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PLANT NATURAL METABOLITES AS ANTIMICROBIAL AGENTS: A REVIEW

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Abstract- In recent years utilization and search of drugs and dietary supplements derived from plants have been accelerated. Scientists and researchers are combing the Earth for phytochemicals and "leads" which could be developed for infectious diseases treatment. Pathogenic microbes have the ability to develop resistance against synthetic formulations. Apart from this, synthetic formulations are very toxic and responsible to destroy the soil fertility and ecological balance. Plant based formulations are least toxic and better for environment balance so it can be replace by synthetic formulations. Secondary metabolites found in plants are the main reason for their antimicrobial potential. Plants are rich in wide variety of secondary metabolites viz. tannins, terpenoids, alkaloids, and flavonoids. This review attempts to summarize the current status of microbiological screening efforts as well as *in vivo* studies of plant extracts and phytochemicals, their effectiveness and toxicity against various microbes.

Keywords- Plant Extracts, Antimicrobial Activity, Phytochemicals, Secondary Metabolites

Introduction

Primary healthcare systems involve use of medicinal plants as an effective source of both traditional and modern medicines. Medicinal plant may be defined as any plant which possesses curative elements or properties in one or more of its organs. Plant based medicaments have been employed since the dawn of civilization for prolonging the life of man and for combating various ailments [1]. World Health Organization (WHO) also advocates the use of traditional medicines as natural and safe remedies for curing ailments of both microbial and non-microbial origins [2]. According to WHO more than one billion people rely on herbal medicines to some extent. 21,000 plants all around the world have been listed for their medicinal uses and it has been estimated that as many as 80 percent of the world's population depends on plants for their primary healthcare needs [3].

A wide range of substances have been found in plants which are used in traditional medicine to treat chronic as well as infectious diseases [4]. Medicinal value of plants depends on these inherent substances that produce a definite physiological action on the human body [5].

India is considered to be a country having rich emporia of medicinal plants and where ancient systems of medicine such as Ayurveda, Siddha and Unani medicines have been in practice for many years. Ayurveda (4000-600 B.C.), Rigveda (4500-1600 B.C.) and Atharvaveda (1200 B.C.) are traditional indigenous systems of medicines [6]. Ayurveda means "Science of life". According to Ayurveda, health is an indication of normal biological processes, which help to maintain mental and physical alertness and happiness of human being. Charak Samhita is the first recorded treatise on Ayurveda which was followed by Susharuta Samhita around 900 B.C. charak samhita dealt primarily with medicine while Sushruta Samhita was concerned with the advanced state of knowledge on the general principles and details of treatment [7]. Lack of facilities available for procurement of standardized and reliable ayurvedic products, lack of utilization information of metals in some ayurvedic preparations as well as physicians in ayurveda were not adequately trained offer another systems of medicine for healing various remedies.

A sea-change observed in traditional medicine is changing the pattern of healthcare systems all over the world [8]. In developing countries herbal medicine still serves as the mainstay of about 75-80% of the whole population [9]. Herbal medicine has better cultural acceptability, better compatibility with the human body and fewer side effects, this quality led herbal medicines superior over any other medicine.

Several rural communities, depend on plant resources mainly for herbal medicines, food, forage, construction of dwellings, making household implements, sleeping mats and for fire and shade [10, 11]. In rural and tribal area of India, people still depend on traditional medicine for their health and treatment of diseases. These traditional tribal medicines are based on the collective knowledge of several generations. Traditional healers claim that their medicine is cheaper and more effective than modern medicine [12]. Thus, herbal folk medicines provide an interesting and still largely unexplored source for drug development with potential chemotherapeutic benefits [13,14]. Hence, potent antimalarial, anti-cancer, anti-diabetic and anti-bacterial compounds have been isolated from plants and used to develop new drugs against these diseases [15]. The traditional village physicians of India are using about 4,500 to 5,000 species of plants for medicinal purpose as well as the oral traditions of the villagers use about 5000 plant for medicinal purpose. Large number of tribal communities inhabited in India, possess a precious and unique knowledge about the use of wild plants for treating human diseases.

