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Role of Natural Products against Microorganisms

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Abstract

Since antiquity, man has used plants to treat common infectious diseases and some of these traditional medicines are still included as part of the habitual treatment of various maladies. Natural product chemistry facilitated a vast array of several bioactive secondary metabolites that have been discovered from marine and terrestrial sources to combat infectious diseases. In this review natural products and their isolates from various sources are used against microorganisms along with mechanism of action has been discussed.

Introduction

Microorganisms or microbes are literally microscopic organisms, which can only be seen properly with the aid of a microscope and the most common are bacteria, viruses, fungi and the group of protozoa. All microorganisms are not harmful to the human being, animals or other living organisms. The role of natural products as medicines has been described throughout history in the form of traditional medicines, remedies, potions and oils with many of these bioactive natural products still being unidentified. The dominant source of knowledge of natural product uses from medicinal plants is a result of man experimenting by trial and error for hundreds of centuries through palatability trials or untimely deaths, searching for available foods for the treatment of diseases [1]. A disease is any condition that impairs the normal function of a body organ and/or a system, of the psyche, or of the organism as a whole, which is associated with specific signs and symptoms. Infectious diseases are generally caused by microorganisms. The microorganisms enter into the host *via* mouth, nose, eyes, skin and the genital openings and damage to the tissues. Resulting, to release of toxin or enzymes by the microorganisms into the host and damage the normal function of host organs or the system [2]. It has been estimated that this bacterial genus alone elaborates ca. 100,000 secondary metabolites with at least some antimicrobial activity, suggesting that continuation of traditional antibacterial screening strategies would be likely to unearth new compounds with mechanisms of action distinct from those of current, clinically relevant antibiotics [3]. In recent years, a large number of studies have been conducted for searching the antimicrobial activity of natural products. Plants, especially herbs and spices, are being given more attention. Nowadays, there are over 1,340 plants with defined antimicrobial activities, and over 30,000 antimicrobial compounds have been isolated from plants [4]. Endophytes are reported to produce a number of bioactive metabolites in a single plant or microbe which served as an excellent source of drugs for treatment against various diseases [5]. A significant number of novel metabolites with pharmacological potential have been discovered from marine organisms, such as polyketides, alkaloids, peptides, proteins, lipids, shikimates, glycosides, isoprenoids, and hybrids, which exhibit several biological activities including antibiotic properties [6]. This review will discuss in brief the natural products and their isolates from different sources used against microorganisms along with mechanism of action.

Natural product as traditional medicine

The majority of the world's population depends on traditional medicine for their health, and local providers are consulted owing to perceptions of a positive outcome [3]. Some of the fungi *viz.*, *Piptoporusbetulinus* and *Agaricuscampestris* are valued as disinfectant, antiseptic and throat cancer [1]. The red algae *Chondruscrispus* commonly called Irish moss or carrageen moss and *Mastocarpusstellatus* also called Cluimhin Cait (cats' puff), carrageen, or false Irish moss are found in the marine environment and traditionally used to cure for colds, sore throats, chest infections including tuberculosis [1]. Several terrestrial medicinal plants such as *Abutilon indicum, Acacia leucophloea, Acacia nilotica, Achillea millefolium, Aegle marmelos, Agrimonia eupatoria, Bacopa monnieri, Bombax ceiba, Calotropis procera, Chlorophytum borivilianum, Chlorophytum laxum, Chlorophytum tuberosum, Delonix elata, Enicostemma axillare, Hieracium pilosella, Holoptelea integrifolia, Hypericum alpestresubsp. polygonifolium, Ipomoea pandurata, Jatropha gossypifolia,*

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Justicia zelanica, Lantana camara, Lilium armenum, Mangifera indica, Merremia tridentata, Mollugo cerviana, Phyllanthus emblica, Phyllanthus urinaria, Pithecellobiumdulce, Rumexobtusifolius, Sanguisorba officinalis, Saraca asoca, Solanum incanum, Solanum surattense, Tamarindus indica, Tephrosia purpurea, Thevetia nerifolia and Woodfordia fruticosaare used in Ayurveda and various traditional medicinal system for treatment of manifestations caused by microorganisms [7-10].

