International Journal of Herbal Medicine
Available online at www.florajournal.com

E-ISSN: 2321-2187
P-ISSN: 2394-0514
IJHM 2019; 7(4): 10-18
Received: 06-05-2019
Accepted: 10-06-2019

Tegegn Dilbato
Jimma University, College of Agriculture and Veterinary Medicine, School of Veterinary Medicine, Jimma, Ethiopia

Feyissa Begna
Jimma University, College of Agriculture and Veterinary Medicine, School of Veterinary Medicine, Jimma, Ethiopia

Rakesh Kumar Joshi
Department of Education, Government of Uttrakhand, India

Correspondence
Tegegn Dilbato
Jimma University, College of Agriculture and Veterinary Medicine, School of Veterinary Medicine, Jimma, Ethiopia

Reviews on challenges, opportunities and future prospects of antimicrobial activities of medicinal plants: alternative solutions to combat antimicrobial resistance

Tegegn Dilbato, Feyissa Begna and Rakesh Kumar Joshi

Abstract
The effective prevention and treatment of an ever-increasing range of infections caused by bacteria, parasites, viruses and fungi, and at country level worldwide both in humans and animals was endangered by the emergence of conventional antimicrobial resistance. As result, the world interestingly, forward-looking to the natural products of medicinal plants as alternative remedies in the field of medical sciences in view of the novel molecules delivered by this discipline of science. In spite of the fact that, traditional medicinal healers have used medicinal plants for treatment of different ailments for centuries, there has always been a frequently asked question about their therapeutic efficacy, validation and standardization. Therefore, the main objective of this paper is to review and enlighten challenges, opportunities and future prospects of antimicrobial activities of medicinal plants as alternative solutions to combat antimicrobial resistance worldwide in humans as well as animals. Moreover, a continuous and progressing systematic researches and investigation using standardized extract develop through advanced analytical procedures need to be conducted to prove the biological ingredients and test the safety, efficiency and to determine the types of compounds responsible for the antimicrobial effects of these medicinal plants will be desirable.

Keywords: Antimicrobial resistance, challenges, medicinal plants, future prospects, opportunities

1. Introduction
Antimicrobial resistance within a wide range of infectious agents is a growing grave public health threat of broad concern to countries and multiple sectors. Increasingly, governments around the world are beginning to pay due attention to a problem so serious that it threatens the achievements of modern medicine. A post-antibiotic era—in which common infections and minor injuries can kill-far from being an apocalyptic fantasy, is instead a very real possibility for the 21st century [1]. Regarding, the emergence of antimicrobial resistance has its roots in the use of antimicrobials in animals and the subsequent transfer of resistance genes and bacteria among animals, animal products and the environment [2]. In addition, the findings of [3] pointed out extra-chromosomal genes were found responsible for these antimicrobial resistant phenotypes that may impart resistance to an entire antimicrobial class. There is association between resistance genes and plasmids which are large, transferable, and extra-chromosomal DNA elements. In addition, plasmid contains DNA mobile elements such as, transposons and integrons. These DNA mobile elements transmit genetic determinants for antimicrobial resistance mechanisms and may cause rapid dissemination of resistance genes among different bacteria. The emergence of multiresistant bacteria to antimicrobial drugs has increased the need for new antibiotics or modifications of older antibiotics [4]. According to [5] traditional medicine is undoubtedly the total knowledge, skills and practices based on theories, beliefs, and indigenous cultural experience (whether explicable or not) used in the maintenance of health, diagnosing, preventing, or eliminating physical, mental or social diseases. The studies relating to natural products have been very well supported by World Health Organization and other governing bodies worldwide. Some of the earlier reports indicated that more than 80% of the total population of the globe is still benefiting with the use of herbs and herbal products and more than 100 countries have regulations for herbal medicines stated by [26] [6]. Plants have served as a valuable source of ingredients for traditional medicines for millennia. Historical records and modern ethnobotanical field studies highlight their importance in the traditional treatment of infectious disease [7]. The studies of [6] pointed out there is scarcity in communicating and documenting the benefits of natural antibiotic substances to mankind, even in presence of potent synthetic compounds.

The modern knowledge of phytochemistry, scientific equipment and technology has had a great impact upon natural product chemistry, including isolation, extraction, purification and structure determination, but the discipline still demands more from the research investigators in terms of establishing the clinical significance of natural compounds to be recognized as a drug. The antibiotics from natural sources still needs considerable attention in terms of more organized studies to understand their behavior and targeted comparative studies to ascertain their clinical significance before highlighting any benefits over the existing antibiotics or the synthetic antimicrobials. Though, the international regulatory bodies and organizations are supporting such studies, but nevertheless it needs considerable funding to encourage scientist to work more and explore superior products of commercial value. There are diversified chemicals available in plants still remains largely uninvestigated for potentials in improving the clinical efficacy of antibiotics. Most interestingly are medicinal plants and food plants which are inadvertently used with antibiotics in common community practices providing opportunities for interactions? As many medicinal plants antimicrobial activity still remain unexplored, there are enormous opportunities for the discovery of novel resistance modifying compounds of plant origins. Screening of antibiotic resistance modifying compounds from plants sources are expected to provide the basis for identifying leads for the isolation of therapeutically useful compounds. This could in future be followed by *in vivo* assessments to determine the clinical relevance of such compounds. This represents a potential area of future investigation] [8]. According to [9] estimated 250,000 to 500,000 species of higher plants are to be present in the world. In spite of that, the higher plants, still largely seems to be unexplored for the identification of potent compounds active against microorganisms. Very few studies have been carried out so far to isolate and test active compounds of huge number of plant species reported to be present in the globe, while the overall percentage of the plants so far been explored out of these huge numbers, the antimicrobials lies between 1 to 10% stated by [6]. For example, in Ethiopia, plant remedies are still the most important and sometimes the only sources of therapeutics for nearly 80% of human and more than 90% in livestock population. Estimated floras of 6500 to 7000 species of higher plants are of medically important and out of these medicinal plants 12% are endemic to Ethiopia [10, 11]. Therefore, the main objective of this paper is to review the challenges, opportunities and future prospects of antimicrobial activities of medicinal plants as alternative solutions to combat drug resistance.