Tribals of Western Maharashtra use decoction of *Baliospermum montanum* for treatment of asthma [16]. Gargles with decoction made from *Acacia nilotica* bark is effective in treatment of spongy gums, sore throat and for cleaning of haemorrhagic ulcers and wounds [17]. Teas prepared from dried leaf powder of *Mikania cordata* are used in gastric ulcer [18]. A poultice made from flowers of *Melia azadiracta* is used to kill lice and cure eruptions of scalp [19].

Abere, et al [20] reported the *in vitro* antimicrobial activity of the extract of *Mitracarpus scaber* leaves formulated as syrup. Kala [21] reported that almost all the parts of Bael tree are used in preparing herbal medicine. Bael is used to cure the gastrointestinal disorders. Tirkey [22] investigated that in Chhattisgarh certain plants belongs to family Fabaceae have been used ethnomedicinally by local tribals viz. *Abrus precatorius* for skin disease and poor eye sight and *Sesbania sesban* for abortion and as antifertility agent etc. Chavellier [23] reported that decoction of the astringent leaves and flowers of *Butea monosperma* is taken for diarrhoea, heavy menstrual bleeding and fever. Pawar and Thaker [24] investigated that cinnamon oil is applied externally on the body to treat diseases caused by *Aspergillus niger* by incorporating them into creams, lotions, drops etc. Seeds of *Juniperus indica* are eaten to get relief from kidney problems whereas its leaf juice is used as a cure for cough, cold and paralysis [25]. Ethanol extracts from the sticks and leaves of *Streblus asper* have been reported to inhibit the growth of *Streptococcus* mutans [26].

Ancient Chinese herbalists knew the potential benefits of herbs, acupunture, massage and diet in maintaining and restoring health and in alleviating human suffering. They use only their own senses and perceptions to obtain the knowledge about nature of a person's health imbalance and to make decisions as to which technique or herbs to use [27,28]. Chinese herbal medicine as health care has evolved into a sophisticated body of knowledge throughout the rise and decline of numerous dynasties. Chinese medicine has been described as a complex system of medical practice with its own philosophy, diagnosis, treatment systems and pharmacology [29]. *Achyranthus bidentata* roots are used in traditional Chinese medicine as a tonic, emmenagogue, antiarthritic, diuretic and antifertility agent to nourish the liver and kidneys, strengthen bones and muscles and invigorate circulation [30]. *Eupatorium chinense* grows in the south of China and is used for colds, snakebite and inflammation [31]. Li, et al [32] reported that *Portulaca oleracea*, grows widely in China, and is used for alleviating pain and swelling. It has antibacterial, antiviral, antidiabetic and immuno-modulating activity [32]. Plants constitute an important source of drugs in modern medicine. Continuous use of antibiotics leads to the problem of microbial resistance so there is a need for new antimicrobial compound. Therefore, it is necessary to search for new or novel compounds to develop new drugs, either synthetic or natural [33]. Because of the realization of health hazards and toxicity associated with indiscriminate use of synthetic drugs and antibiotics, there has been considerable resurgence in the use of herbs and herbal drugs all over the world and especially in USA and Europe. American public paid more than $ 10-12 billion for the cost of plant drugs alone in 2003 [34]. Countries like India, Pakistan, Afganistan, Nepal and Srilanka obtain more than 80% of their therapeutic agents from plants. Recent researches suggests that medicinal plants increase the immune power of human body thereby preventing infection. These and various other advantages of herbal therapeutics over synthetic medicines has attracted the attention of researchers to study the various aspects of these drugs, their physiological impact on human health and their pharmacological and microbiological aspects [35].

Plant Extracts as Antimicrobials

During last decade intensive studies has been done on extracts and biologically active compounds isolated from plants used for natural therapies or herbal medicine [36]. Antimicrobial properties of herbs, spices and their derivatives such as essential oils, extracts and decoctions has been established in the past three decades [37-39]. Differential antimicrobial activity of the crude extract of leaves of *Sesame radiatum* against some common pathogenic microorganisms has been studied [40].

