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Phytochemicals and Their Antimicrobial Activity: An Update on Their Mode of Action

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Abstract

Introduction: Plants have been considered as potential alternative for antimicrobial antibiotics owing to vast reserve of secondary metabolites. Last few decades have experienced an upsurge in demand and delivery of herbal products for health benefits as plant derived bioactive compounds have capability to interact with a wide variety of targets. The main focus of this review was to congregate vital information related to imperative bioactive components of medicinal plants having therapeutic potential with particular reference to antimicrobial activity against pathogenic bacteria. Our study intended to comprehend the mode of action of these phytopharmaceuticals for their scientific validation and drug development. **Methods:** A narrative review of papers reporting antimicrobial activity of medicinal plants against pathogenic bacteria, identification of the prospective bioactive compounds with antimicrobial potential and understanding their mechanism of action has been envisaged. **Results:** This review includes anthology of recent published information on phytoconstituents of various medicinal plants belonging to different families around the globe, tested and validated against various pathogenic bacteria. This study unveils the treasure of antimicrobial potential of plant species, which is also an appraisal of information related to mechanism of action of these phytochemicals required for their antimicrobial activity. **Conclusions:** There is resurgence in use of herbal medicines and identification of pharmacologically active compounds with their scientific validation. It will play a pivotal role in perpetuating and promoting wider usages of drugs based on plant extracts. A missing link for establishment of phytocompounds as an alternative drug requires understanding their mode of action and exploitation.

Keywords

Medicinal plants, secondary metabolites, phytochemicals, antimicrobial activity, mode of action

Introduction

Medicinal plants have been rich source of therapeutically important compounds, used traditionally worldwide as remedies for the treatment of a number of diseases. Plants synthesize myriad biologically active phytochemicals which allow them to exist in their environment including defense against biotic stress [1]. Since antiquity plants have been used by man to treat common infectious diseases. In the past few decades the search for new antimicro-

bials has engaged many research groups in this field [2]. Approximately 100,000 plant species have a record of medicinal use [3] and they pose to be prospective reservoirs for new drug discovery [4]. Newman [5] reported that out of 109 new antibacterial drugs which got approval between 1981 and 2006, 69% are of natural product origin. Therapeutic use of formulations having physiologically active constituents has a record in folk medicines for treatment of various infectious diseases and possess a unique combination of secondary metabolites having potent biological activities and can be used as an alternative for the treatment of diseases especially in developing countries where people don't have access to health care [6]. Traditional system of medicine is practiced in many developing countries [7]. Richness in bio-diversity of Indian flora was well recognized all over the world which helped in documentation of natural resources in the form of books, treaties and research papers *etc*. It is very interesting to know that even in 21st century, 70% of population in villages use herbal therapy for health problems and Ayurvedic system is still proving itself to the needy people. Advanced tools and analytical techniques help in extraction of these active principles for use in modern medicine [8]. One major asset of medicinal plant-based drug discovery is the existence of ethnopharmacological information providing hints for compounds therapeutically effective in humans [9]. Phytochemicals which are mostly secondary metabolites are exceptionally complex with low molecular weight and difficult to synthesize. Medicinal plants are named as "Ultimate factories" as they are crucial for attaining health.World Bank reported that there is an annual increase in growth rate of herbal medicine from 5% to 15% [10]. WHO recognized the importance of traditional medicine integrated with other sciences. It has also been focusing on evidence-based strategy of traditional medicines as global health care needs to be strengthened.

A substantial proportion of deaths worldwide are owing to infectious diseases. Treatment of many infectious diseases is threatened by the growing resistance of pathogens to the drugs. Excessive use of antibiotics is responsible for emergence of antibiotic resistant bacteria, which renders current antibiotics insufficient to control bacterial infection. Epidemiology of resistance is complex and moreover the problem is aggravated by lack of success in developing novel antibiotics. There is a renewed interest in the study of medicinal plants as potential sources of new antibacterial agents; it is an important line of research owing to antibiotic resistance acquired by microorganisms [11]. There are several reports mentioning the role of secondary metabolites as potential antibacterial agents [12].

Plant extracts provide therapeutic modalities with broad spectrum antimicrobial activities against various pathogens [13]. Last few decades have experienced an upsurge in demand and delivery of these herbal products for health benefits. Currently herbal therapy has taken a front seat and researchers are identifying pharmacologically active compounds, their biological activities and scientific validation. It will play a pivotal role in perpetuating and promoting wider usages of drugs based on plant extracts. Plant extracts possess multidimensional health benefits, phytoconstituents are also beneficial in maintenance and boosting of general health conditions. There are variations in active principles; however, it forms a bunch of safer, cost effective and easily available medicines [13, 14]. A missing link of use of phytochemicals as antimicrobials is their mode of action. There are large number of publications which report antimicrobial activity of isolated pure compounds against bacterial pathogens. However, only few report their mode of action. There is a resurgence of use of herbal medicine. Natural products are considered as privileged group of compounds which interact with wide variety of targets. Plant extracts as complete mixture of secondary metabolites also exude synergistic effect with conventional antibiotics [15].

Conventional therapy using antibiotics is found to be untreatable to many of existing infectious diseases due to the presence of multidrug-resistant bacteria. Therefore, efforts are being made to target bacterial resistance mechanisms by developing new drugs obtained from natural products, especially plants. Plants have structurally diverse and complex compounds with unique properties showing outstanding performance. Researchers are focusing on innovative strategies to eradicate multidrug-resistant bacteria by using these phytochemicals [16]. Even though plant-derived phytochemicals are many times weaker compared to antibiotics produced by bacteria [17], plants can fight against these infections effectively. There should be a serious consideration of unusual infections causing adverse side effects for solving actual health problems of society [18]. A thorough review is mandatory to investigate and validate the plant extracts with better understanding of their biological and pharmacological properties.

This review is an attempt in this direction to compile the antimicrobial activity of plant extracts and get an insight into their mode of action. Authors have made an attempt to compile the information about various plants with antimicrobial applications and role of their phytoconstituents to combat microbial infection to understand their mode of action as an alternative to conventional antibiotics it also discusses the potential of phytochemicals for drug development.

Phytopharmaceuticals; Pharmacologically significant compounds:

Crude extracts serve as wonderful drugs to humans for treatment of various diseases thus explaining the potential

of medicinal plants and their extracts for development of novel drugs [19]. *Lavatera thuringiaca L*. extracts rich in bioactive compound were found to possess wide range of biological activities such as antimicrobial, antioxidant, cytotoxic, antiviral, antiallergic, anti-inflammatory and many more [20]. Three halophyte species *viz. Arthrocnemum macrostachyum, Halimione portulacoides* and *Salicornia europaea* were considered for novel phytopharmaceuticals development as they were found to be potential sources of biologically-active compounds [21]. *Euphorbia denticulata* was identified as a promising source of phytochemicals which help in the development of novel functional formulations [22]. *Plantago lanceolata* plant was scientifically justified for its use against various diseases affecting humans as its leaves are identified to be good source of important phytochemicals [23].

Andrographis paniculata extract was analyzed for its phytochemical profile; compounds identified include phenols, esters and aromatic carboxylic acids, which might be responsible for antimicrobial activity against Gram positive and Gram negative bacteria [24]. *Gymnema sylvestre* was analyzed for its phytochemical and antimicrobial activity using various solvents and high activity was exhibited by aerial and root parts. The compounds oleic acid, eicosane, vitamin E and stigmasterol were anticipated to be responsible for its excellent antimicrobial activity [25].

All the strategies using phytochemicals can be used for the advancement of novel compounds with enhanced therapeutic activity. Natural products may be difficult to supply and working may be slow, but chemical diversity of natural products gives successful drugs against multidrug resistant pathogens [26]. Medicinal herbs can either influence the immune status of the host or the pathogenicity of the pathogen and can even modulate the disease production site. Some active ingredients in thyme such as Thymol and Carvacrol exhibit their antimicrobial action by penetration into Gram negative bacteria resulting in lysis of bacterial cell [27, 28]. Phytochemicals such as Vitamin C and carotenoids increase the antigenic surveillance of the immune system thereby reducing the risk of infections [29- 31]. The roots of Ashwagandha were found to have steroidal alkaloids and lactones which enhance the engulfing power of macrophages and other immune cells which in turn helps in antimicrobial action against *Salmonella* [32, 33]. Canberry was found to interfere with bacterial adherence to bladder lining and helps to prevent infection. Many herbal plants inhibit cyclooxygenase-2, 5-lipoxygenase and glutathione S-transferase which further inhibit prostaglandin biosynthesis and exhibit anti-inflammatory action. Some herbs decrease the production of inflammatory agents such as histamine, serotonin and enhance the activity of cortisol which help in removal of bacterial toxins out of body [34, 35].