2. Antimicrobial activity of medicinal plants

According to [12] the impact antimicrobial resistance is considerable with treatment failures associated with multidrug-resistant bacteria and it has become a global concern to public health. For this reason, discovery of new antibiotics is an exclusively important objective. Natural products are still one of the major sources of new drug molecules today. They are derived from prokaryotic bacteria, eukaryotic microorganisms, plants and various animal organisms. Microbial and plant products occupy the major part of the antimicrobial compounds discovered until now [13]. Herbal medicines commonly referred to as 'Phyto medicines' exhibit some peculiar characteristics, namely: the active principles are frequently unknown; standardization, stability and quality control are feasible, but not easy; the availability and quality of raw materials are frequently problematic; well controlled, double-blind clinical and toxicological studies to prove their efficacy and safety are rare. Concerned with use in folk medicine is a very important characteristic; they have a wide range of therapeutic uses and are suitable for chronic treatments; the occurrence of undesirable side effects is less with herbal preparations, but well-controlled, randomized clinical trials have revealed that they also exist; they are usually affordable and cost less than synthetic drugs [14]. According to [15] the antimicrobial compounds from plants may inhibit bacterial growth by different mechanisms than those presently used antimicrobials and may have a significant clinical value in treatment of resistant microbial strains. Extracts isolated from several plants have been reported to have biological activity such as antimicrobial, anti-inflammatory and antioxidant activities [16].

Table 1: Antimicrobial activity of some medicinal plants

Plant Name	Family name	Used part	References
Combertum molle	Combertaceae	Bark	[17].
Xanthium strumarium		Leaf	[17, 18].
Measalanceolata,	Myrsinaceae	Fruit	[19].
Dodonae angustifolia	Sapindaceae	Leaf	[19].
Asparagus africanus	Asparagaceae	Leaf	[20].
Aloe barbarae Dyer	Xanthorrhoeaceae	Aerial parts	[21].
Cissus quadrangularis L.	Vitaceae	Stem	[22].
Jatropha zeyheri Sond.	Euphorbiaceae	Root	[22].
Ziziphus mucronata Willd.	Rhamnaceae	Leaves	[23].
Datura stramonium	Solanaceae	Leaf	[24].
Lantana camara	Verbenaceae	Leaf	[24].
Gentiana punctata L.	Gentianaceae	Root	[25].
Peltophorum africanum Sond.	Fabaceae	Root and barks	[26].
C. macrostachyus	Euphorbiaceae	Leaf	[20, 27].
C. aurea	Fabaceae	Leaf	[20].
Phyllanthus discoideus (Baill.) Muel-Arg	Euphorbiaceae	Bark	[28].
Strychnos spinosa	Loganiaceae)	leaves	[29].
Pterospermum acerifolium	Stericuliaceae	Stem,bark	[21].
Madhuca longifolia	Sapotaceae	Leaves, stem, bark	[21].

The efficacy, safety and quality of raw medicinal plant materials and plant products depend on intrinsic or extrinsic factors. Accidental contamination by microbial or chemical agents during any of the production stages can also affect the

quality, efficacy and safety. Medicinal plants collected in the wild may be contaminated by other species or plant through mis-identification, accidental contamination or intentional adulteration, all of which may have unsafe consequences [30]. According to [31] medicinal properties of the plants used in phytotherapy are due to the large amount of active compounds that can be found in the vegetable kingdom. Often, active principles extracted from plants are equivalent to synthetic drugs, according to their therapeutic efficacy; for this reason they are utilized in veterinary medicine, mainly as antibacterial, antimycotic, antiparasitic, disinfectants and immuno-stimulants. In organic farms, not only herbal drugs such as plant extracts and essential oils, but also homeopathic products, nutraceuticals and oligoelements, such as sodium, calcium, phosphorus, magnesium, and sulfur, are considered the main drugs to administer to animals for the treatment of different diseases. Nevertheless, it is possible to use synthetic allopathic drugs only when the previous products are ineffective; in such an eventuality, it is preferable to choose drugs that are metabolized rapidly, with a low environmental impact and less adverse effects on the animals. In addition, studies conducted on different antimicrobial and phytochemical constituents of medicinal plants confirmed their use for treatment of microbial infections (both topical and systemic applications) as possible alternatives to modern drugs to which many infectious microorganisms have become resistant. Literature reports and ethnobotanical records suggest that plants are the basis for modern drugs in the pharmaceutical industry. They constitute a natural source of antimicrobial drugs that will provide novel or lead compounds that may be employed globally [32].

3. The challenges of antibiotic resistance

Currently, antimicrobial resistance is a complex global public health challenge, and no single or simple strategy will suffice to fully contain the emergence and spread of infectious organisms that become resistant to the available antimicrobial drugs. The development of antimicrobial resistance is a natural phenomenon in microorganisms, and is accelerated by the selective pressure exerted by use and misuse of antimicrobial agents in humans and animals. The current lack of new antimicrobials on the horizon to replace those that become ineffective brings added urgency to the need to protect the efficacy of existing drugs [1].