Initial screening of plants for possible antimicrobial activities typically begins by using crude aqueous or alcohol or hydroalcohol extracts. Preparation of an extract with an organic solvent was shown to provide better antibacterial activity due to better solubility of plant compounds in alcohols over water [41]. Ethanol extract of plants possess relatively high potency, since nearly all of the active components isolated from plants are aromatic or saturated organic compounds [42]. Irobi and Daramola [43] assayed the antimicrobial effect of hot distilled water and 95% ethanol extract of leaves and inflorescence of *Mitracarpus villosus* against *E. coli*, *Staphylococcus aureus*, *Bacillus subtilis* and *Streptococcus faecalis* and reported that ethanolic extracts appeared to exert more inhibitory action against the bacteria than the hot water extracts.

In vitro antimicrobial activity of crude plant extract against viruses, bacteria, fungi and protozoans has been reported by several workers [44-52].

Bhandari, et al [53] investigated antimicrobial activity of crude extracts from *Berberis asiatica* stem bark. Crude aqueous extract of *Caesalpinia digyna* seeds and dry fruits showed antimicrobial activity against *Staphylococcus aureus*, *Salmonella typhi*, *Salmonella* sp., *E. coli*, *Pseudomonas aeruginosa*, *Yerssinia enterocolitica* and *Candida albicans*. Antibacterial activity of aqueous herbal extract of Palash (*Butea frondosa*) was investigated against various bacteria [54]. Antibacterial activity of crude methonolic extract and fractions of aerial parts of *Anthemis tinctoria* against several gram positive and gram-negative bacterial strains has been reported [55]. Djeussi, et al [56] have reported the antibacterial activities of seven Cameroonian dietary plants (*Adansonia digitata, Aframomum alboviolaceum, Aframomum polyanthum, Anonidium. mannii, Hibiscus sabdarifa, Ocimum gratissimum* and *Tamarindus indica.* The extracts of *A. digitata, H. sabdarifa, A. polyanthum, A. alboviolaceum* and *O. gratissimum* showed the best spectra of activity, their inhibitory effects being recorded against 81.48%, 66.66%, 62.96%, 55.55%, and 55.55% of the 27 tested bacteria respectively. The extract of *A. polyanthum* was very active against *E. aerogenes* EA294 with the lowest recorded minimal inhibitory concentration (MIC) of 32 µg/ml. The results of the present study highlighted the useful baseline information for the potential use of the studied plants against both sensitive and MDR phenotypes.

Effect of cold water and methanol extracts of *Lantana* sp. against *E. coli* has been also studied [57]. Crude ethanol extracts of *Achillea santolina*, *Salvia dominica* and *Salvia officinalis* were found to inhibit the growth of *Candida albicans* [58]. Buwa and Van Staden [59] investigated antibacterial and antifungal activity of aqueous, ethanolic and ethyl acetate extracts of plants found in South Africa for the treatment of veneral diseases. Crude methanolic leaf extract of *Newbouldia* has been reported for antibacterial and antifungal activity [60]. Usman, et al [61] reported the antimicrobial effects of crude

ethanolic extract of *Chrozophora senegalensis* against several bacteria and fungi. Anticandidal effect of crude aqueous pod extract of *Lecaniodiscus cupanioides* has been also evaluated [62]. Sheikh, et al [63] investigated the antimicrobial potential of eleven different aqueous leaf extracts on *Xanth- omonas campestris*, *Agrobacterium rhizogenes* and *Aspergillus fumigatus* based on formation of the zone of inhibition (ZOI). *Prosopis juliflora* showed maximum and significant inhibition on the growth of all tested pathogens.

Antimicrobial activity of extract prepared in various organic solvents is studied to find out the classes of phytochemicals reponsible for inhibitory activity of plants. Kuete, et al [64] evaluated that methanol extract and fractions from the stem bark of *Trichodesmostemon omphalocarpoides* (Sapotaceae) possess significant anticandidal and antibacterial effect. Chloroform and Benzene extracts of leaves of *Tinospora cordifolia* were found to possess significant antibacterial activity as compared to standards [65].

