are effective against MRSA infection. Moreover, aqueous and hydromethanolic extracts have been reported to have antibacterial activity against bacterial pathogens isolated from the cases of bovines mastitis (Sato *et al*., 1997; Chaudhari and Mengi, 2006; Vashney *et al*., 2012).

***Capsicum minimum*:** This particular plant along with other peppers both strengthes and improves digestion as well as lesser the chance of bacterial infections due to unsanitary food as well as water consumption practices (Grubben and Denton, 2004).

***Arnebia densiflora*:** The genus *A. densiflora*, member of family Boraginaceae, contain alkannin derivatives,

namely β, β-dimethylacrylalkannin, teracrylalkannin and isovalerylalkannin, α-methyl-n-butylalkannin, naphthoquinones and shikonin; which are known for their potential antibacterial, anti-inflammatory and wound healing properties (Kosger *et al*., 2009).

***Agathosma betulina* (Buchu):** The leaves of this plant have an effective antimicrobial as well as anti-inflammatory potential. 'Buchu' oil is obtained from this plant is among most renowned botanical assets of South Africa (Posthumus *et al*., 1996; Lis-Balchin *et al*., 2001; Moolla *et al*., 2007).

***Laurus nobilis* (Bay Leaf):** Bay leaf oil exhibits bactericidal effect against *S. enterica* and *E. coli* (Friedman *et al*., 2002). The activity may be attributed due to the presence of essential oils extracted from bay leaf (Raharivelomanana *et al*., 1989; Rahman *et al*., 2008).

***Acalypha indica*:** *A. indica* contains flavonoids, acalyphamide, alkaloids and glycosides which exerts antibacterial efficacy by inhibiting pathogens like *E. coli* and *V. cholerae* (Nahrstedt *et al*., 2006; Krishnaraj *et al*., 2010).

Herbal antimicrobial as feed additives: The exact mechanism by which antibacterial agents improve growth performance is not known, however, several theories have been proposed to explain their beneficial effects:

- Because they reduce the thickness of small intestinal epithelium and nutrients are more efficiently absorbed from the intestinal lumen (Boyd and Edward, 1967; Fuller *et al*., 1984)
- Nutrients are spared because the number of competing microorganisms is reduced (Eyssen, 1962)
- The different microorganisms responsible for subclinical infections are either reduced or eliminated completely (Barnes *et al*., 1978)
- There is a reduction in production of the growth-depressing toxins or metabolites by intestinal microflora (Dang *et al*., 1960)

Literature supports that the use of herbal preparations not only act as dietary supplements but also as agents to avert or control various bacterial infections especially enteric, respiratory or systemic infections. Organic extracts of many herbal preparations are available in Indian market viz., *Triphala churna*, *Hareetaki churna*, *Dashmula churna*, *Manjistadi churna*, *Sukhsarak churna*, *Ajmodadi churna*, *Shivkshar pachan churna*, *Mahasudarshan churna*, *Swadist virechan churna* and *Pipramool churna*. These were tested for their antibacterial potential against enteric bacterial pathogens such as *E. coli*, *S. aureus*, *E. aerogenes*, *P. aeruginosa*, *B. subtilis*, *K. pneumoniae*, *S. typhi*, *S. epidermidis*, *S. Typhimurium* and *P. vulgaris*, respectively. Result revealed potent antibacterial activity of Triphala churna, Hareetaki churna, Dashmula churna against *S. epidermidis*, *P. vulgaris*, *S. aureus*, *E. coli*, *P. aeruginosa* and *S. typhi* (Anesini and Perez, 1993; Tambekar *et al*., 2007; Tambekar and Dahikar, 2011).