According to [33] millions of lives have been saved due to substantial reduction in mortality achieved with antibiotic therapy. However, the antibiotic effectiveness almost all the available antibiotics is being threatened by the rising resistance of microorganisms The major cause of this resistance is the over-use and misuse of antibiotics which is exerting undue selective pressure on microorganisms. This has made infections more difficult to treat which is contributing to the high morbidity and mortality of previously treatable infections [34]. The emergence and spread of microbes that are resistant to cheap and effective first-choice drugs has become a common occurrence. The problem is even more evident in bacterial infections which contribute most to the global infectious disease burden such as diarrheal, respiratory tract, meningitis, sexually transmitted infections, and tuberculosis [35]. Concerning large animals, phytotherapy is mainly utilized in organic farms to reduce the use of allopathic drugs more and more. For the animal market, many of the currently used antimicrobial feed additive antibacterial, endectocide and anticoccidial drugs are either natural products or synthetics based on natural products [36]. The study of [37] pointed out the majority of these natural products are produced from the fermentation broth of microorganisms, though plants have also been an important source of bioactives. There is an increasing public concern regarding the use of pharmaceuticals in the animal industry. Much of this has been as a result of the emergence of drug resistance. Pathogenic micro-organisms become resistant to modern antibiotics through different mechanisms [38]. Natural adaptation is one of the mechanisms of the development of resistance in bacteria to the presence of an antimicrobial agent that inhibits susceptible organisms and selects the resistant ones. Under continued selection pressure, the selected resistant organisms multiply and spread to other geographic locations as well as to other microbes by transfer of resistance genes [39]. According to [40] some pathogenic microorganisms became resistant to lactam antibiotic by modifying the antibiotic or releasing some enzymes such as transferases which inhibit or break down the chemical structure of antibiotics which is called antibiotic inactivation. Whereas of Gram-negative bacteria, the aminoglycoside group of antibiotics becomes ineffective due to the modification of the antibiotic molecule through phosphorylation, adenylation and acetylation. Over 1000 naturally occurring -lactamase enzymes have been identified so far by [41, 42]. The recent findings of [42] have provided that target modification is one of the mechanisms in which antimicrobial agents act on a particular site where they bind and alter the normal function; this is called the target site. The bacterial cells become resistant to some antibiotics due to the modification of these target sites. The alteration or modification of the target site may be the result of constitutive and inducible enzymes produced by the bacteria. The resistance of some pathogenic species to antibiotics is due to the mechanism of active efflux. The intrinsic antibiotic resistance in bacterial genomes is caused by efflux pump proteins encoded by genes that are involved in the maintenance of cellular functions [43]. Most of the efflux mechanism systems in bacteria are non-drug-specific proteins [42]. The studies of [44] stated that the acquisition of new genetic material from other resistant organisms is responsible for the resistance in some bacteria. The transfer of genetic material between the same bacterial species or different species, other than the transfer through the parent to its progeny, is termed horizontal transfer (HGT). Bacterial species may exchange the genetic material through the processes of transformation, conjugation and transduction. These processes of genetic transmission are facilitated by a mobile genetic element, i.e., transposons. Plasmids may carry resistant genes and transmit these to other bacteria, particularly Gram-negative bacteria through conjugation. During conjugation, pilus form between two bacterial cells, through which the genetic material or plasmid carrying resistant genes are transferred. Enterococcal pheromone-responsive plasmids constitute the mobile genetic element (MGE). The donor cell in the presence of pheromone produces a proteinaceous structure on the cell surface called aggregation substance (AS) which binds to the enterococcal binding substance (EBS) present on the surface of the recipient. A mating channel is formed between the donors and recipient that enables the transfer of the plasmid DNA. After acquiring the plasmid, the recipient stops the production of pheromone and initiates the production of a specific encoded inhibitor peptide which serves to desensitize the bacterial cell to a low level of endogenous and exogenous pheromone produced by the donor. Ethiopia is well known for its traditional knowledge of medicine since dates back to several

millennia; a vast number of medicinal plants are described which have immense potential to treat illnesses caused by bacteria, fungi, parasites and ectoparasites both in human and animal diseases. While few studies have been carried out to evaluate the therapeutic efficacy and safety of herbal remedies; many survey studies have been found in the literature relating to document the use of plants and plant materials in ethnobotany and ethno-veterinary practices. This might help people should be informed that the use of herbal drugs in humans as well as domestic animals does not imply the absence of risks, particularly if they are administered at the same time with synthetic drugs or when plants for which scientific evidence able to justify their therapeutic use does not exist or in the case of utilizing unsafe herbs.

3.1. Pharmaceutical dosage form and presentation

According to [6] the successful commercialization of any research product finally depends upon how the product is delivered to achieve the desired therapeutic effect and this leads to design of appropriate dosage form suitable for the patient. The history of pharmaceutical dosage form for human application is quite old and a gradual improvement has been observed with the advancement in pharmaceutical technology and engineering. The design of a suitable dosage form, especially of natural antibiotics is of considerable importance as the desired level of the drug is required to be present in the blood stream to achieve antimicrobial activity. The solid oral dosage form is perhaps the most suitable and effective way to deliver natural antibiotics from plant and marine sources. However, in view of vast majority of compounds active against skin, oral flora, creams, ointments and lotion for dermatological application along with mouth washes should also be considered effective way of presentation. The activity of some compounds against bacterial conjunctivitis, also justifies the preparation of sterile ophthalmic dosage form. The injectable form should also be investigated, if the drug is degradable in the GIT because of the enzymatic interaction or if the oral absorption is limited. In such cases more sophisticated techniques can be used to ascertain the safety profile.

In recent years, antibiotics are associated with adverse effects on host, which include depletion of beneficial gut and mucosal microorganisms, immunosuppression, hypersensitivity and allergic reactions. The drug resistant bacteria have further complicated the treatment of infectious diseases in immunocompromised, AIDS and cancer patients especially in the case of nosocomial infections [45]. The studies of [46] pointed out that high cost of important conventional drugs and/ or inaccessibility to western health care facilities has led to over-reliance on traditional medicine since it is affordable and available to people. On the other hand, even when western health facilities are available, traditional medicine is viewed as an efficient and an acceptable system from a cultural perspective.

3.2. Antimicrobial susceptibility tests

Antimicrobial susceptibility testing can be used for drug discovery, epidemiology and prediction of therapeutic outcome. A variety of laboratory methods can be used to evaluate or screen *the in vitro* antimicrobial activity of an extract or a pure compound. The most known and basic methods are the disk diffusion and broth or agar dilution methods. Other methods are used especially for antifungal testing such as poisoned food technique. To further study the antimicrobial effect of an agent in depth, time-kill test and flow cytofluorometric methods are recommended, which provide information on the nature of the inhibitory effect (bactericidal or bacteriostatic) (time-dependent or concentration-dependent) and the cell damage inflicted to the test microorganism. Owing to the new attraction to the properties of new anti- microbial products like combating multidrug-resistant bacteria, it is important to develop a better understanding of the current methods available for screening and/or quantifying the anti- microbial effect of an extract or a pure compound for its applications in human health, agriculture and environment [47].