Petroleum ether, acetone, methanol and water extracts of the thalamus of *Sphaeranthus indicus* were found to inhibit bacteria and fungi [66]. Amalraj, et al [67] investigated the antimicrobial activity of petroleum ether and chloroform extracts of seeds and leaves of fenugreek (*Trigonella foenum-graecum*) and reported that seed extracts were more effective against *Escherichia coli*, *Salmonella typhi* and *Staphylococcus aureus*. Hexane, methanol and water extracts of leaf, stem and roots of white flowered variety of butterfly pea *Clitoria ternatea* (Fabaceae) were used to evaluate antibacterial activity. It was reported that methanol extract showed the highest activity and no activity was recorded with water extract. Hexane and methanolic extracts of root showed highest and most significant antibacterial activity against both gram-positive and gram-negative bacteria. No activity was recorded with stem extracts. Ravichandran, et al [69] reported that chloroform, petroleum ether, ethyl acetate and alcoholic extracts of roots of *Croton sparciflorus* show antibacterial activity against *Pseudomonas aesuginosa* while chloroform extract show activity against *Bacillus subtilis* and *Escherichia coli*. Bouamama, et al [70] studied antimicrobial activities of the leaf extracts of two Moraccan *Cistus* L. species. They reported that *Cistus villosus* extracts exhibited more significant activity than *Cistus monspeliensis* extracts against *Staphylococcus aureus* and *Candida glabrata*. Murthy, et al [71] studied the antimicrobial activities of bharangin and bharangin monoacetate compounds obtained from the hexane extracts of root nodules of *Premna herbacea* against several gram-positive and gram-negative bacteria and fungi. Prasannabalaji, et al [72] evaluated the *in vitro* antibacterial activity of different solvent extracts of traditional medicinal plants found in South India. *Ocimum sanctum*, *Ocimum gratissimum*, *Aegle marmelos*, and *Adhatoda vasica* leaves against pathogens of human origin and the result demonstrated that the Indian traditional medicinal plants *Ocimum sanctum*, *Ocimum gratissimum*, *Aegle marmelos* methanol leaf extract has potent antibacterial activity and the plants studied are considered as a source of obtaining novel antibacterial compound used for treating drug-resistant human pathogens.

Plant extracts are also known to inhibit plant pathogenic fungi. Zore, et al [73] studied antifungal activity of ethanolic, methanolic and aqueous extracts of roots of *Taverniera cuneifolia* (Roth) Arn. and *Glycyrrhiza glabra* against five fungal pathogens viz. *Fusarium oxysporum* f sp. *vasinfectum* (NCIM 1072), *Fusarium oxysporum* f sp. *vasinfectum*, *Fusarium moniliformae*, *Macrophomina phaseolina* and *Alternaria brassicicola*. Aqueous plant extracts of leaves of *Allium cepa*, *Azadirachta indica*, *Eucalyptus globulus, Prosopis juliflora, Datura stramonium*, *Poinsettia pulcherrima*, *Thevetia peruviana* and bulb of *Allium sativum* were observed to inhibit the growth and sclerotial production of *Rhizoctonia solani* [74].

Plant preparations have a very special characteristic that distinguishes them from chemical drugs. A single plant may contain a great number of bioactive phytocompounds and a combination of plants even more. This complexity is one of the most specific challenge to phytoscientists attempting to identify a single bioactive phytocompound. Several attempts have been made to purify and identify secondary metabolites by Paper chromatography (PC), Thin layer chromatography (TLC), High performance liquid chromatography (HPLC), Column chromatography (CC) and Gas chromatography (GC) etc. The choice of technique depends on the solubility and volatile property of the compounds to be separated.

Guleria and Kumar [75] extracted lipoplilic constituents of fresh leaves of *Zanthoxylum alatum* and *Vitex negundo* by dichloromethane and the biologically active constituents present in the extract were eluted by using 2D-TLC as well as antifungal activity was assayed by bioautographic method. They reported that the active constituents present in both plant extracts were found to inhibit the growth of *Alternaria alternate*. Column fractions obtained from methanolic extract of leaves of *Agave americana* showed high antimicrobial activity and the active compound responsible for antimicrobial activity is due to a steroidal saponin [76]. Chinou, et al [77] investigated chemical composition of the essential oil obtained from the aerial parts of the cultivated *Helichrysum amorginum* by GC and GC/MS. It was found that the oil exhibited a moderate antimicrobial activity against four gram-negative bacteria, two gram-positive bacteria and three pathogenic fungi. Shah, et al [78] investigated that an ethanolic extract of the Australian medicinal plant *Eremophila luttonii* possess activity against additional gram-positive bacteria including *Clostridium perfringens*, *Listeria monocytogenes* etc. They evaluated that Thin layer chromatography (TLC) was used to separate the extract into seven coloured fractions invisible light, one of which was shown by Bioautography to contain antibacterial activity. The purity of the component was verified by High-performance liquid chromatography and a time kill experiment indicated that the purified component showed identical bactericidal activity to the whole extract.