Some herbs were found to proliferate CD4+ T-helper and B-cells, and some block NF-eB pathway in infected cells which causes bacterial death by damaging cell membrane causing loss of electrolytes and intracellular contents [36-43].

Antibiotic resistance:

Bacteria have the capability to develop simultaneous resistance to numerous classes of antibiotics [44]. There is also a risk concern to human and ecological health by the detection of genetic resistance determinants in microbial community [45]. Absence of effective natural antimicrobial agents and increase of multiple drug resistant bacteria focused global concern for health care at present [46].

Various mechanisms are displayed by bacteria for defending themselves against different antimicrobial agents. Emergence of resistant phenotypes is contributed by various factors such as [47, 48]:

- Extent of the expression exhibited by resistance determinants.
- The capacity of bacteria to sustain resistance mechanisms.
- Transmission capacity.
- Fitness of bacteria.
- Reversibility potential.

Bacteria which are susceptible may turn into resistant species by usage of antibiotics through many complex mechanisms (Figure 1):

- Reducing antibiotic permeability by preventing its contact to target site.
- Increasing the expression of antibiotic efflux pumps.
- Antibiotic target site alteration.
- Production of antibiotic degrading enzymes.

Mechanisms of anti-microbial action:

Most of the antimicrobials exert their effect by any of the following mechanism of action (Figure 2):

Inhibition of Cell Wall Synthesis [49]:

- Inhibiting peptidoglycan synthesis.
- Disrupting peptidoglycan cross-linkage.
- Disrupting peptidoglycan precursors movement.
- Disrupting synthesis of mycolic acid or arabinoglycans.

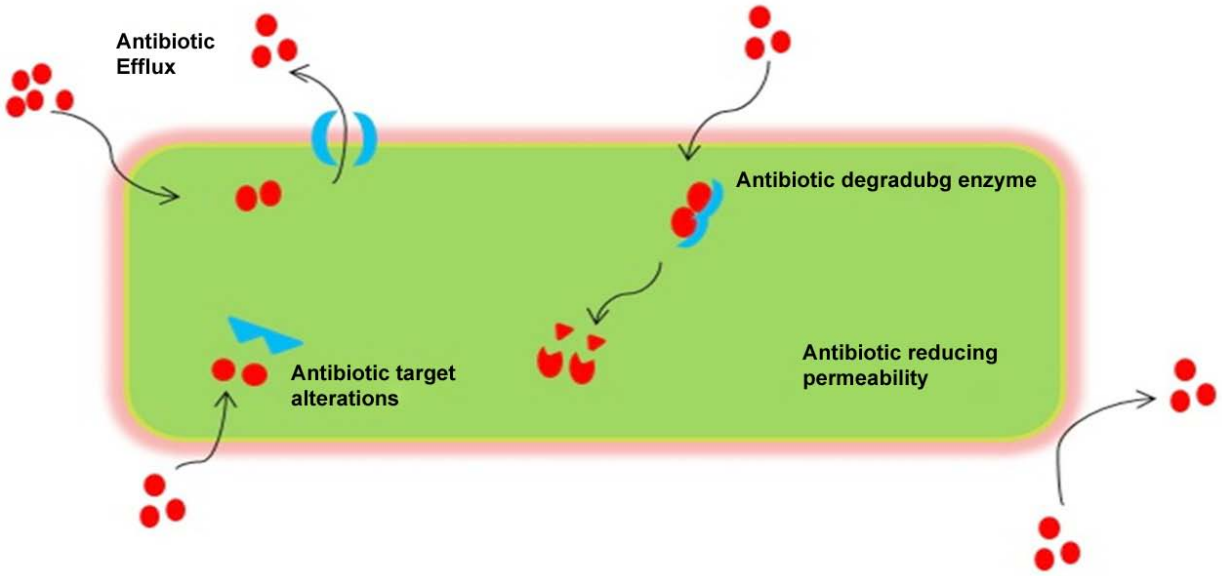

Figure 1. Various resistance mechanisms exhibited by bacteria to antibiotics.

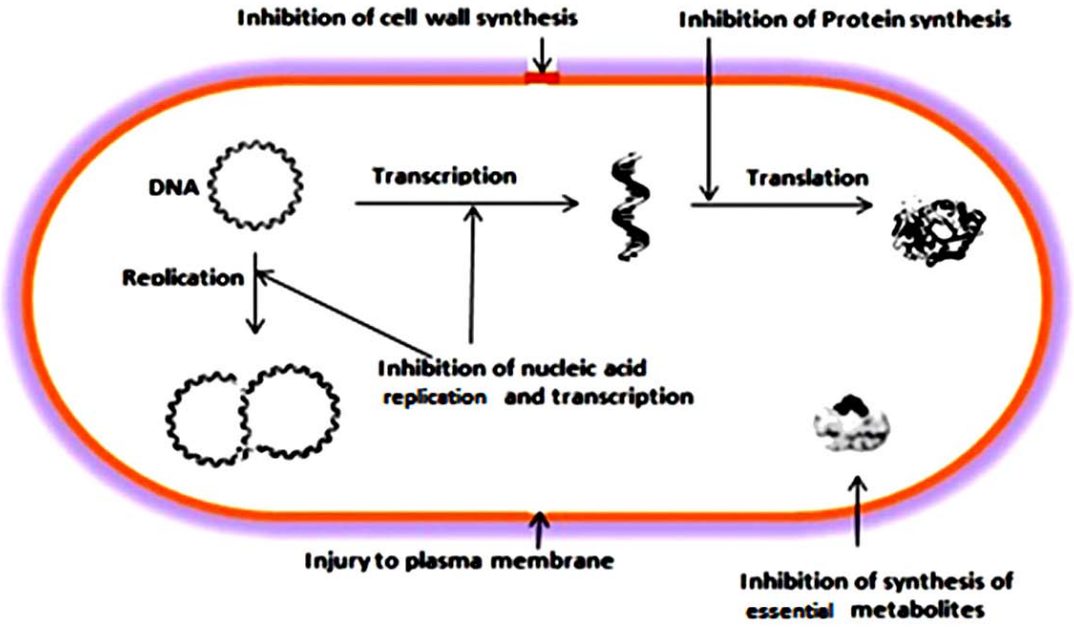

Figure 2. Mechanisms of anti-microbial action of phytochemicals.

Inhibition of protein synthesis

- Irreversible binding of antibacterial compound to 30S ribosomal binding site.
- Blocking the tRNA from binding to 30S ribosome-mRNA complex.
- Blocking peptide elongation by binding of antibacterial compound to peptidyltransferase site of 50S ribosome.
- Blocking peptide elongation by reversible binding of antibacterial compound to 50S ribosome.

- Blocking peptide elongation by binding of antibacterial compound to 50S ribosome, thereby inhibiting peptidyltransferase from interfering with amino acid-acyl-tRNA complex.

Alteration of cell membranes

- Cationic detergent-like activity.
- Disruption of cytoplasmic membranes.

Inhibition of Nucleic Acid Synthesis:

- Inhibiting topoisomerases from binding to alpha subunit required for supercoiling of DNA thereby inhibiting DNA synthesis.
- The antibacterial compound generated as cytotoxic byproduct during metabolism causes disruption to DNA.
- Inhibition of RNA synthesis by binding of antibacterial compound to DNA-dependent RNA polymerase enzyme.
- Inhibition of RNA transcription.

Antimetabolite action:

- Preventing the synthesis of folic acid by competing with p-aminobenzoic acid (PABA).
- Preventing synthesis of folic acid by inhibiting dihydrofolate reductase.
- Sulfamethoxazole synergism.