Use of natural product against microbes

Natural products originated from microorganisms and plants make exceptionally useful secondary metabolites for production of drugs. This review contains role of natural products against harmful microorganisms or microbial disease. The first antimicrobial agent was discovered by Fleming in 1928 from the natural source, a fungus from the genus *Penicillium*. Subsequently, Streptomycin, an amino glycoside antibiotic, was obtained from the soil bacterium *Streptomyces griseus*. Thereafter, chloramphenicol, tetracycline, macrolide, and glycopeptide (e.g., vancomycin) were discovered from soil bacteria [11]. The microbial disease is an illness or ailment caused by the introduction or infection with one of four types of microbes *viz.*, viruses, bacteria, protozoa or fungi of the millions of types that exist, only about 1,400 are pathogenic in humans (but critically only 150 have both the capability of human-to-human transmission and the potential to cause epidemics. Natural products are secondary metabolites or chemical compounds produced by the living organisms and that have the bio-activity. Metabolites are classified into two broad types, primary and secondary. Primary metabolites are essential to growth and life in all living systems and are formed by a limited number of metabolic reactions [12]. Primary metabolites serve as building blocks for the synthesis of macromolecules, proteins, nucleic acids, carbohydrates, and lipids. Secondary metabolites are not essential to the life of the producing organism and are formed from primary metabolites. Many of the secondary metabolites enhance the survival fitness of the organism and may serve for example as chemical weapons used against bacteria, fungi, insects and large animals [12]. Medicinal plants as a bio-resource are used since antiquity for treatment of various infectious diseases. Earlier literature revealed that 14% to 28% of higher plant species are medicinal and that of 74% of plants were found active compounds based on ethnomedicinal uses [13]. The diverse active components of the plants contain various classes such as alkaloids, terpenoids, saponins, flavonoids, coumarins, phenolics etc. This biodiversity has been exploited by nichepharmaceutical companies and institutions as a source of anti-cancer, antiviral and antipsychotic drugs, either approved or under clinical development, but marine micro-organisms remain an under utilized source of novel anti-infective agents [3]. Chemical structures of marine products often differ from terrestrial secondary metabolites in being halogenated with bromine and/or chlorine. One monoterpene from a red alga has a molecular formula $C_{10}H_{12}Br_3C_{13}$, with 50% by weight of bromine and 22.3% of chlorine [14]. Some of the halogenated materials have shown antibiotic properties; laurinterol, $C_{15}H_{19}OBr$, from a red alga, has activity against gram-positive bacteria comparable to that of streptomycin [15].

Endophytes are an endosymbiotic group of microorganisms that colonize in plants and microbes that can be readily isolated from any microbial or plant growth medium. They act as reservoirs of novel bioactive secondary metabolites, such as alkaloids, phenolic acids, quinones, steroids, saponins, tannins, and terpenoids that serve as a potential candidate for antimicrobial, anti-insect, anticancer and many more property [5]. Antimicrobial agents from endophytes are an alternative arsenal to overcome the increasing drug resistance by pathogens. Many bioactive antimicrobial compounds such as sordaricin [16], multiplolides A and B have been isolated from *Xylaria* sp., an endophytic fungus and are active against *Candida albicans* [17]. Similarly, the compounds and 3,7-dimethyl-9-(-2,2,5,5-tetramethyl-1,3-dioxolan-4-yl)nona-1,6-dien-3-ol, and 7-amino-4-methylcoumarin isolated from the strain *Xylaria* sp., exhibited antibacterial and antifungal activities [18,19]. An endophytic fungus isolated from the stem of the plant *Hypericum perforatum* (St. John's Wort) an Indian medicinal plant, isolated the compounds hypericin and emodin showed promising antimicrobial activity against broad spectrum of bacteria and fungi including *Staphyllococcus aureus* sp., *aureus*, *Klebsiela pneumonia* sp., *ozaenae*, *Pseudomonas aeruginosa*, *Salmonella enteric* sp., *enteric* and *Escherichia coli* and fungal strains *Aspergillus niger* and *Candida albicans* [20]. An endophytic streptomycete (NRRL 30566) isolated from the fern-leaved grevillea (*Grevillea pteridifolia*) produces, novel antibiotics, kakadumycins and showed antibiotic activity, especially against Gram-positive bacteria along with impressive activity against the malarial parasite *Plasmodium falciparum* [21].