Saleh, et al [79] isolated two major volatile compounds from the fresh leaves of *Artemisia herba alba* and identified them by GC/MS, GC/IR and NMR spectroscopy as carvone and piperitone. They also reported the antifungal activity of these compounds against *Penicillum citrinum* (ATCC 10499) and *Mucora rouxii* (ATCC 24905). Dichloromethane extract of the bark of *Ocotea usambarensis* (Lauraceae) showed antifungal activity against *Cladosporium cucumerinum*. Activity was found to be linked with its essential oil GC-MS analysis of which allowed the identification of about seven compounds responsible for the activity [80]. Lee [81] evaluated fungicidal activity of volatile compounds isolated from *Acorus gramineus* rhizome against phytopathogenic fungi. These volatile compounds were first isolated by using silica gel column chromatography as well as further separation of active fraction was done by HPLC. 4-hydroxy-3-methoxy benzoic acid in stem, roots, flowers and leaves from *Gomphrena celosioides* was isolated and reported to be inhibitory against *Salmonella typhi* (ATCC 19430), *Proteus mirabilis* (ATCC 15290) and *Pseudomonas aeruginosa* (ATCC 15442) [82].

Plant extracts also exhibit trypanocidal, antiplasmodial, leishmanicidal, molluscicidal, antiviral, antitumor and antimalarial activity. Park [83] reported that methanol extracts of some Korean medicinal plants exhibit strong activity against influenza virus type A. Whelan and Ryan [84] investigated that ethanolic extracts of *Euphorbia* and other ethnobotanical species possess pharmacological potential as antineoplastic agents against the HEp-2 cell line and demonstrated that this extract can be used as inhibitor of human tumour cell growth. Garlic (*Allium sativum*) extract modulates immune response. It augments parasite *Leishmania major* engulfment and destruction of intracellular amastigotes by macrophages [85]. Extracts obtained from spiny amaranth, *Amaranthus spinosus* (Amaranthaceae) and erect spiderling *Boerhaavia erecta* (Nyctaginaceae) were found to possess significant antimalarial activities [86]. Singh and Singh [87] reported that aqueous extract of latex of *Thevetia peruviana, Alstonia scholaris* (Apocyanaceae) and *Euphorbia pulcherrima* (Euphorbiaceae) exhibits toxicity against two harmful fresh water snails, *Lymnaea acuminata* and *Indopla-norbis exustus*. Essential oil obtained by hydrodistillation of the leaves of *Strychnos spinosa* was found to be active against *Trypanosoma brucei brucei* bloodstream forms [88]. Mbatchi, et al [89] reported moderate activity of ethanolic and dichloromethane extracts of *Cassia siamea* (bark), *Landolphia lanceolata* (roots and leaves), *Millettia versicolor* (leaves), *Pseudospondias microcarpa* (leaves) and *Vernonia brazzavillensis* (leaves) against *Plasmodium*. Mbwambo, et al [90] reported that stem bark of *Vismia orientalis* possessed antimalarial, leishmanicidal and trypanocidal activity. Crude alcoholic extracts of *Phlomis brunneogaleata* can be used as antimalarial and leishmanicidal agent [91].

Prytzyk, et al [92] reported inhibitory activity of acetone and ethanol extracts of Bulgarian propolis against *Trypanosoma cruzi*. Methanolic extracts of the Vietnamese plant *Maesa balansae* were tested for their antileishmanial activity by Germon prez, et al [93].

Secondary Metabolites as Antimicrobials

Secondary metabolites such as phenols, flavonoids, alkaloids, terpenoids, essential oil are proved to be responsible for the antimicrobial activity of plants. These secondary metabolites are not essential for the plant itself; however they play an important role in plant's defense system and give protection against pathogens and herbivores [94]. There are many reports which suggest that secondary metabolites possess antimicrobial activity [95-102].