Phytochemicals as antimicrobial agents:

Secondary metabolites of plants are rich source of antimicrobial, antioxidant and anticancer compounds [50-52]. 20th century can be stated for commencement of post-antibiotic era against clinical Multidrug-Resistant Bacteria. The problem of high resistance of pathogenic bacteria is interconnected with many factors. But the major cause of it is indiscriminate use of antibiotics in aquaculture, veterinary medicine and human medicine [53]. Medical treatment using plant extracts is gaining fame in recent days as synergistic reactions of natural plant extracts operate on a range of diseases rather than on a single disorder. This is a global concern at present which challenges us in overcoming resistant antimicrobials by doing research in antimicrobial therapy. Plant extracts are probable sources against bacterial pathogens as they have many antimicrobial compounds. Crude plant extracts are more potent compared to isolated pure compounds for anti-microbial screening. Plant extracts of known anti-microbial properties are validated for knowing their impact in treatment of diseases. This technique of inhibiting pathogens is used for going forward in research of phytomedicine providing exciting results. Release of biologically active principles was well understood in solvents such as ethanol, methanol, n-hexane, etc. Plant extracts were proven to be more dynamic against Gram positive bacteria than Gram negative bacteria [54] and hence Gram negative bacteria are more resistant to plant extracts than Gram positive bacteria. This is due to the peptidoglycan layer of Gram positive bacteria which serves as ineffective permeability barrier to lipophilic solutes, whereas the cell wall of Gram negative bacteria is surrounded by an additional lipopolysaccharide layer which serves as an effective barrier which blocks the penetration of lipophilic solutes [55]. *Phyllanthus amarus* was tested against various bacterial cultures responsible for urinary tract infections using various solvents and methanolic leaf extract of plant proved to have high inhibitory activity. This was owing to the presence of phenols, flavonoids, alkaloids and triterpenes, which was confirmed by phytochemical analysis [56].

Novel resistance mechanisms have been enormously observed to novel antibiotics. Hence innovative strategies are needed to be developed by use of bioactive compounds. During the past decade, pharmaceutical companies have drawn attention towards potential plant-derived substances exhibiting antimicrobial activity. This is a period of rebirth for usage of herbal medicine [57]. Antimicrobial compounds produced by plants may regulate the resistance of plants indirectly [17]. Plants have capacity to produce drug-resistant inhibitors which have direct application against clinical pathogens [58]. Ethno botanical importance of leaf extracts of *Phyllanthus wightianus* dealing with antimicrobial activities on various human bacterial and fungal pathogens were reported. GC-MS analysis was done for analyzing active bioactive constituents. Major compounds include N-hexadecanoic acid and 9, 12-octadecaenioic acid which relates their presence with antimicrobial activity [59]. *Alpinia galanga* was evaluated for its antimicrobial activity against numerous pathogens using various solvents. Methanolic extracts exhibited excellent activity towards these pathogens, which may be due to the presence of compounds such as benzyl alcohol, 5-hydroxymethyl furfural, 3-phenyl-2-butanone, methyl cinnamate and 1, 2, benzene dicarboxylic acid that was

identified through GC-MS analysis [60]. A woody climber *Salacia oblonga* was evaluated for its antimicrobial activity against various pathogens using various solvents. Ethyl acetate solvent exhibited good activity using aerial and root parts [61]. The fruits of *Terminalia chebula* were studied for antimicrobial activity using aqueous solvent against Gram positive and Gram negative bacteria [19]. Ethanolic leaf extracts of *Vernonia amygdalina, Vernonia aemulans* and *Lantana camara* were tested against food spoilage bacteria such as *Staphylococcus aureus, Escherichia coli, Salmonella typhimurium* and *Bacillus subtilis*, for beer preservation in African brewing industry [62]. It was found that these plants exhibited antimicrobial activity thereby improving shelf life due to the presence of secondary metabolites in plants. This helps us to know the importance of medicinal plants in food technology [62]. Chloroform extract of leaves of *Phyllanthus fraternus* and phytoconstituents present in them were analysed and they were found to contain compounds such as alkaloids, terpenoid, saponin, tannins and steroids. Hence this plant was also justified for use in traditional medicine [63].

Mode of action of plant secondary metabolites:

- Phytochemicals were found to be a source of Quorum-Sensing inhibitors/ Biofilm inhibitors where intercellular communication for coordinating the expression is blocked preventing pathogenicity of various Gram-positive and Gram-negative bacteria [64-66].
- Phytochemicals also have great chelating property with metal ions thereby preventing bacterial growth and colony formation [67, 68].
- Phytochemicals were reported to inhibit the expression of efflux pumps where the microbial tolerance is reduced [69].
- Plants have also been identified as resistance modifiers and a source of antibiotic adjuvants [57] [65].
- Phytochemicals help in regulation of gene expression and signal transduction pathways [70-72].
- Phenolic compounds of plant were found to be responsible for controlling human pathogenic infections by various molecular mechanisms [73].
- Phytochemicals help in modulation of transcription factors [74] and redox signaling mechanisms [72].

Bacterial infections are becoming difficult to treat as pathogens develop biofilm which aids in host establishment, expansion and disease proliferation. The biofilm structure facilitates survival of these bacteria under hostile conditions including antibiotics. There is a need to develop antibacterial agents which can inhibit and also destroy the mature biofilms thereby increasing susceptibility of microbes to antibiotics. Antibiofilm agents may influence biofilm formation by damaging microbial membrane structure by inhibiting peptidoglycan synthesis or modulating quorum sensing. Plant steroids associate themselves with bacterial proteins and inhibit microbial adhesion, enzymes, cell envelop and transport proteins [75-76]. Effective treatments for the disruption of established biofilms may decrease health care costs related to the treatment and potential replacement of infected implanted prosthetic devices [77]. Mozirandi [66] evaluated antimicrobial activity of chondrillasterol isolated from *Vernonia adoensis*as biofilm inhibitor.

Famuyide [78] evaluated anti adherence activity of *Syzygium* and *Eugenia* plant extracts to understand whether they interfere with the initial process of bacterial adhesion, which is an initial strategy for a few bacterial species in their pathogenesis. Targeting bacterial adhesion may be a novel tool for drug discovery and development to deal with selective pressure for resistance [79].

Plant extracts are potential resistance modifying agents (RMAs) performing multiple modes of action to restore the efficacy of antibiotics against resistant bacteria, which include action on modified target sites, inhibiting bacterial enzymes that inactivate antibiotics, membrane permeabilizing agents and inhibitors of efflux pumps [15]. There are very few reports which have given an insight into their prevalence for resistance reversibility. Secondary metabolites of plants exhibit beneficial effects on mankind due to their potential target site similarities for their action against endogenous ligands, signal transduction molecules or neurotransmitters, hormones and metabolites. The general mechanisms exhibited by phytochemicals mainly include microbial growth inhibition, induction of cellular membrane perturbations, interfering with the processes of microbial metabolism, modulation of redox signaling [80].

Essential oils act as β- lactamase inhibitors and bacterial efflux pump inhibitors. Plant derived essential oils can be used in combination with antibiotics as treatment modalities against bacterial infections. [12]. reviewed antimicrobial properties of flavonoids, their mode of action and also discussed the scope of possible replacement of conventional antibiotics. They also discussed about the synergy and additive effect between flavonoids and antibiotics. These are named as resistance modifiers or reversal adjuvants. Essential oils such as the terpenoids, carvacrol and

thymol, occur extensively in nature and contribute plant flavours and aromas.

Phenols combine with nuclear receptors involved in growth and maintainance of adipogenesis. Active phenol molecules penetrate the cytoplasmic membrane by passive or active diffusion enabling the accumulation of products in bacteria and exhibit its action on cytoplasmic membrane [81].

Plant peptides form ion channels in the membrane of bacterial cells and inhibit the binding of microbial proteins to host polysaccharide receptors [82, 83].

Phytochemical screening of aqueous pulp extract of *Tamarindus indica* [84] and leaves of *Zapoteca portoricensis* [85] revealed the presence of high concentration of alkaloids which exhibited antimicrobial activity not only against Gram positive bacteria viz. *Staphylococcus aureus* but also against Gram negative bacteria viz. *Escherichia coli*, *Pseudomonas aeruginosa*. Plants belonging to families *Fabaceae, Amaryllidaceae, Mimosaceae, Capparaceae, Rubiaceae, Compositae* and *Rutaceae* were rich in alkaloids and were found to exhibit antibacterial activity against various bacteria [86]. Steroidal alkaloids can also interact with target receptors. Some alkaloids viz. tetrandrine, berbamine and cepharanthine have also been reported to interfere with membrane integrity [87]. Several alkaloids show their effect on multiple functions. Mechanism of antibacterial action of alkaloids was found to differ among alkaloid classes. Synthetic quinolone alkaloids were found to have respiratory inhibition effects. Cell division was inhibited by perturbing the Z-ring using Isoquinolines alkaloids such as berberine, sanguinarine, protoberberine, and benzophenanthridine [88].