However, some clinical isolates can also be used to detect the antimicrobial activity against resistant strains. The initial screening tests are followed by the determination of minimum inhibitory concentration (MIC). The MIC is defined as the lowest concentration able to inhibit any visible microbial growth. The diffusion assays can be performed by disc diffusion assay, thus is., by using paper disc (of specific diameter) impregnated with a suitable concentration of natural extract or by well diffusion assay, where extract sample is poured into a well (of specific diameter). In both assay cases suitable solid medium, such as Tryptic soy agar, or Mueller-Hinton agar containing appropriate concentration (around 10^4 – 10^8 CFU) of 24 hours old bacterial or 18 hours fungal culture (inoculum) is used to spread on the agar surface or mixed into agar media. The plates are incubated for 18 to 24 hours at 35 ^oC to 37 ^oC depending upon the type of microorganisms used and the sensitivity or spectrum of activity is recorded by measuring the zone of inhibition. In case of dilution assays, which are usually applied to determine the MIC, it is usually carried out in liquid media, such as Tryptic soy broth or Mueller-Hinton broth. In some cases, solid media (agar dilution assay) can also be used where the microbial cell suspension is spread over the surface of the solid medium, inoculated in the centre of the plate by streak method or by mixing with the medium as performed in the broth dilution assy. The natural products are dissolved in DMSO (10% of the final volume) and usually diluted with culture broth at a concentration of 2 mg/ml. The determination of MIC is followed by the estimation of minimum bactericidal concentration (MBC) or minimum fungicidal concentration (MFG) by plating out samples completely inhibited dilution cultures and assessing growth after incubation [6]. In addition, the bioautographic technique is an excellent and very fast way to detect the antimicrobial activity of natural extracts or compounds. The method utilizes the application of samples on TLC plates prepared from silica gel G60 F254. The plates are run with the suitable solvent system and after drying, the plates can be irradiated with UV light to detect the florescent spots. The chromatogram is then transferred to a sterile petri dish and suitable solid medium (as described under diffusion assays) containing required concentration of the test organism (similar to diffusion assays) is poured over the chromatogram and incubated in a similar way as described above. At the end of the incubation period, the growth inhibiting zones yielded by the active substance are difficult to visualize on bioautographic plates because of the opacity. Therefore, indicator solutions, such as 0.2% triphenyltetrazolium chloride and 0.5% glucose are required to spray over the plate. The plates are further incubated for one hour and then the inhibitory zones can be visualized as light coloured areas against dark colored growth of organisms [48, 6].

3.3. Phytochemical screenings of medicinal plants

According to [7] the current percentage of approved antibacterial drugs from plants, however, does not accurately reflect the potential of plant natural products for future applications as antimicrobial therapies. In part, there are some inherent difficulties in the development of plant natural products as antimicrobial pharmaceuticals. Plant extracts are incredibly chemically complex – much more so than fungi, for example, as a single extract preparation may contain hundreds of different chemical entities. The isolation of single compounds with the desired antimicrobial bioactivity can be time consuming and requires a large amount of bulk plant material. Rediscovery of the same compounds from different sources presents problems, and much attention must be paid to careful dereplication early in the discovery process in order to avoid time and effort spent chasing known molecular entities. On the other hand, the antimicrobial activity of medicinal plant is equally challenging in view of great regulatory issues, poor financial support for research and lack of coordination between academia and pharmaceutical industries in generating efficient, meaningful and constructive data [6].

Moreover, many plant-based therapies work via synergistic pathways. Synergism among compounds in a complex mixture presents unique difficulties as the scientific technology to study multiple compounds acting in unison on potentially multiple biological targets has not yet been fully developed. On the other hand, it could be argued that the synergistic activity of certain plant extracts may present a unique opportunity in the face of growing antibiotic resistance. It raises the question of whether more chemically complex formulations can outlast monotherapies by making it more difficult for microbes to evolve resistance to a multi-sided attack [7].

4. Opportunities for antimicrobial activities of medicinal plants

4.1. Using ethno-veterinary and ethnobotany medicine in the economic development

The pharmaceutical industries are investing a lot to enter into the natural product business and trying hard to commercialize their research products. The research activities relating to antibiotics from natural source other than microorganisms has thus also occupied a prominent place and as a result few valuable products have been discovered and marketed very successfully. Medicinal plants have tremendous opportunities to bring new molecules and compounds which can fight against resistant organisms [6].

According to [49] ethn-oveterinary technologies can be the starting point for drug and technology development. Ideally, information obtained from local people should be used within the communities of its origin to ensure that they benefit from their own knowledge. Or a selected remedy can be improved outside of the community through pharmacological and clinical research and then be returned, 'value-added', to its place of origin. In addition, medicinal plants play a great role as source of appropriate technologies, source of human resources, input into monitoring and evaluation, and basis for common ground.

Many hundreds of plants worldwide are used in traditional medicine as treatments for bacterial infections. Some of these have also been subjected to *in vitro* screening but the efficacy of such herbal medicines has seldom been rigorously tested in controlled clinical trials. Conventional drugs usually provide effective antibiotic therapy for bacterial infections but there is an increasing problem of antibiotic resistance and a continuing need for new solutions. Although natural products are not necessarily safer than synthetic antibiotics, many people prefer to use herbal medicines. For these reasons, many researchers have attempted to find natural materials to replace antibiotics to treat bacterial infections [31].

4.2. Plants as sources of new antimicrobials to combat drug resistance

Plants have traditionally provided a source of hope for novel drug compounds, as plant herbal mixtures have made large contributions to human health and well-being [50]. Owing to their popular use as remedies for many infectious diseases, searches for substances with antimicrobial activity in plants are frequent [51]. In addition, Plants are rich in a wide variety of secondary metabolites, such as tannins, terpenoids, alkaloids, and flavonoids, which have been found *in vitro* to have antimicrobial properties [52].