Phenol and polyphenol group of compounds consist of thousands of diverse molecules with heterogenous structure with common feature of having one or more phenol ring. Phenolic compounds are synthesized in plants by shikimic acid pathway. The site and numbers of hydroxyl groups on the phenol ring is related to their toxicity to microorganisms, hence increased hydroxylation results in increased toxicity [103]. Several workers have reported that phenolic compounds such as gallic acid, coumarins, polyphenols, caffeic acid, cinnamic acid, pyrogallol, eugenol etc. show antimicrobial activity against virus, bacteria and fungi [104-107].

Skocibusic and Benzic [108] reported presence of phenolic monoterpene charvacol, charvacol methyl ether, burneol, thymol and thymol methyl ether in oil of *Satureja montana* L. This oil was also found to be active against *Pseudomonas aeruginosa*, *E. coli*, *Staphylococcus aureus*, *Candida albicans* and *Saccharomyces cerevisiae* [108]. Nine-2-arylbenzofurans isolated form *Morus* species showed antimicrobial activity against methicillin-sensitive *Staphylococcus aureus*, methicillin-resistant *S.* aureus, *E. coli, Bacillus subtilis, Pseudomonas aeruginosa* and *Proteus vulgaris* [109]. Polyphenols isolated from *Rosmarinus officinalis* alcohol extracts showed antimicrobial activity against gram-negative and gram positive bacteria [110]. Deachathai, et al [111] isolated dulcisxanthones C-F and dulcinone together with 22 known compounds from flowers of *Garcinia dulcis* and reported that some of these compounds act as radical scavangers and antibacterial agents. Tripathi, et al [112] isolated kaempferol from methanolic extract of *Acacia nilotica* bark and reported its antifungal activity.

Flavonoids represent a widespread group of water soluble derivatives which are mostly brightly coloured. Nine classes of flavonoids are recognised and are of great interest in phytochemistry. These are anthocyanins, aurones, biflavonoids, catechins, chalcones, dihydrochalcones, flavones, flavonols, isoflavonoids and proanthocyanidins [113]. Flavonoids are polyphenolic compounds with 15 carbon atom (C_{15}) based on a skeletal structure of two benzene rings joined by a linear C_3 chain (C_6-C_3-C_6 system). They are synthesized by plants in response to microbial infection [114]. Flavonoids have the ability to form complexes with bacterial cell wall and disrupt microbial membranes [115].

Flavonoids compounds exhibit antimicrobial effect against multiple viruses. Numerous studies have documented the effectiveness of flavonoids such as swertifranchiside, glycyrrhizin and chrysin against HIV [116-118]. Chacha, et al [119] isolated two isoflavones and a flavonone from the stem wood of *Erythrina latissima* and reported the antimicrobial activity of these compounds against *E. coli*, *Staphylococcus aureus*, *Bacillus subtilis* and *Candida mycoderma*. Citoglu, et al [120] isolated flavonoids like kumatakenin pachypodal, 5-hydroxy 3'4'-trimethoxy flavone, vetulin, salvigenin, retusin, corymbosin from aerial parts of *Ballota glandulosissima* and found them to be active against *Candida albicans*, *C. krusci* and *C. glabrata*. Flavonoids isolated from root bark of *Bolusanthus* species were found to possess strong anticandiasis activity [121]. Germ tube inhibition of rice blast fungus *Pyricularia grisea* by 3-butyl isocoumarins has been reported [122]. Inhibition of *Trypanosoma cruzi* and *Plasmodium falciparum* by flavonoids has been reported [123-125]. Muzitano, et al [126] obtained quercitin from aqueous extract of *Kalanchoe pinnata* and demonstrated that this compound is antileishmanial compound with a low toxicity profile.

Catechins are most reduced form of the C_3 unit of flavonoid compounds. These compounds were found to be inhibitory for *Vibrio cholerae*, *Streptococcus mutans* and *Shigella* sp. [127,128].

Friedman, et al [129] evaluated antimicrobial activities of seven green tea catechins and four black tea thaeflavins against *Bacillus cereu*. Rauha, et al [130] screened thirteen phenolic substances and twenty nine extracts of Finnish plants against selected fungi and bacteria and found that flavone, quercetin and naringenin were most effective in inhibiting growth of microbes. Pegnyemb, et al [131] isolated a biflavonoid, sulcatone from aerial parts of *Quratea sulcata* and reported its antimicobial activity against range of microorganisms.