Most of the flavonoids were found to exhibit antioxidant, anti-inflammatory and antitumor activities. In presence of other phytochemicals, these flavonoids were found to exhibit antibacterial activities [89]. Phenols and flavonoids in different plant parts of *Phyllanthus amarus* were found to be responsible for its antimicrobial activity [90]. Aqueous leaf extracts of *Zapoteca portoricensis* were found to exhibit anti-*Pseudomonas aeruginosa* activity due to the presence of flavonoid [85]. The leaf and root ethanol extracts of *Morinda citrifolia* were found to exhibit antimicrobial activity against *Pseudomonas aeruginosa* and *Staphylococcus epidermidis* due to the presence of high flavonoid content in them [91]. Plants belonging to families *Fabaceae, Amaryllidaceae, Rubiaceae, Labiatae* and *Rutaceae* were rich in Flavonoids and were found to be exhibit antibacterial activity against various bacteria [86]. Flavonoids with more (OH) groups had a greater antimicrobial activity. Flavonoids lacking hydroxyl groups on their β-rings were more active in membrane disruption in microbial targets [15]. Flavonoid glycosides such as quercetin, apigenin, and luteolin damage cell wall by formation of pores [15]. Phenols and flavonoids in different plant parts of *Phyllanthus amarus* were found to be responsible for its antimicrobial activity [92].

Tannins were found to exhibit antifungal and antibacterial activities [93] [7]. Ethanol extracts of stem bark of *Psidium guajava* were found to exhibit antibacterial activity against *Staphylococcus aureus, Streptococcus faecalis, Bacillus subtilis, Escherichia coli* and *Salmonella* species. This activity was found to be due to the high concentration of tannins in these plant extracts [94]. Methanolic extract of *Acacia nilotica* was found to exhibit anti-*Staphylococcus aureus* activity and anti-*Pseudomonas aeruginosa* activity, which was found to be due to the presence of high concentration of tannins. In presence of other phytochemicals, these tannins were found to exhibit antibacterial activities [89]. Plants belonging to families *Myrtaceae, Fabaceae, Mimosaceae, Rubiaceae* and *Labiatae* were rich in tannins and were found to exhibit antibacterial activity against various bacteria [86]. In *Combretaceae*, flavonoids and ellagitannins were found to exhibit Quorum sensing/biofilm inhibition [95].

Terpenoids the derivatives of terpenes and the ethanol extracts of stem bark of *Psidium guajava* were found to have high concentrations of terpenoids. In presence of other phytochemicals of this bark, these terpenoids were found to exhibit anti-*Streptococcus faecalis* activity [94]. Plants belonging to families *Myrtaceae, Compositae, Rubiaceae, Rutaceae, Caesalpinaceae, Amaranthaceae* and *Labiatae* were rich in Terpenes and were found to exhibit antibacterial activity against various bacteria [86]. A terpenoid carvacrol is obtained from oregano [96] [97] and a terpene Eugenol is obtained from clove [97-100].

Antimicrobial study was performed using naphthoquinone enantiomers viz. alkannins and shikonins by Papageorgious [101]. They were very effective in showing wound healing properties by exhibiting antimicrobial and antiinflammatory properties against ulcer development. These naphthoquinone enantiomers were found to exhibit broad antimicrobial spectrum and were proved to exhibit *anti-Staphylococcus aureus* activity and *anti-Staphylococcus epidermidis* activity [101]. Plants belonging to families *Boraginaceae, Plumbaginaceae, Ebanaceae and Droseraceae*, rich in quinones were found to exhibit antibacterial activity against various bacteria [86].

The aqueous pulp extract of *Tamarindus indica* revealed the presence of two specific resins viz. saponins and glycosides, which were highly active to S*taphylococcus aureus* [84]. In presence of other phytochemicals, these resins were found to exhibit many biological activities [89]. Ethanolic leaf extract of *Ocimum gratissimum* revealed the presence of several phytochemicals including saponins and were found to exhibit antimicrobial activity against

Pseudomonas aeruginosa, *Proteus* species, *Staphylococcus aureus* and *Shigella dysentriae* [102]. Plants belonging to families *Labiatae* and *Fabaceae* are rich in resins and were found to exhibit antibacterial activity against various bacteria [86]. Saponins exert toxicity on tissues and exhibit antibacterial activity [103]. Lectins are secondary metabolites of plants, found to exhibit anti-microbial action by cell-cell interaction against Gram positive and Gram negative bacteria [104]. Lectins are proteins or glycoproteins that have at least one binding site without catalytic function or immunological characteristics [105]. Hamed [106] reported separation of lectins from five cultivars of *Phaseolus* and evaluated their antimicrobial activity against Gram-negative bacteria *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*, and Gram-positive bacteria *Staphylococcus aureus*, the mode of action of lectins was potential agglutination of bacterial cells which was confirmed by scanning electron microscope (SEM) [107] [108] [109]. Lectins in *Phaseolus vulgaris* were found to agglutinate and aggregate bacterial cells together [106]. Berger [110] reported that glycerol ethers and related compounds present in dimethyl ether extract may be responsible for the antimicrobial activity due to respiratory collapse. Compounds having methoxy group exhibit antimicrobial action by causing distortion to cell surface [111, 112]. Benzophenone is a photoreactive group and is used for the development of antimicrobial coatings as it interacts with phospholipid bilayer of bacterial cell membrane and alters its structure. This causes stress on the cell wall spilling cytoplasmic material and causing cell death [112]. In *Aloe vera*, fumaric acid which is an organic acid has been reported as antibacterial component [113]. A series of diphenyl methane compounds display antimicrobial action against various microorganisms [114]. In Malaysian *Mangifera indica*kernel, Phenol, 2, 4-Bis (1, 1-Dimethyl ethyl) was identified and reported to have antibacterial activity [115]. Sulfur-containing phytochemicals in *Brassicaceae* and *Liliaceae* were found to down-regulate the expression of quorum-sensing (QS) virulence factors [116]. In *Asteraceae*, Chondrillasterol was found to exhibit Biofilm inhibition by leakage of nucleic acids and damage of the lipid layer of the membrane by inhibiting peptidoglycan synthesis, and/or modulating quorum sensing [66]. Secondary metabolites of plants and their modes of action were shown in Table 1.

Various phytochemicals displaying antimicrobial activity is represented in Figure 3. Antimicrobial activities of bioactive compounds of medicinal plants against bacteria were reported in Table 2.

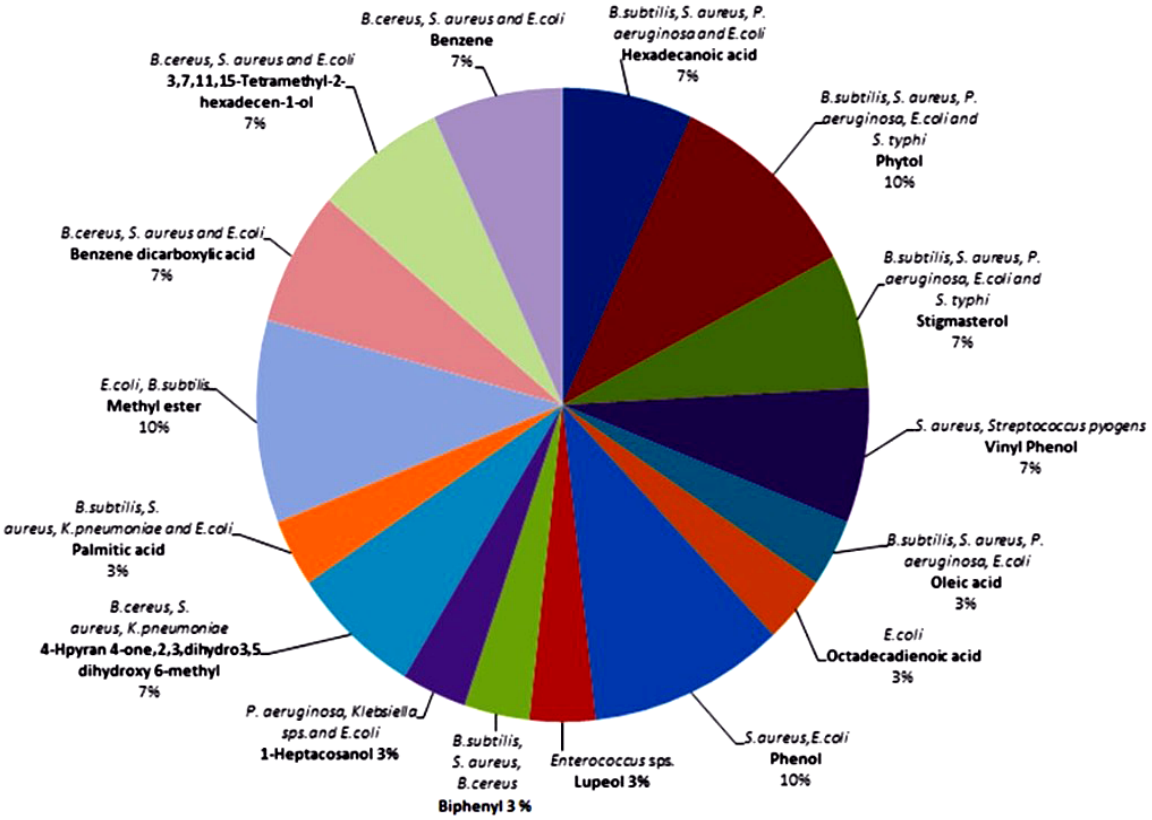

Figure 3. Phytochemicals displaying anti-microbial activity.