OTHER CONVENTIONAL/TRADITIONAL AND EMERGING ANTIBACTERIAL THERAPEUTICS

The Complementary and Alternative Medicine (CAM) system includes long standing remedies passed on to generations to be practiced by common people such as herbal, Ayurveda, Siddha, Iranian, Unani, Islamic, Chinese, Acupuncture, Vietnamese and African health care practices all over the globe. Historical evidences suggest that in ancient times, honey, wine, vinegar, turmeric, indigenous herbs and dietary therapies were very successfully used for the management of wound. Some parts of plants can be used as a part of diet to support and hasten the healing process such as turmeric in lukewarm milk and citrous fruits to yield vitamins. These plants thus boost the formation of healthy granulation tissue network. At the time of war, commonly available materials like for treating gunshot wounds were boiling oil, egg yolk, turpentine, yogurt, oil from tea leaves, honey, palm oil and thin peelings of potato which have been used as therapeutic agents. The use of honey in infected wound management has even been described in the holy books like Bible and the Quran. The first documentary proof of the use of honey as a natural remedy in wound management is well documented in 2000 BC old Egypt literature (Tiwari *et al*., 2013b). Being viscous and hypertonic in nature honey shows effective antiseptic as well as anti-inflammatory action. Also, because of hyperosmolarity of honey, it absorbs the exudates from the wound and enhances the healing process (Yusof *et al*., 2007; Tiwari *et al*., 2013b). Furthermore, honey is rich in antibacterial, antifungal and anti-inflammatory properties especially against *S. aureus,* coagulase negative *staphylococci*, community-acquired MRSA, *E. coli* O157:H7 and *S. typhimurium infections.* The anti-bacterial properties are mainly due to the multifarious interaction of the various components of honey *viz.* hydrogen peroxide, bee defensin-1 and methylgyoxal. Moreover, concentrated and medical grade honey has greater anti-bacterial action (Badawy *et al*.,

2004; Kwakman *et al*., 2008; Moussa *et al*., 2012). In recent years, researchers have also revived their interest in pancghavya element of cow urine for the treatment of various diseases and disorders viz., rheumatoid arthritis, bacterial/viral infections, tuberculosis, chicken pox, hepatitis, leucorrhoea, leprosy and many others (Dhama *et al*., 2013d). Studies revealed that cow urine can kill a number of drug resistant bacteria and viruses. Owe to its medicinal properties, cow urine has been granted U.S. Patents (No. 6896907 and 6,410,059), particularly for its use along with antibiotics for the control of bacterial infection and as a bioenhancer of anti-tuberculous drugs (Dhama *et al*., 2013d; Randhawa, 2010). Apart from these, in the current era of emerging drug resistance, various other novel and emerging antibacterial therapeutic regimens are upcoming nowadays viz., bacteriophages, enzybiotics, avian egg antibodies, probiotics, immunomodulators, nutritional elements (Dhama *et al*., 2008, 2013c, d; Tiwari *et al*., 2014a, c). To overcome with hurdles of evoloving microbial resistance these various alternative and novel therapies are opening new avenues to fight against various bacterial pathogens.

CONCLUSION AND FUTURE PERSPECTIVES

Encountering a bacterial infection is a routine part of the human and animal life. New treatment modalities are constantly sprouting with the advances in medicinal science. Use of various herbs and traditional medicine is safe as well as economical in the present scenario of escalating health care cost. Emergence of MDR microorganisms and a decrease in efficacy of allopathic medicines has driven health care professionals and practitioners to revisit the old ancient healing methods of traditional and alternative medicines. Hence, an abreast is required to dig out as much as possible from the treasure of nature in order to shore up the good health among the advancements in various therapeutic regimens for getting desired protection from several diseases and ailments. A thorough reviewing is therefore mandatory in order to observe and describe and at the same time investigate and validate experimentally the various indigenous drugs along with better understanding of their biological and pharmacological properties. In the safety class rating there is great variation in case of herbal therapy. Many of them are though biologically more active they have the concurrent disadvantages of being toxic as well which must be viewed very carefully regarding dose standardization and extraction procedures. Every phytoconstituent has its pharmacological activity that varies with concentration and presence of another phytoconstituent. Synergistic as well as antagonistic action of phytoconstituents may be beneficial or harmful as toxicity of phytoconstituents at higher concentrations is well documented. Moreover, various pharmacological activities of individual pytoconstituents or their combinations are yet to be established. At the same time a much needed emphasis is required on traditional remedies and new therapeutic approaches. However, at every point a full detailed and well organised and scientifically proved facts based on molecular mechanisms and clinical trilas are required in order to avoid the popularized bias towards thi important medical sector. Herbal therapy acts thus as a much cheaper, safer and most widely accepted concept of humanity throughout globe, possessing multi-dimensional health benefits.. However, traditional medicinal plants require exhaustive scientific validation as well as standardization and safety evaluation before they can be accepted for commercialization. In the present scenario of emerging MDR, herbal therapy is opening new avenues to prevail over superbugs also. Last but not the least, in the field of antibacterials, herbal therapy has immense scope of development for which modern methodology must be employed by new investigations in addition to clinical studies on animals as well as humans. In the current era of "One World One Health One Medicine Concept", these efforts would altogether pave a way to develop novel broad spectrum antibacterial herbal formulations out of the natural resources for safeguarding several health issues of humans as well as their companion animals.

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