Tannins are polymeric phenolic substances, formed by condensation of flavon derivatives by polymerization of quinone units. Tannins are divided into two group; Hydrolysable tannins which yield gallic acid and ellagic acid on hydrolysis by acid and enzyme and condensed tannins, also called as phylotatannins proanthocyanidins. The antimicrobial action of tannins may be due to their ability to inactivate microbial adhesins, enzymes, cell envelope, transport

protein etc. They also form complexes with polysaccharide [132]. Condensed tannins have been known to bind with cell wall of ruminal bacteria and prevent growth and protease activity [133]. Martino, et al [134] isolated tannin fraction from *Terminalia triflora* and studied its inhibitory activitiy against polymerase and ribonuclease activities of HIV reverse transcriptase. Azad [135] reported that tannin is the most abundant compound in the plant whose major effect is anti-diarrhoeal because of water absorption and protein precipitation.

Ho, et al [136] studied antimicrobial activity of six tannins isolated from *Vaccinium vitisidaea* L. against *Porphyromonas gingivalis* and *Prevotella intermedia*. Antimicrobial activity of Azuki beans (*Vigna angularis*) against *Staphylococcus aureus*, *Aeromonas hydrophila* and *Vibrio parahaemolyticus* is due to proanthocyanidins [137].

Quinones are aromatic rings with two ketone substitutions. They are ubiquitous in nature and are characteristically highly reactive. Quinones are known to complex with nucleophilic amino acids in proteins, leading inactivation of protein and loss of function [138]. Therefore, antimicrobial effect of quinones is significant and their probable targets in microbial cells are surface exposed adhesins, cell wall polypeptides and membrane bound enzymes.

Anthraquinones block reproduction of HIV and herpes virus [140]. Inouge, et al [141] reported antimicrobial activity of five terpenoid quinone, three quinones and a quinone containing essential oil against two bacterial and three fungal strains. A new napthoquinone -anthraquinone coupled pigment (new bouldiaquinone) isolated from roots of *Newbouldia laevis* showed antimalarial activity against *Plasmodium falciparum* and antimicrobial activity against *Candida glabrata* and *Enterobacter aerogens* [142].

The fragrance of plants is due to presence of quinta essentia or essential oil fractions. These oils are highly enriched secondary metabolite compounds that are based on an isoprene structure. They are also called as terpenes. Their general chemical structure is $C_{10}H_{16}$ and they occur as diterpenes, triterpenes and tetraterpenes (C_{20}, C_{30} and C_{40}) as well as hamiterpenes (C_5) and sesquiterpenes (C_{15}). When the compounds contain additional elements usually oxygen, they are termed as terpenoids.

Antiviral, antibacterial, antifungal, antiprotozoal activity of terpenes or terpenoids have been reported [143-153].

Antibacterial activity of essential oil of *Pistacia lentiscus* var. *chia* and *Satureja spinosa* against *E. coli*, *Staphylococcus aureus, Bacillus subtilis, Bacillus cereus, Listeria monocytogenes, Salmonella enterica* and *Salmonella serovar* has been studied [154,155]. Demirci, et al [156] investigated antifungal activity of volatile constituents against *Colletotrichum acutalum*, *Colletotrichum fragariae* and *Colletotrichum gloeosporioides*. Antifungal activity of essential oil of *Origanum syriacum, Thymbra spicata, Lavendula stoechas, Rosmarinus officinalis, Foeniculum vulgare* and *Lauras noblis* against *Phytophthora infestans* has been also reported [157]. Pitarokili, et al [158] have reported that oxygenated monoterpenes alpha and beta thujone show antifungal activity against *Rhizoctonia solani*, *Verticillium dahliae* and *Fusarium* species.

Heterocyclic nitrogen compounds called alkaloids are synthesized by decarboxylation of aminoacids. Diterpenoid alkaloids isolated from the family Ranunculaceae are commonly found to have antimicrobial properties [159]. Two alkaloids oriciacridone A and B isolated from the stem bark of *Oriciopsis glaberrima* were found to be active against a range of microorganisms [160].