Table 1. Mode of action of plant secondary metabolites

S. No	Secondary metabolite	Mode of action	Reference
1.	**Essential oils**	1. Membrane disruption through lipophilic products. 2. Quorum sensing inhibition. 3. Expansion of membrane, increase of fluidity and permeability of membrane, disturbance of membrane embedded proteins, respiratory inhibition and alteration in processes of ion transport in both Gram-positive and Gram-negative bacteria.	[124] [125] [57] [126-129]
2.	**Polyphenols**	1. Bind to bacterial enzymes such as dihydrofolate reductase and gyrases, which inhibit supercoiling activity of *E.coli*. They bind to bacterial DNA which mediates DNA cleavage and bacterial growth stasis by inducing topoisomerase IV enzyme. 2. Polyphenols affect intestinal Microbiota by modifying their active form or by changing the composition of the intestinal microbiota probably inhibiting pathogenic bacteria and enriching beneficial bacteria. 3. Polyphenols and terpenoids possess strong binding affinity to proteins and glycoproteins owing to their lipophilicity which is responsible for their great affinity for cell membrane and can permeate through cell wall leading to leakage of cell contents. 4. Curcumin induces ROS, membrane pore formation, inhibition of morphogenetic switch and biofilm formation 5. Resveratrol isolated from grapes was found to induce apoptosis. 6. Polyphenols and Terpenoids inhibit biofilm formation by disturbing the cytoplasmic membrane integrity of bacteria affecting the electron transport chain, changing the pH homeostasis, disrupting the proton motive force and coagulation of cell contents(*Lamiaceae, Asteraceae*).	[130] [103] [15] [119] [131] [132] [119] [131] [132] [133] [134]
3.	**Phenols**	1. Phenol damages the external membrane of the bacterial wall by disturbing the organization of the membrane by binding at specific sites. 2. Phenols exhibit their action on bacterial spores by destabilizing the structure in spores. 3. The phenol mechanism may even operate on nucleus at chromosome level. 4. Inhibition of enzymes through reactions with sulfhydryl groups on the proteins through non-specific interacions. 5. Phenols and phenolic acids destruct the cell by change in shape and size. 6. Affect multiple target sites, decrease in cytoplasmic pH and cell wall disruption. 7. Phenolics and flavonoids were found to inhibit cell wall and/or membrane formation(*Fabaceae*). 8. Biofilm inhibition (*Myrtaceae* and *Juglandaceae*).	[81] [81] [81] [15] [15] [135] [95] [136]
4.	**Alkaloids**	1. Alkaloids show their mode of action either by affecting cell division, Respiratory inhibition and enzyme inhibition in bacteria, Bacterial membrane disruption or affecting virulence genes. 2. Toxic mechanisms of action of alkaloids arise due to enzymatic alterations which affect the physiological processes. They intercalate with nucleic acids inhibiting DNA synthesis and repair mechanisms. 3. An alkaloid berberine obtained from barberry plant was found to exhibit its mode of action through DNA	[15] [137] [138-140]

		binding, inhibition of CDR1, Induction of apoptosis. 4. Many members of the *Solanaceae* have Steroidal alkaloids such as solanine and tomatine, which form complexes with the cholesterol present in biomembranes leading to membrane disruption by forming holes on biomembranes rendering the cell leaky. 5. Phenanthridineisoquinoline alkaloid was found to act by inhibiting nucleic acid synthesis by targeting dihydrofolate reductase. 6. Inhibit bacterial adherence to the surface of teeth, exerting an anti-plaque action by perturbing bacterial FtsZ Z-ring formation and inhibiting bacterial cytokinesis (*Piperaceae, Rubiaceae, Berberidaceae* and *Apocynaceae*).	[87] [88] [116]
5.	**Flavonoids**	1. Flavones form complexes with bacterial cell walls, extracellular and soluble proteins which induce microbial cell membrane perturbations. 'B' ring of the flavonoids was identified to play a role in intercalation, which shows their inhibitory action on DNA and RNA synthesis. 2. Flavones, Flavonoids, and Flavonols form complexes with bacterial cell wall, extracellular proteins and soluble proteins. They disrupt cell membranes. 3. Flavonoids show their mode of action either by membrane disruption, Biofilm inhibition, Inhibition of cell envelope synthesis, Inhibition of nucleic acid synthesis, chelation of metal ions or Inhibition of bacterial toxins. 4. Isoquercitirin isolated from Starwart was known for membrane disruption. 5. A Flavonoid, Cathechin isolated from Green tea was found to cause cell wall damage. 6. A Carotenoid, Lycopene isolated from Tomato was known to cause membrane damage by inducing fungal apoptosis. 7. Quercetin was found to inhibit ATAase enzyme activity by binding to GyrB subunit of E. coli DNA gyrase. 8. Quercetin was also reported to increase the permeability of the inner bacterial membrane. 9. Flavonoids were found to Inhibit DNA gyrase, cell membrane function and bacterial energy metabolism by Interacting with DNA helicases, proteins essential for DNA replication, repair and recombination and to prevent dNTPs binding. They also inhibit PriA helicase activity of *S. aureus*. They damage the lipid layer of the membrane and biofilm inhibition and binding enterotoxin B (*Camellia sinensis and Poaceae*).	[141] [15] [12] [142] [143] [144-146] [147] [148] [116]
6.	**Tannins**	1. Tannins suppress microbial metabolism by blocking proteolytic macerating enzyme production which inhibit bacterial cell proliferation. Tannins have the ability to inactivate microbial adhesins, enzymes, cell envelope transport proteins, etc. which show their antimicrobial action by stimulating phagocytic cells, host-mediated tumor activity and a wide range of anti-infective actions. Condensed tannins bind to cell walls of ruminal bacteria, thereby inducing protease activity and bacterial stasis. 2. They form complexes with proteins by covalent and non-covalent interactions. They also form complexes with polysaccharides.They bind to the cell walls of ruminal bacteria, inhibiting growth, and protease activity.	[149] [15]

		3. Non-flavonid polyphenol groups *i.e* phenolic acids, stilbenes, coumarins and tannins were found to exhibit induced morphological changes in bacterial cells leading to an irregular shape with a wrinkled surface and induced leakage of cytoplasmic components and inhibit bacterial adhesion and prevent biofilm formation. They alter the fatty acid composition and disruption of the outer membrane of the cell (*Poaceae* and *Rubiaceae*).	[116]
7.	**Terpenoids**	1. Inhibit Calcium stress and Biofilm formation. 2. Perturbation of cytoplasmic permeases, Inhibition of ergosterol biosynthesis, Interference with the integrity of the cell membrane and biofilm inhibition. 3. In *Cupressaceae*, Monoterpenes and sesquiterpenes were found to exhibit Quorum sensing/biofilm inhibition. 4. Caffeic acids obtained from Tarragon were known to inhibit biofilms. 5. In *Lamiaceae*, terpenes/terpenoids, flavonoids were found to inhibit cell wall and/or membrane formation. 6. In *Lauraceae*, Aldehydes, aromatic alcohols, terpenoids, acid and derivatives were found to inhibit cell wall and/or membrane formation. 7. In *Myrtaceae*, Monoterpenes and flavonoids were found to exhibit Quorum sensing/biofilm inhibition. 8. In *Zingiberaceae*, Monoterpenes and flavonoids were found to inhibit cell wall and/or membrane formation. 9. *Lamiaceae, Euphorbiaceae, Verbenaceae, Orchidaceae,* Terpenoids were found to exhibit Anti-biofilm and Anti-QS activities.	[96] [97] [98] [97] [99] [100] [95] [150] [95] [95] [95] [95] [116]
8.	**Quinones**	1. Quinones block the cellular processes by inactivation of proteins or by forming complexes with aminoacids of proteins causing antimicrobial effects. The main targets of Quinones are the adhesins of microbial cell surface, cell wall polypeptides and membrane-bound enzymes. They also make the substrates unavailable to the microorganism. 2. Irreversible complexes were formed with amino acids in proteins. They attack surface adhesions and polypeptides in the cell wall and membrane enzymes. They sequester substrates required by the microorganisms. They inactivate enzymes by binding to adhesins on the microbial cell surface and binding to cell wall proteins, thereby interacting with substrates, rendering them unavailable to the microorganism, complexing with metal ions.	[151] [15]
9.	**Saponins**	1. Alter the permeability of cell walls. 2. They elicit changes in cell membranes thereby changing the cell morphology, which leads to cell lysis.	[103]
10.	**Lectins**	1. They bind reversibly to specific carbohydrates without any chemical modification. 2. The binding of plant lectins to bacterial cell wall peptidoglycans (such as muramic acid, N-acetyl muramic acid, N-acetyl glucosamine and muramyl dipeptides) are responsible for its antibacterial activity.	[105] [107-109]