4.3. Active compounds of plants with antimicrobial properties

For the alternative antimicrobial drugs, screening of plants as a source is now being conducted all over the world. Antimicrobial properties in plants are attributed to the presence of active compounds, e.g., quinones, phenols, alkaloids, flavonoids, terpenoids, essential oil, tannins, lignans, glucosinolates and some secondary metabolites. Other antimicrobial agents of plants include the peptides forming their defense systems which are similar to human antimicrobial peptides in structure and function [42]. Regarding, alkaloids are phytochemicals commonly found in Angiosperm and rarely found in Gymnosperm. The importance of the medicinal properties of alkaloids first came into existence when morphine was isolated from Papaver somniferum which is generally used as pain killer. A few examples of alkaloids that have known medicinal values are caffeine, quinine, cineline, strychnine, brucine, emetine and narcotine. Additionally, Berberine is also an example of an alkaloid found in Berberis spp., Cortex phellodendri and Rhizoma coptidis and has antimicrobial activity against Streptococcus agalactiae. The mechanism of action of berberine is due to its ability to intercalate with DNA and disrupt the membrane structure by increasing the membrane permeability of bacteria [53]. Flavonoids are well known phytochemicals that occur in a wide range of plant parts and products mainly in honey, fruits, seeds, vegetables, wines and tea. These phytochemicals are known to have antimicrobial, antiviral, antiallergic and anti-inflammatory properties stated by [42]. According to [54] flavones are hydroxylated phenolics containing one carbonyl group (two in quinones), while the addition of a 3-hydroxyl group yields a flavonol. The antimicrobial activity of six flavonoids isolated from Galium fissurense, Viscum album ssp. album and Cirsium hypoleucum was shown against extended-spectrum -lactamase, producing multidrug-resistant bacteria *K. pneumoniae.* Essential oils are another example of plant secondary metabolites that have compounds with isoprene structure, also known as terpenes, with the typical formula C10H16. Different types of terpenes are known such as diterpenes, triterpenes and tetraterpenes (C20, C30, and C40), as well as hemiterpenes (C5) and sesquiterpenes (C15). Essential oils are more active against Gram-positive bacteria than Gram-negative bacteria; the possible mechanism of action is membrane permeabilisers. When the compounds contain oxygen as an additional element, they are called

terpenoids. The terpenoids, also known as isoprenoids, are basically a different class of naturally-occurring organic chemicals similar to terpenes. These compounds are multicyclic structures and differ from one another in their basic carbon chains as well as in functional groups. These are the largest group of natural products and can be found in all classes of living things. Plant terpenoids are used for their aromatic qualities. They play a role in traditional herbal remedies and are under investigation for antibacterial, antineoplastic, and other pharmaceutical functions [42]. According to [55] terpenenes or terpenoids are active against bacteria, fungi, viruses, and protozoa. Trichodesma amplexicaule contains a mixture of terpenoids: _-sitosterol, _-amyrin, lupeol, hexacosanoic acid, ceryl alcohol and hexacosane. The term tannin (from tanna, German word for oak or fir tree) refers to the use of wood tannins from oak galls and these serve as the source of tannic acid. Tannins have an ability to combine with proteins, resulting in the tanning of animal hides into leather. Chemically, tannin is a large polyphenolic compound containing hydroxyls and carboxyl groups. Tannins present in plant impart astringent (clean the skin and constrict the skin pores) properties and cause a puckering feeling in the mouth when taken orally, e.g., red wine and unripened fruits. The presence of tannins in plants has a defensive role against predation by animals [42]. According to [56] phenolic compounds are one of the most diverse groups of secondary metabolites found in edible plants. They are found in a wide variety of fruits, vegetables, nuts, seeds, stems and flowers as well as tea, wine, propolis and honey, and represent a common constituent of the human diet. In nature they are involved in plant growth and reproduction, provide resistance from pathogens and predators and protect crops from disease and pre-harvest seed germination [57]. Lectins and polypeptides are often positively charged and contain disulphide bonds. Their mechanism of action may be the formation of ion channels in the microbial membrane or competitive inhibition of adhesion of microbial proteins to host polysaccharide [58]. Regarding, [59] pointed out the last few decades have seen a notable shift to a natural health care system and more and more people are resorting to the use of plant-based drugs. Scientific validation of the traditional health care system prevalent in tribal societies, ethnobotanical literature and plants described in using modern analytical tools, is currently an active area of research. There is growing interest in testing the efficacy of medicinal plants for treating various ailments; also, individual plants as well as combinations of medicinal plants against bacterial species which have become resistant to multiple drugs are being tested.

5. Opportunities of medicinal plants associated with biotechnology

5.1. Cultivation to control the content of active compounds

According to [60] controlled growth systems also make it feasible to contemplate manipulation of phenotypic variation in the concentration of medicinally important compounds present at harvest. The aim is to increase potency, reduce toxin levels and increase uniformity and predictability of extracts. The target compounds are almost invariably secondary metabolites, which, for the plant, frequently serve as adaptations to fluctuating temperature and light conditions (e.g. antioxidants), stress (e.g. proline), infection (e.g. flavonoids) or herbivory (e.g. alkaloids).

5.2. Traditional breeding principles as applied to medicinal plants

By bringing herbs into cultivation, traditional and biotechnological plant-breeding techniques can be applied at the genetic level to improve yield and uniformity, and to modify potency or toxicity. Seed production and viability are target traits in which considerable success can be expected simply by selecting vigorous and fertile genotypes, a process that also establishes a population adapted to the growing conditions provided [60].

5.3. Genetic transformation systems for medicinal plants

The studies of [60] discussed genetic transformation systems for medicinal plants. Direct manipulation of DNA sequences to alter gene expression in medicinal plants is an area that is ripe for expansion. Provided a trait can be related to one or a small number of genes, in principle, it is open to modification. Although the primary target for trait manipulation in medicinal plants is the content of active compounds, for development as crops, basic agronomic characters related to uniformity, stability, growth and development, and resistance to biotic and abiotic stresses, must also be improved [61]. On the other hand, the application of biotechnological approaches to medicinal plants does not start from a low baseline. There is already considerable interest in manipulating plant biosynthetic pathways to produce drug precursors, food components or pesticides; for example, through trichomes, specialized surface organs that manufacture, store and exude secondary metabolites [62]. There is a long history of experimental and commercial production of high-value phytochemicals by tissue culture, an *in vitro* system for growing plant organs, explants, tissues, cells or protoplasts. Genetic transformation of cultures using bacterial vectors to transfer genes into the cultured plant DNA has been widely employed to improve product output in such systems [60].