Inhibition of replication of HIV-1 by alkaloids has been reported [161,162]. Garcia, et al [163] and Morel, et al [164] reported antibacterial activity of pentacyclic oxindol alkaloids isolated from *Uncaria tomentosa* and cyclopeptide alkaloid isolated from *Scutia buxifolia* towards gram-positive, gram-negative bacteria and yeasts. Several workers have reported that alkaloids have antiplasmodial, antileishmanial, cytotoxic and trypanocidal activity [165-168].

Plants have been considered a boon of nature for their medicinal and antimicrobial properties since ancient times. Plant extract inhibit vegetative growth, decrease cell number, inhibit sporulation and has a deleterious effect on the mophology of the pathogens as well as it has the ability to affect the protein, carbohydrate and lipid content of plasma membrane and also effect the extracellular enzyme secretion of microbes. All these activities are due to the activity of secondary metabolites i.e. phenols, alkaloids, terpenoids, saponins etc. present in plant extracts. Several workers have reported that phenolics and flavonoids have ability to alter the cell membrane and change the membrane permeability [169-170]. Gruiz, et al [171] reported that saponin changed the composition of fungal membrane such as sterols, proteins and phospholipids.

Several phenolic compounds like tannins present in the cells of plants are potent inhibitors of many hydrolytic enzymes such as pectolytic macerating enzymes used by plant pathogens [172]. Jeong, et al [173] isolated two triterpenoid compounds ursolic acid and uvaol from *Crataegus pinnatifida* leaves. They reported that ursolic acid inhibits chitin synthase II from *Sachharomyces cerevisiae*.

Inhibition of synthesis of DNA, RNA, protein, lipid and carbohydrate by plant extract is due to presence of secondary metabolites. They are target specific and their biochemical and molecular targets are mainly proteins such as receptors, enzymes and polynucleotides like DNA and RNA [174]. The loss of plasmid DNA and suppression of high molecular weight protein in *E. coli* were observed after treatment with an alkaloid isolated from *Holarrhena antidysenterica* [175]. Knobloch [176] investigated the site of action of terpenoids appeared to be at the phospholipid bilayer, caused by biochemical mechanisms catalyzed by the phospholipid bilayers of the cell. These processes include the inhibition of protein translocation, electron transport, phosphorylation steps and other enzyme dependent reactions.

Secondary metabolites are also responsible for the growth inhibition of bacteria for eg. Triterpenoids having dammarane or epoxydammarane skeleton were isolated from ether extracts of the leaves of *Betula* species. Results of *in vitro* antimicrobial activity indicated that polyol beutalafolienetetraol inhibited the reproduction of *Staphylococcus aureus* [177]. Cuadra, et al [178] reported the inhibitory effect of 8-O-(2-methyl-2-butenoyl)-5,7-dihydroxy-3-methoxylavone isolated from the resinous exudate of *Gnaphalium robustum* on *E. coli* K-12 strain. The inhibitory effect on bacterial growth was quantified using optical density and electrical conductance measurements and found this compound to be nearly as active as phenol. Thadepalli, et al [179] evaluated that extracts of *Allium sativum, Syzygium aromaticum* and cloves inhibited the growth of *E. coli* by 3 to 4 logs for a period of 24 hrs. or more as well as *Bacteroides fragilis*, a strict anaerobic pathogen was inhibited by 3 to 4 logs at 24 hour period.

Conclusion

Plants have been used throughout the world for their preservative

and medicinal powers since ancient time. Scientific experiments on the antimicrobial properties and their components have been documented in the late 19th century [180]. In India, several plants are used in the form of crude extracts, infusions or plaster to treat common infections without specific evidence of efficacy [181]. An increasing reliance on the use of herbal products in the industrialized societies has led to the extraction and development of several drugs and chemotherapeutics from plants [182].

Hence, it has been concluded that medicinal plant extracts and phytochemicals can used for development of several drugs due to its antimicrobial nature. Antimicrobial nature of plant extracts is mainly due to the presence of secondary metabolites. However these extracts do not possess any side effects and residual affects but need to be analysed for toxicity and quality assurance.

Upcoming scenerio will be on the plant based medicine due to comparable efficacy of purified preparation with chemical one. In addition, microbes have also developed multi drug resistance against existing medication and in this case require the replacement with safe and ecofriendly drugs i.e. plant based drugs.

Conflicts of Interest: None declared.

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