An endophyte *Aspergillus versicolor* MF359 isolated from the sponge of *Hymeniacidon perleve*, yielded 5-methoxydihydrosterigmatocystin, showed potent activity against *Staphylococcus aureus* and *Bacillus subtilis*. The compound diaporthalasin yielded from the fungus *Diaporthaceae* sp. from marine sponge displayed potent antibacterial activity against both *S. aureus* and Methicillin-resistant *S. aureus* (MRSA) with equal MIC value of 2 μg/ml [6].

It has been estimated that as many as 30% of people in industrialized countries suffer from a food borne disease each year and in 2,000 at least two million people died from the diarrhoeal disease worldwide. One of the compound fulyzaq (crofelemer), the first anti-diarrheal drug for HIV/AIDS patients has been recently approved by U.S. Food and Drug Administration. The compound crofelemer is a proanthocyanidin oligomer, isolated from there d latex of the plant *Croton lechleri* (Euphorbiaceae) found in the western Amazonian regions of South America [22]. Native populations of South America have used the sap of the plant for self-treatment of secretory diarrhea for many years [23]. Crofelemer is a first-in-class agent that may be useful for different types of secretory diarrhea since it prevents chloride and fluid secretion into the bowel by directly inhibiting 2 distinct intestinal chloride channels [23]. Crofelemer possesses a unique mechanism of action through inhibition of both cyclic adenosine mono phosphate stimulated cystic fibrosis transmembrane conductance regulator and calcium-stimulated chloride intestinal Channels [23]. The drug crofelemer has been investigated for the treatment of several types of secretory diarrhea, including traveler's diarrhea [24], AIDS-associated diarrhea and infectious diarrhea such as cholera [25].

Since antiquity, man has used plants to treat common infectious diseases and some of these traditional medicines are still included as part of the habitual treatment of various maladies. For example, the use of bearberry (*Arctostaphylos uva-ursi*) and cranberry juice (*Vaccinium macrocarpon*) to treat urinary tract infections have been reported in different manuals of phytotherapy, while species such as lemonbalm (*Melissa officinalis*), garlic (*Allium sativum*) and tee tree (*Melaleuca alternifolia*) are described as broad-spectrum antimicrobial agents [26]. Several essential oils such as *Acorus calamus* [27], *Plectranthus mollis* [28], *Ocimum basilicum* [29], *Artemisia absinthium* [30], *Ocimum gratissimum*, *Ocimum sanctum* [31], *Cyathocline purpurea* [32], *Senecio belgaumensis* [33], *Lantana camara* [34], *Tridax procumbens* [35], *Phlomis bracteosa* [36], *Feronia elephantum* [37], *Craniotome furcata* [38] and *Anaphalis nubigena var. monocephala* [39] have been reported to exhibit promising *in vitro* antimicrobial activity. An estimated 3,000 essential oils are known, of which about 300 are commercially important-destined chiefly for the flavours and fragrances market. Besides antibacterial properties, essential oils or their component shave been shown to exhibit antiviral, antimycotic, antitoxigenic, antiparasitic, insecticidal, antimutagenicity, cytoprotective, moderation of insulin secretion analgesic, neuroprotective, antioxidant, antiproliferative proapoptotic anxiolytic-like effect etc. Many of these microorganisms can cause undesirable reactions that deteriorate flavor, odor, color, sensory, and textural properties of foods. Microbial growth is a major concern because some microorganisms can potentially cause food-borne illness. In packaged foods, growth and survival of common spoilage and pathogenic microorganisms such as *Listeria monocytogenes, Escherichia coli O157*, *Salmonella, Staphylococcus aureus, Bacillus cereus, Campylo bacter, Clostridium perfringens, Aspergillus niger,* and *Saccharomyces cerevisiae* are affected by a variety of intrinsic factors, such as pH and presence of oxygen or by extrinsic factors associated with storage conditions, including temperature, time, and relative humidity. Main natural compounds are essential oils derived from plants (e.g., basil, thyme, oregano, cinnamon, clove, and rosemary), enzymes obtained from animal sources (e.g., lysozyme, lactoferrin), bacteriocins from microbial sources (nisin, natamycin), organic acids (e.g., sorbic, propionic, citric acid) and naturally occurring polymers (chitosan). In this context, plant essential oils are gaining a wide interest in the food industry for their potential as decontaminating agents, as they are Generally Recognized as Safe (GRAS) [40]. In other words, nature is a generous source of compounds, with the potential to treat diseases, including infectious diseases. Studies exploiting the mechanism of action and the structure-activity aspects of these natural compounds may provide both additional antimicrobial leads and drugs, and also significant insight into potential possibilities to overcome the antimicrobial resistance.