5.4. Pathway engineering in medicinal plants

The study of [63] reviewed the increasing production of active phytochemical constituents is a well-established target for genetic manipulation but presents some severe challenges. In particular, the metabolic pathways by which active compounds are biosynthesized are mostly poorly understood, and relatively few genes for key enzymatic or regulatory steps have been isolated. Nevertheless, there are examples of pathway engineering leading to improvements of potential value in the breeding of medicinal plants. New genomic approaches and efficient gene isolation methods applied to difficult secondary pathways in medicinal plant metabolism will undoubtedly expand the range and precision of manipulations via transgenesis, providing potentially superior material for the breeder (justifiable) [60].

6. Future prospects

Medicinal plants are currently in considerable significance view due to their special attributes as a large source of therapeutic phytochemicals that may lead to the development of novel drugs. Most of the phytochemicals from plant sources such as phenolics and flavonoids have been reported to have positive impact on health and cancer prevention [64].
Generally, there is an abundance of published data validating the antimicrobial activity of medicinal plants commonly used in folk medicine; this has not resulted in the identification of commercially exploitable plant derived antibacterial agents

[52]. The findings of [65] have provided a foundation for a rationale on the potential actions of plant derived antimicrobial compounds and other compounds with no intrinsic antimicrobial value. It has already been established that crude extracts of some medicinal plants and some pure compounds from such plants can potentiate the activity of antibiotics *in vitro*. This search for antibiotic resistance modulators in plants represents a new dimension to addressing the problem of antibiotic resistance [8].During a time of rapidly rising antibiotic resistance, new approaches are necessary to fill the antimicrobial drug development pipeline. Moving forward, there are clearly several innovative strategies to pursue in the search for novel therapies. Plants remain a unique and underexploited source of bioactive compounds, and ethnobotanical research tools can be used to guide future research efforts and narrow down the search to the most likely source candidates. In addition, to tests for classic bacteriostatic and bactericidal activity, it is also imperative to examine complex plant extracts and individual compounds for activity against alternative bacterial targets, such as virulence and pathogenesis, as well as host-directed targets [7]. Medicinal herbs are taking their place alongside the likes of bio-energy crops, sources of renewable industrial feedstock's and bioremedials as potential beneficiaries of technological solutions originally devised for the food chain. The twin political issues of world energy security and management of landscapes to sustain rural communities and urban expectations are likely to keep the biotechnological option on the agenda. A particular challenge for medicinal plants is the degree to which synergistic effects (a major part of the herbalist rationale) can be not only conclusively demonstrated but also realistically defined for biotechnological intervention. Otherwise, increasing understanding of what the active components in herbs are and how they work will simply lead to their isolation as plant-derived drugs, and biotechnological interest in the plants and whole extracts from them will not be justifiable [60]. Currently, the discovery of new antibiotics is an exclusively important objective due to considerable impacts with treatment failures associated with multidrug-resistant bacteria and it has become a global concern to public health. Natural products are still one of the major sources of new drug molecules today. They are derived from prokaryotic bacteria, eukaryotic microorganisms, plants and various animal organisms. Microbial and plant products occupy the major part of the antimicrobial compounds discovered until now [47]. Over the next few years, the study of medicinal plants as antimicrobial agents should be focused in part on ascertaining specific information about the plant's antimicrobial activity, avoiding studies in which researchers use this criterion merely as a complement to a phytochemical study. The isolation of active compounds should be undertaken in light of the known activity of the plant and likewise follow a guided isolation of potential principles. Thus, when the activity of fractions and compounds is inferior to the total extract or fraction, rather than invalidating the results, this should confirm the known anti-infection properties of the plant. The fact that a plant extracts exhibits activity is of interest, but it is only a preliminary piece of data and should be followed by the identification of the active compounds by means of a bio-guided assay [66].

7. Conclusion

Currently, the emergence of antimicrobial resistance has a great challenge to the world. In addition, antibacterial drugs have become less effective or even ineffective, resulting in an accelerating global health security emergency that is rapidly outpacing available treatment options. Faced with such difficulties and challenges, there is an urgent requirement and opportunities to search for new antimicrobial molecules or compounds from plant sources which have a broad spectrum of activity against pathogenic species as well as having immunomodulatory action. Indeed, traditional medicinal plants have emerged as a boon in medical sciences as they are relatively available and have almost no side effects both in humans and animals. These medicinal plants produce a variety of secondary compounds having very important as antimicrobial agent and have therapeutic properties. The identification and isolation of active compounds from the plants is still a challenge for most of the countries rich in plant diversity. However, antimicrobial activities of plants are being increasingly reported from different countries of the world due to drug resistance development from conventional medicine. Furthermore, special attention should be given to antimicrobial activity of medicinal plants as a new hope to combat danger threats of antimicrobial resistance worldwide; continuous and exhaustive efforts are being made to explore and investigate the plant kingdom in order to find novel drugs that could save human as well as animal life from noxious microbial and viral infections.