Table 2. Antimicrobial activity of bioactive compounds of medicinal plants against bacteria

S.No	Name of the Plant	Bacterial pathogens affected	Nature of compound	Name of compound	Ref-erence
1.	*Abelmoschas moschatus*	*Bacillus subtilis, Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Proteus vulgaris, Salmonella enterica paratyphi and Candida albicans*	Hydrocarbon Carboxylic acid Alcohol	Tetradecane Tridecanoic Acid 1-Octadecanol	[152] [153]
2.	*Abrus precatorius*	*Staphylococcus aureus*	Diterpene Sesquiterpenoid	Phytol β-lonone	[154]
3.	*Albizia adianthifolia*	*Pseudomonas aeruginosa, Bacillus subtilis*	Acid Sterol	oleic acid chondrillasterol	[155]
4.	*Aloe vera* (L.), *Calendula officinalis* L. and *Matricaria recutita* L.	*Escherichia coli, Pseudomonas aeruginosa* and *Staphylococcus aureus*	Flavonoids and saponins	camphene , limonene 1,8-cineole, camphor , and α-pinene , where α-bisabolol oxide	[156]
5.	*Anabasis aretioïdes* Coss. & Moq.	*Staphylococcus aureus, Bacillussubtilis , Listeria innocua, Escherichia coli* K12, *Protéus mirabilis* and *Pseudomonas aeruginosa*	Polyphenols and Tannins	cathechic tannins, saponins, sterols and phenolic compounds	[157]
6.	*Aristolochia krysagathra*	*Bacillus subtilis, Proteus vulgaris*	Terpene alcohol	3,7,11,15-Tetramethyl-2-hexadecen-1-ol	[158] [159]
7.	*Bauhinia nakhonphanomensis*	*Staphylococcus aureus, Escherichia coli, Salmonella typhi, Vibrio cholerae*	Phenolic compound	Phenol	[160]
8.	*Bidens sulphurea, Bidens pilosa*and *Tanacetum vulgare*	*Staphylococcus aureus , Enterococcusfaecalis , Escherichia coli* , and *Pseudomonas aeruginosa*	Flavonoids and terpenoids	artemetin, β-sitosterol, 5-methylheptan-2-amine, isohumulone, costunolide, tridecanoic acid, and octadecanoic acid methyl ester	[161]
9.	*Boesenbergia rotunda*	*Escherichia coli, Helicobacter pylori, Staphylococcus aureus, Staphylococcus epidermis*	Biphenyls Biphenyls	3′-hydroxy-5-methoxy-3,4-Methylenedioxybiphenyl 3′-hydroxy-5,5′-dimethoxy-3,4-methylenedioxybiphenyl	[162]
10.	*Broussonetia luzonica*	*Staphylococcus aureus*	Glycerol ester Alkane	Propanetriol monoacetate Tetracosane	[163]
11.	*Bruguiera cylindrica*	*Escherichia coli, Klebsiella pneumonia, Staphylococcus aureus, Pseudomonas aeruginosa, Proteus mirabilis*	Diterpene Phenol	2-Cyclopenten-1-one, 2-hydroxy Phenol	[164] [164-167]

12.	*Calanthe triplicata*	*Proteus vulgaris and Klebsiella pneumoniae*	Flavanoid	4H-Pyran-4-one, 2,3-dihydro-3,5- dihydroxy-6-methyl	[168] [169]
13.	*Ceratonia siliqua*	*Pectobacterium atrosepticum, Listeria monocytogenes, Salmonella enteritidis, Brocthrix thermosphacta*	Alcohol Triterpenoid alcohol Isoflavone Phenol Flavanone Polyphenol	n-nonadecanol Lupeol Genistein Geraldone Liquiritigenin Epigallocatechin-3-gallate	[170]
14.	*Curcuma longa*	*Listeria monocytogenes , Staphylococcus aureus , Bacillus cereus, Micrococcus flavus, Pseudomonas aeruginosa, Escherichia coli, Aspergillus flavus , A. ochraceus , A. niger, Penicillium ochrochloron, P. funiculosum* and *Candida albicans*	Carboxylic acid Ester	Benzenedi carboxylic acid, di-isooctyl ester	[171] [172]
15.	*Cyperus rotundus*	*Staphylococcus aureus, Escherichia coli, Bacillus Subtilis, Pseudomonas aeruginosna and Proteus vulgaris*	Terpene alcohol	3,7,11,15-Tetramethyl-2-hexadecen-1-ol	[158] [159]
16.	*Eupatorium odoratum*	*Staphylococcus aureus* and *Escherichia coli*	Phenol	1-heptacosanol	[173]
17.	*Eupatorium triplinerve*	*Salmonella typhi, Shigella sonnei*	Alcohol Steroid Acid Ester Hydrocarbon Heterocyclic compound Phenol Phenol	19-D-Torulosol Stigmasta-5,22-diene, 3-methoxy-,(3.beta.,22E) 1,2-Benzenedicarboxylic Acid 9,12-Octadecadienoic acid, methyl ester 2,6,10-trimethyl,14-ethylene-14-pentadecane 2(4H)-Benzofuranone, 5,6,7,7a tetrahydro-4,4,7 2-Methoxy-4-vinylphenol Phenol, 2-methyl-5-(1-Methylethyl	[174]

			Phenol	) Phenol, 5-methyl-2-(1-Methylethyl)	
18.	*Ficus religiosa*	*E.coli, Pseudomonas aeruginosa, Staphylococcus aureus*	Flavanoid	4H-Pyran-4-one, 2,3-dihydro-3,5- dihydroxy-6-methyl	[168] [169]
19.	*Hugonia mystax*	*E.coli, Proteus vulgaris, Pseudomonas aeruginosa, Salmonella typhi, Vibrio parahaemolyticus and Vibrio vulnificus*	Aldehyde compound Phenolic compound Coumaran compound	2-Furancarboxaldehyde ,5-(hydroxymethyl) 2-Methoxy-4-vinylphenol Benzofuran, 2,3-dihydro	[175]
20.	*Isodon rugosus*	*Staphylococcus aureus, E. coli, B. cereus, K. pneumonia, Salmonella typhi*	Carboxylic acid Alcohol Triterpene Diterpene Ester Ketone Ketone Ester Ester Phytosterol	Palmitic acid Hinokiol α-amyrin Phytol Ethyl linolate Hinokione Cyclohexanone Methyl palmitate Ethyl palmitate Stigmasterol acetate	[176]
21.	*Michelia champaca*	*Aeromonas hydrophila, Escherichia coli, Edwardsiella tarda, Flavobacterium spp., Klebsiella pneumonia, Salmonella typhi, Vibrio alginolyticus, V. parahaemolyticus, V. cholerae and Pseudomonas aeruginosa*	Acid Ester	5,8,11,14-eicosatetraenoic acid methyl ester, (all Z)-	[177]
22.	*Ocimum sanctum*	*Salmonella enteritica, Vibrio parahaemolyticus, Escherichia coli, Staphylococcus aureus, Escherichia coli and Listeria monocytogenes*	Sesquiterpene alcohol Alcohol	Farnesol Geranylgeraniol (Diterpene)	[178]
23.	*Olea europaea*	*Campylobacter jejuni, Helicobacter pylori, Staphylococcus aureus, Salmonella enteritidis, Bacillus cereus, Klebsiella pneumoniae, Escherichia coli, Enterococcus faecalis, Streptococcus thermophilus and Lactobacillus bulgaricus*	Phenol	Hydroxytyrosol	[179]
24.	*Piper longam*	*Escherichia coli, Bacillus megaterium, Staphylococcus albus, Pseudomonas aeruginosa*	Fatty alcohol Aromatic hydrocarbon	8-Heptadecene Naphthalene	[172]
25.	*Plectranthus*	*Staphylococcus aureus,*	Diterpene	Phytol	[180]