8. Ethics approval and consent to participate: Not applicable

9. Funding: Not applicable

10. Acknowledgement: Not applicable

11. References

1. World Health Organization. Antimicrobial resistance: global report on surveillance. 2014.
2. McEwen SA, Fedorka-Cray PJ. Antimicrobial use and resistance in animals. Clinical Infectious Diseases. 2002; 34(3):93-106.
3. Touitou I, Lesage S, McDermott M, Cuisset L, Hoffman H, Dode C *et al*. Infevers: an evolving mutation database for auto- inflammatory syndromes. Human mutation. 2004; 24(3):194-198.
4. Tollefson L, Miller MA. Antibiotic use in food animals: controlling the human health impact. International journal of food microbiology. 2000; (83):245-254.
5. World Health Organization. Traditional Medicine. Availa ble at: http://www.who.int/medicines/areas/traditional/en/ index.html, 2006.
6. Mahmood SBZ. Antibiotic natural products: Opportunities and challenges, 2013.
7. Quave CL. Antibiotics from nature: traditional medicine as a source of new solutions for combating antimicrobial resistance, 2016.
8. Sibanda T, Okoh AI. The challenges of overcoming antibiotic resistance: Plant extracts as potential sources of antimicrobial and resistance modifying agents. African Journal of Biotechnology. 2007.
9. Borris RP. Natural products research: perspectives from a major pharmaceutical company. Journal of Ethnopharmacology. 1996; 51(1-3):29-38.
10. Tadeg H, Mohammed E, Asres K, Gebre-Mariam T. Antimicrobial activities of some selected traditional Ethiopian medicinal plants used in the treatment of skin disorders. Journal of ethnopharmacology. 2005; 100(1-2):168-175.
11. Giday M, Asfaw Z, Woldu Z. Medicinal plants of the

Meinit ethnic group of Ethiopia: an ethnobotanical study. Journal of Ethnopharmacology. 2009; 124(3):513-521.
12. Guschin A, Ryzhikh P, Rumyantseva T, Gomberg M, Unemo M. Treatment efficacy, treatment failures and selection of macrolide resistance in patients with high load of *Mycoplasma genitalium* during treatment of male urethritis with josamycin. BMC infectious diseases. 2015; 15(1):40.
13. Bérdy J. Bioactive microbial metabolites. The Journal of antibiotics. 2005; 58(1):1.
14. Calixto JB. Efficacy, safety, quality control, marketing and regulatory guidelines for herbal medicines (phytotherapeutic agents). Brazilian Journal of Medical and Biological Research. 2000; 33(2):179-189.
15. Shankara SR, Rangarajana R, Sarada DV, Sreenath KC. Evaluation of antibacterial activity and phytochemical screening of *Wrightia tinctoria* L. Pharmacogn J. 2010; 2:19-22.
16. Yusuf S, Mehta SR, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK *et al*. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. The Lancet. 2001; 358(9281):527-533.
17. Habitamu K, Fekadu R, Mebratu A, Ayana W. The *in vitro* antibacterial effect of three selected plant extracts against Staphylococcus aureus and Streptococcus agalactiae isolated from bovine mastitis. Journal of Veterinary Science and Technology. 2015.
18. Khond Mangesh JD, Bhosale Tasleem Arif, Mandal TK, Padhi MM, Rajesh Dabur. Screening of some selected medicinal plants extracts for *in vitro* antimicrobial activity. Middle-East J Sci Res. 2009; 4(4):271-278.
19. Mengiste B, Hagos Y, Moges F, Tassew H, Tadesse G, Teklu A. *In vitro* Antibacterial Screening of Extracts from Selected Ethiopian Medicinal Plants. Momona Ethiopian Journal of Science. 2014; 6(1):102-110.
20. Kalayou S, Haileselassie M, Gebre-egziabher G, Tiku'e T, Sahle S, Taddele *et al*. *In vitro* antimicrobial activity screening of some ethnoveterinary medicinal plants traditionally used against mastitis, wound and gastrointestinal tract complication in Tigray Region, Ethiopia. Asian Pacific Journal of Tropical Biomedicine. 2012; 2(7):516-522.
21. Ndhlala AR, Amoo SO, Stafford GI, Finnie JF, Van Staden J. Antimicrobial, anti-inflammatory and mutagenic investigation of the South African tree aloe (Aloe barberae). Journal of ethnopharmacology. 2009; 124(3):404-408.
22. Luseba D, Elgorashi EE, Ntloedibe DT, Van Staden J. Antibacterial, anti-inflammatory and mutagenic effects of some medicinal plants used in South Africa for the treatment of wounds and retained placenta in livestock. South African Journal of Botany. 2007; 73(3):378-383.
23. Mc Gaw, Lyndy Joy, Van der Merwe D, Jacobus Nicolaas Eloff. *In vitro* anthelmintic, antibacterial and cytotoxic effects of extracts from plants used in South African ethnoveterinary medicine. The Veterinary Journal. 2007; 173(2):366-372.
24. Prathiba HD, Manjunath NH. Preliminary phytochemical screening of five Indian medicinal plants. MSR Journal of Sciences. 49.
25. Wynn Susan G, Barbara Fougere. Veterinary herbal medicine. Elsevier Health Sciences, 2007.
26. Bizimenyera ES, Githiori JB, Eloff JN. Swan GE. *In vitro* activity of Peltophorum africanum Sond. (Fabaceae) extracts on the egg hatching and larval development of the parasitic nematode Trichostrongylus colubriformis. Veterinary Parasitology. 2006; 142(3-4):336-343.
27. Aylate A, Agize M, Ekero D, Kiros A, Ayledo G, Gendiche K. *in vitro* and *in vivo* Antibacterial Activities of Croton macrostachyus Methanol Extract against E. coli and S. aureus, 2017.
28. Akinyemi KO, Oluwa OK, Omomigbehin EO. Antimicrobial activity of crude extracts of three medicinal plants used in south-west Nigerian folk medicine on some food borne bacterial pathogens. African Journal of Traditional. Complementary and Alternative Medicines. 2006; 3(4):13-22.
29. Isa Adamu I, Maurice DA, Jean PD, Mohammed A, Rabiu AM *et al*. Some Strychnos spinosa (Loganiaceae) leaf extracts and fractions have good antimicrobial activities and low cytotoxicities. BMC complementary and alternative medicine. 2014; 14(1):456.
30. Adewunmi CO, Ojewole JAO. Safety of traditional medicines, complementary and alternative medicines in Africa. African Journal of Traditional Complementary and Alternative Medicine. 2004; 1:1-3.
31. Severino L, Ambrosio L. Herbal Drugs Used for Domestic Animals. Medicinal Plants: Biodiversity and Drugs, 2012, 334.
32. Akinpelu DA, Onakoya TM. Antimicrobial activity of medicinal plants used in folklore remedies in southwestern Nigeria. Afr. J. Biotechnology, 2006; 5(11): 1078-1081.
33. Paphitou NI. Antimicrobial resistance: action to combat the rising microbial challenges. International journal of antimicrobial agents. 2013; 42:25-28.
34. Byarugaba DK. A view on antimicrobial resistance in developing countries and responsible risk factors. International Journal of Antimicrobial Agents. 2004; 24:105-110.
35. World Health Organization. Antimicrobial resistance, Fact sheet no. 194. World Health Organization: Geneva, Switzerland, 2002.
36. Ruddock JC. Secondary metabolites as a vital source of animal health products. Special Publication-Royal Society of Chemistry, 2000, 45-56.
37. Barton MD. Antibiotic use in animal feed and its impact on human health. Nutrition research reviews. 2000; 13(2):279-299.
38. Andersson DI. The ways in which bacteria resist antibiotics. International Journal of Risk and Safety in Medicine. 2005; 17(3-4):111-116.
39. Levy SB, Marshall B. Antibacterial resistance worldwide: causes, challenges and responses. Nature medicine. 2004; 10(12):122.
40. Wright GD. Bacterial resistance to antibiotics: enzymatic degradation and modification. Advanced Drug Delivery Reviews. 2005; 57(10):1451-1470.
41. Bush K, Fisher JF. Epidemiological expansion, structural studies, and clinical challenges of new β-lactamases from gram-negative bacteria. Annual Review of Microbiology. 2011; 65:455-478.
42. Chandra H, Bishnoi P, Yadav A, Patni B, Mishra AP, Nautiyal AR. Antimicrobial Resistance and the Alternative Resources with Special Emphasis on Plant-Based Antimicrobials-A Review. Plants. 2017; 6(2):16.
43. Lomovskaya O, Bostian KA. Practical applications and

feasibility of efflux pump inhibitors in the clinic-a vision for applied use. Biochemical pharmacology, 2006; 71(7):910-918.
44. Wardal E, Sadowy E, Hryniewicz Waleria. Complex nature of enterococcal pheromone-responsive plasmids. Pol J Microbiol. 2010; 59(2):79-87.
45. McGaw LJ, Rabe T, Sparg SG, Jäger AK, Eloff JN, Van Staden J *et al*. An investigation on the biological activity of Combretum species. Journal of ethnopharmacology. 2001; 75(1):45-50.
46. Munguti K. Indigenous knowledge in the management of malaria and visceral leishmaniasis among the Tugen of Kenya leishmaniasis among the Tugen of Kenya. Indigenous knowledge and development monitor. 1997; 5:10-12
47. Balouiri M, Sadiki M, Ibnsouda SK. Methods for *in vitro* evaluating antimicrobial activity: A review. J Pharma. Anal, 2016; 6(2):71-79.
48. Kalemba D, Kunicka A. Antibacterial and antifungal properties of essential oils. Current Medical Chemistry Journal. 2003; 10:813-829.
49. Mathias E. Introducing ethnoveterinary medicine. Bergisch Gladbach, Germany, 2001.
50. Iwu MW, Duncan AR, Okunji CO. New antimicrobials of plant origin. Perspectives on New Crops and New Uses. ASHS Press, Alexandria, VA, 1999, 457-462.
51. Betoni JEC, Mantovani RP, Barbosa LN, Di Stasi LC, Fernandes JA. Synergism between plant extract and antimicrobial drugs used on Staphylococcus aureus diseases. Memórias do Instituto Oswaldo Cruz. 2006; 101(4):387-390.
52. Lewis K, Ausubel FM. Prospects for plant-derived antibacterial. Nature biotechnology. 2006; 24(12):1504.
53. Peng L, Kang S, Yin Z, Jia R, Song X, Li L *et al*. Antibacterial activity and mechanism of berberine against Streptococcus agalactiae. International journal of clinical and experimental pathology. 2015; 8(5):5217.
54. Özçelik B, Orhan DD, Özgen S, Ergun F. Antimicrobial activity of flavonoids against extended-spectrum β-lactamase (ESβL)-producing Klebsiella pneumoniae. Tropical Journal of Pharmaceutical Research. 2008; 7(4):1151-1157.
55. Banso A. Phytochemical and antibacterial investigation of bark extracts of Acacia nilotica. J Med. Plants Res. 2009; 3:82-85.
56. Sher A. Antimicrobial activity of natural products from medicinal plants. Gomal Journal of Medical Sciences. 2004; 7(1):1-5.
57. Ross JA, Kasum CM. Dietary flavonoids: bioavailability, metabolic effects, and safety. Annual review of Nutrition. 2002; 22(1):19-34.
58. Kaigongi MM. Antimicrobial activity, toxicity and phytochemical analysis of four medicinal plants traditionally used in Msambweni District, Kenya (Doctoral Dissertation, School of Biological Sciences, University of Nairobi), 2014.
59. Ling LL, Schneider T, Peoples AJ, Spoering AL, Engels I, Conlon BP *et al*. A new antibiotic kills pathogens without detectable resistance, Nature. 2015; 517(7535):455.
60. Canter PH, Thomas H, Ernst E. Bringing medicinal plants into cultivation: opportunities and challenges for biotechnology. Trends in Biotechnology. 2005; 23(4):180-185.
61. Dubey T, Guerra DJ. Use of biotechnology for growing medicinal plants. Recent Progress in Medicinal Plants. 2002; 5:47-61.
62. Stevenson R. Chemical harvest. Chemistry and Industry, 2004, 16-18.
63. Charlwood BV, Pletsch M. Manipulation of natural product accumulation in plants through genetic engineering. J Herbs Spices Med Plants, 2002, 139-151.
64. Venugopal R, Liu RH. Phytochemicals in diets for breast cancer prevention: The importance of resveratrol and ursolic acid. Food Science and Human Wellness. 2012; 1(1):1-13.
65. Tegos G, Stermitz FR, Lomovskaya O, Lewis K. Multidrug pump inhibitors uncover remarkable activity of plant antimicrobials. Antimicrobial agents and chemot herapy. 2002; 46(10):3133-3141.
66. Rios JL, Recio MC. Medicinal plants and antimicrobial activity. Journal of ethnopharmacology. 2005; 100(1-2):80-84.