	amboinicus	*Bacillus subtilis, Staphylococcus epidermis, Enterococcus faecalis, Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumonia, Streptococcus mutans*	Palmitic acid Sesquiterpenoid Isoprenyl Phenol Sesquiterpenes Phytosterol	Hexadecanoic acid Neophytadiene Carvacrol Caryophyllene oxide Stigmasterol	
26.	*Pterocarpus angolensis*	*Staphylococcus aureus, Enterobacter cloacae, Entamoeba histolytica*	Acid Ester Hydrocarbon Phytosteroid Ketone	Hexadecanoic acid Methyl ester Tetratriacontane 7-dehydrodiosgenin Friedelan-3-one	[155]
27.	*Saudi propolis*	*Bacillus subtilis, Micrococcus, Proteus vulgaris, Pseudomonas aeruginosa, Escherichia coli*	Diterpenoid phenol	Totarol	[181]
28.	*Solanecio mannii*	*Staphylococcus aureus, Streptococcus faecalis, Bacillus cereus, Pseudomonas aeruginosa, Shigella dysenteriae, Shigella flexneri, Klebsiella pneumoniae*	Ester	Hexacosanol, acetate	[182]
29.	*Terminalia arjuna*	*Vibrio cholera, Staphylococcus aureus and Pseudomonas aeruginosa*	Alcohol	2-Furanmethanol(Furfuryl alcohol)	[172]
30.	*Zingiber officinale*	*Staphylococcus aureus, Escherichia coli , Pseudomonas aeruginosa, Vibrio cholera, Klebsiella spp., Salmonella spp.*	Aldehyde Sesquiterpenoid Sesquiterpenoid Sesquiterpene Sesquiterpene Alcohol Cyclohexenones Carboxylic acid Ketone Methoxy compound Sulphonic compound	Decanal Benzene,1-(1,5-dimethyl-4 hexanyl)-4-methy- α-Farnesene 1,6,10 Dodecatrien-3-ol,3,7,11- 3,7,11-Trimethyl 6,10-Dodecadien-1-yn-3-ol , 3,7,11- Trimethyl Spiro(4,5)dec-6-en-8-one,1,7-dimethyl 10,13-Octadecadieynoic acid 3-Decanone Dimethyl-octa dimethoxy	[172]

				(2,6,6-Trimethylcyclohex-1 - enylmethanesulfonyl) benzene	
31.	*Phyllanthus amarus*	*Bacillus cereus, Bacillus subtilis, Escherichia coli, Klebsiellapneumoniae*	Acid Ether	Hexadecanic acid dimethyl ether	[90]
32.	*Salacia Oblonga*	*Staphylococcus aureus, Pseudomonas aeruginosa and Klebsiella pneumoniae*	Ester Acid Acid Sterol	Hexadecanoic acid 3-hydroxy methyl ester Tetradecanoic acid 9-Octadecenoic acid γ-sitosterol	[183]
33.	*Drimia sanguinea, Elephantorrhiza elephantina, Helichrysum paronychioides, Senecio longiflorus*	*Shigella flexneri, Candida glabrata, Trichophytonrubrum, Trichophyton tonsurans*	Alkane Heterocyclic compound Alkane Acid Sterol Acid Acid	Dotriacontane, Benzothiazole, heptacosane, phthalic acid, stigmasterol, hexanoic acid and eicosanoic acid	[184]
34.	*Curcuma longa, Punica granatum, Justicia adhatoda, Acalypha indica*	*Staphylococcusaureus, Streptococcus pneumonia, Mycobacterium tuberculosis*	Acid Phenol Alkaloid Alkaloid Flavonoid glycoside Polyphenol Acid	Ascorbic acid, curcumin, vasicine, piperine, quercetin, myricetin , gallic acid	[185]
35.	*Cleome ciliata*	*Klebsiella pneumoniae, Streptococcus pneumoniae, Staphylococcus aureus, Salmonella typhi, Pseudomonas aeruginosa, Rhizopus stolonifer , Fusarium oxysporum, Penicillium chrysogenum*	Flavonoids, phenols, terpenoids.	-----	[186]
36.	*Syzygium cumini , Eucalyptus globulus , Aegle marmelos, Azadirachta indica*	*Staphylococcus aureus, Escherichia coli*	Phenols	-----	[187]
37.	*Mespilus germanica*	*Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumonia, Enterococcus faecalis, Salmonella typhi, Salmonella paratyphi, Escherichia coli, Klebsiellapneumoniae, Klebsiellapneumoniae, Yersinia enterocolitica, Serratiamarcescens, Shigelladysenteriae, Citrobacter freundii*	phenols, flavonoids , carotenoids	-----	[188]
38.	*Berberis*	*Enterococcus faecalis ,*	Diterpenes,		[189]

	aristata	*Staphylococcus aureus, Staphylococcus epidermidis , Escherichia coli, Klebsiella pneumonia, Pseudomonas aeruginosa, Salmonella typhimurium , Candida albicans*	Flavonoids, Tannins	-----	
39.	*Tinospora cordifolia*	*Streptococcus mutans*	Quinones, polyphenols, alkaloids, flavonoids, tannins, coumarins, terpenoids, lectins, and polypeptides	-----	[190]
40.	*Laennecia confusa*	*MRSA* *Staphylococcus aureus* *K. pneumoniae*	Triterpenes Saponins Flavonoids Tannins	-----	[191]
41.	*Psidium guineense*	*MRSA*	Tannins, flavonoids, condensed proanthocyanidins, leucoanthocyanidins and sugar	-----	[191]
42.	*Hydrastis canadensis*	*MRSA*	Alkaloid and flavonoid	-----	[191]
43.	*C. circinalis and C. revoluta*	*Staphylococcus aureus, MRSA*	Biflavonoids	-----	[191]
44.	*Abrus schimperi*	*Staphylococcus aureus, MRSA*	Amorphaquinone and pendulone	-----	[191]
45.	*Bersama engleriana Gurke*	*Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Klebsiella pneumonia, Morganella morganii, Proteus mirabilis, Pseudomonas aeruginosa, Shigella dysenteriae, Salmonella typhi, Streptococcus faecalis, Staphylococcus aureus, Bacillus cereus, Bacillus stearothermophilus, Bacillus subtilis*	Flavonoids Phenols Triterpenes Anthraquinones	-----	[191]
46.	*Xanthium strumarium*	*MSSA, MRSA*	Phenolic acids, flavonoids tannins, triterpinoids	-----	[191]
47.	*Holoptelea integrifolia*	*Bacillus cerculences, Pseudomonas aeruginosa, Bacillus subtilis, Klebsiella aeruginosa, Staphylococcus aureus, Escherichia coli*	Alkaloids, flavonoids tannins, terpenoids, glycosides	-----	[191]
48.	*Piper umbellatum*	*E.coli, K. pneumoniae, P. aeruginosa, S. typhimurium, Shigella flexneri, E. faecalis, S. aureus, S.pyogenes,*	Flavonoid, alkaloid, terpene, and sterolclasses	-----	[191]

		S. epidermidis			
49.	*Lemongrass, oregano, rosemary thyme, neem, tulsi, aloe vera bryophyllum*	*Multi-drug resistant Staphylococcus aureus, K. pneumoniae, E. coli*	Sugars, alkaloids, anthraquinones, glycosides flavonoids tannins, steroids, saponins, triterpenoids, phlobatanins	-----	[191]
50.	*Helicanthus elastica*	*A. hydrophila, K. pneumoniae, E.coli, V. fischeri, B. subtilis, MRSA, P. aeruginosa, S. pyogenes*	Phenolic composition	-----	[191]
51.	*Ephedra procera*	*Proteus vulgaris P. aeruginosa Enterobacter aerogenes B. cereus S. aureus*	Phenolic compound	-----	[191]
52.	*Blechnum orientale Linn*	*B. cereus, Micrococcus luteus, MSSA, MRSA, S. epidermidis*	Flavonoids, terpenoids, Tannins	-----	[191]
53.	*Cocos nucifera*	*S. aureus MRSA*	Procyanidins	-----	[191]
54.	*Clausena heptaphylla*	*B. subtilis, S. aureus, B. cereus, B. polymyxa, B. megaterium, E. faecalis, S. typhi, Klebsiella spp., S. flexneri, S. sonnei, Proteus spp., E. coli*	Flavonoids, alkaloids, saponins, steroids, glycoside, carbohydrate	-----	[191]
55.	*Pupalia lappacea Juss*	*P. aeruginosa, S.aureus, B. subtilis*	Steroids, glycosides, saponins, flavonoids, alkaloids, sugar and phenol	-----	[191]
56.	*Tabernaemontana alternifolia*	*B. subtilis, S.aureus, S. epidermidis, E. col, MRSA , VRSA*	Alkaloids, flavonoids, coumarins, saponins and steroids	-----	[191]
57.	*Chelidonium majus Linn*	*MRSA*	Alkaloids	-----	[191]
58.	*Premna resinosa*	*S. aureus, MRSA, E. coli, K. pneumoniae, P. aeruginosa,*	Flavonoids, Anthraquinones, Terpenoids, Phenols, Alkaloids	-----	[191]

		S. typhi, *S. sonnei*, *M. tuberculosis*			
59.	*B. citriodora*, *T. ferdinandiana*, *C. australasica*, *L. ponticum*	*S. aureus*, *E. coli*, *B. cereus*	Phenolic compounds	-----	[191]
60.	*Terminalia fagifolia*	*S. aureus* , *S.epidermidis* , *S. epidermidis*, *S. epidermidis*	Terpenoids, glucocorticoids, flavonoids polyphenols	-----	[191]
61.	*Moringa oleifera*, *Matricaria recutita*	*P. aeruginosa*, *Klebsiella spp.*, *E. coli*, *Proteus mirabilis*, *Staphylococcus spp.*	Alkaloids, polyphenols, flavonoids, anthraquinones, coumarins, tannins, triterpenes, sterols, saponins, and some other secondary metabolites.	-----	[192]
62.	*Lasiosiphon eriocephalus*	*Klebsiella pneumonia*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*	phenolics, tannins, flavonoids	-----	[193]
63.	*Piper nigrum and Piper longum*	*Staphylococcus aureus*	Alkaloid	Piperidine	[48]
64.	*Glycyrrhiza glabra*	*S. aureus*, *M. tuberculosis*	Flavonoids	Glabrol	[48]
65.	*Rauwolfia serpentina*	*Staphylococcus spp., Streptococcus spp., and Micrococcus spp.,*	Indole alkaloid	Reserpine	[48]
66.	*Lycopersicum esculentum*, *Solanum tuberosum*	*Staphylococcus aureus*	Steroidal alkaloid	Tomatidine	[48]
67.	*Ipomoea muricata*	*Escherichia coli*	Tricyclic ergot alkaloid	Chanoclavine	[48]
68.	*Allium sativum*	*Staphylococcus epidermidis*, *P. aeruginosa*, *Streptococcus agalactiae*	Organosulfur compound	Allicin	[48]
69.	*Vitis vinifera*	*Campylobacter jejuni* , *M. smegmatis*	Phenolic compound	Resveratrol	[48]
70.	*Terminalia chebula*	*M. tuberculosis*	Tannin	Chebulinic acid	[48]
71.	*Asphodelus microcarpus*	*S. aureus, E. coli*, *P. aeruginosa*, *C. albicans and Botrytis cinerea*	Aryl coumarin glucoside Aglycon	asphodelin A 4′-O-β-Dglucoside Asphodelin A	[48]

Challenges and future perception:

About 60% of the Earth's biomass is comprised of microbial species causing infectious diseases leading to mortality. Population across the world is facing threat to health by extraordinary diversity of these microbes in their genetic, metabolic and physiological activities. Plant secondary metabolites have demonstrated immense antimicrobial potential. Plants may prove to be a promising species selective alternative for these microbial pathogens [117]. It is hypothesized that plants do not produce highly potent inhibitors of specific microbial targets. It may be owing to the property of microbes to acquire resistance which forces plants to rely on nonspecific compounds [118]. Prasad [95] used a novel strategy using phylogenetic evidence to determine plant families with high representation of antimicrobial activity and potential source of antibacterial drug discovery. They reconstructed molecular phylo-

geny of plant species displaying antibacterial activity and further mapped their mode of action against bacteria on phylogeny. They identified seven plant families *viz. combretaceae, cupressaceae, Fabaceae, Lamiaceae, Lauraceae, Myrtaceae* and *Zinziberaceae* with higher antibacterial potential. The mode of action of most of the phytochemicals was disruption of bacterial cell membrane or cell wall and inhibition of quorum sensing or biofilm production. They concluded that plant extracts from these families may prove to be promising leads for novel drug development. There are myriad reports of antimicrobial activity of plants, however, it is needed to identify and study the bioactive component responsible for the activity. Further it has to undergo efficacy and potency testing followed by scientific validation of its applications. Phytopharmaceuticals as an alternative to antibiotics would safeguard health issues and also ensure issues related to public health safety viz. presence of antibiotic residues in animal products and zoonotic threats. Herbal therapy has important considerations for safety issues, many phytoconstituents are biologically more active and however, they have concurrent disadvantages of toxicity, which has to be carefully standardized. The pharmacological activity of many phytoconstituents varies with its concentration and presence of other phytoconstituents. This may be synergistic or antagonistic, harmful or beneficial based on the interaction of phytoconstituents. There is a need to establish pharmacological activities of bioactive compounds individually or in combinations. Medicinal plants prove to be much cheaper, safer and have widely accepted health benefits. However, there is a need of exhaustive scientific validation, standardization and safety evaluation before commercialization.

Herbal therapy opens alternative avenues in the present situation to develop broad spectrum antibacterial herbal formulation from these natural resources for safeguarding several health issues [13]. The main constraints associated with application of phytocompounds is its being a complex blend of bioactive compounds and variation in composition due to several biological, processing, and storage factors. Further, the units of application or doses are not standardized [119]. Future research targeting their purification, understanding their mode of action, standardizing appropriate units of administration, compatibility with diet, toxicity, safety and stability assessment, as well as their pharmacodynamics and pharmacokinetic properties is required for establishing them as an effective alternate to antibiotics [120]. Phytotherapy may not replace use of antibiotics completely as treatment agents, however, it may be implemented as preventive and management therapy. To ensure long term sustainable development judicious use of antibiotics is obligatory. There is a need to strengthen and enforce the laws along with the policies pertaining to their uses.Plants have been considered as potential source of antimicrobial compounds, however, there are no antibiotics derived from plants which is surprising with large efforts devoted for mining the plant sources and their chemical defense against pathogens [121]. Barbieri [116] elucidated in their review that plant derived phytochemicals represent a possible source of effective, cheap and safe antimicrobial agents. However, much work needs to be conducted both *in vitro* and *in vivo* to ensure the selection of active and nontoxic antimicrobial phytochemicals. Phytotherapy was proven to be an effective and economical way for managing health of aquatic animals and can be used as a substitute to chemotherapy [122]. This application can also be used by researchers for control of various diseases in aquatic animals using phytochemicals [123].

Renewed scientific interest in plant-derived natural product-based drug discovery is evident from the research publications. Plants produce chemically highly diverse secondary metabolites with different biological functions and are still far from being exhaustively investigated. With the revived scientific interest in natural product-based drug discovery, novel approaches for the identification, characterization and understanding their mode of action have being developed, and that may address some of the challenges associated with drug development. In order to harvest its full potential, an interdisciplinary approach involving ethnopharmacological knowledge, botany, phytochemistry, and pharmacological testing strategies needs to be developed [9]. Establishment of phytocompounds as an alternative to antibiotics requires focus on understanding their mode of action, standardization of units of administration (dose optimization) along with safety, stability and toxicity profiles with their pharmacokinetic and pharmacodynamic properties. There are missing links which need to be investigated in order to elucidate their role for clinical application.

Conclusion:

Various components of plants were effectively used for treatment of many bacterial diseases since centuries. Several classes of bioactive compounds represent key compounds in the management of various diseases with potent *in vitro* activities. As phytochemicals of plants play a major role in maintenance of human health, effort to search for plant based antimicrobial agents is intensified by present day researchers. Pharmaceutical industries use a variety of phytochemical constituents either directly or indirectly. Plant derived products may potentially control microbial growth in diverse conditions and in the particular case of disease treatment, several studies have aimed to describe the chemical structures of these plant antimicrobials and the mechanisms which are involved in inhibition

of microbial growth. Further investigations are needed to study the complex molecular mechanisms which are responsible for these synergistic interactions for developing new drug combinations against multi-drug resistant bacterial infections.

Conflict of interest:

The authors declare that they have no conflict of interest.

Ethical approval:

This article does not contain any studies with human participants or animals performed by any of the authors.

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