Mechanism of action

Microbial infection to the host, over come many surface barriers, includes physical and mechanical elements like skin, mucous membranes and the epithelia of there spiratory system or the gastrointestinal and genitourinary tracts [41]. At the infection stage of immune system of the host activated by chemical mediators which become an effective arsenal to overcome the harmful action of the microorganisms [42]. Several mechanisms of action have been reported, which may involve membrane permeabilization through the formation of pores, membrane thinning or micellization in a detergent-like way [43]. The bacterial membrane can have many roles affecting the action of antimicrobial agents. The membrane presents itself as a barrier that drugs must breach in order to access intermolecular targets. However, this membrane barrier is also responsible for establishing concentration and electrical gradients between the cell and its environment. The cell wall is the first barrier that an antimicrobial agent must counteract. In contrast to gram-positive bacteria, gram-negative organisms have an additional membrane, the so-called outer membrane, that lies over and covers both the cytoplasm membrane and the peptidogly can layer. The outer membrane has an asymmetric distribution of the lipids with phospholipids and lip polysaccharide located in the inner and outer leaflets, respectively [44]. Thus, gram-negative bacteria tend to be more resistant to antimicrobial agents than gram-positive bacteria, because of the presence of the additional protection afforded by the outer membrane. In addition to the outer membrane, both gram-positive and gram-negative bacteria have a cell wall that can protect the cytoplasmic membrane. Antimicrobial agents targeting the cell wall have been known for many years. Among them, the β-lactam antibiotics inhibit cell wall synthesis. However, the effectiveness of these agents is limited as a result of increased expression of bacterial β-lactamases that inactivate these antibiotics [45]. Antimicrobial peptides (AMPs) are key component ofthe innate immune systems of most living organisms and protect them against invading microorganisms. So far, more than 2,000 AMPs have been reported in the antimicrobial peptide database, and they have been isolated from a wide variety of sources, including animals, plants, bacteria, fungi, and viruses [46].

Several modes of action of antimicrobial agents have been reviewed including targeting of specific enzymes or of DNA, or indirectly by stimulating the immune system, role of peptides in immunity and their potential in therapeutics, with biophysical and biochemical mechanisms, transport of bacterial cells to the surface and their initial and reversible adhesion, irreversible attachment, micro colony formation, biofilm maturation and differentiation, and cell detachment with propagation of infection [43,45,46]. The natural products that used by the traditional healers are the complex mixture of the several compounds (polar, mid-polar and non-polar in nature) may act as a synergistic effect against the microbes. The essential oils components are the classical example to understand the mechanism of the action against pathogens. According to [47], the majority of the essential oils assayed for their antibacterial properties showed a more pronounced effect against the gram-positive bacteria. The resistance of gram-negative bacteria to essential oil has been ascribed to their hydrophilic outer membrane, which can block the penetration of hydrophobic compounds into target cell membrane [48]. If the major constituents in the oils contain hydrophilic in nature can be attributed better antimicrobial activities against gram-negative bacteria rather than gram-positive bacteria. Moreover, due to the steric hindrance of the functional group in the compounds e.g. the hydroxyl group in the compound eugenol may not be involved completely for hydrogen bonding due to the presence of –OMe group in ortho position [31]. Due to the hydrophobic and hydrophilic amino-acid patches, creating an amphiphilic protein surface of fungi, are able to invert the polarity of surfaces on which they self-assemble very effectively [49]. As the amphiphilic nature of the fungi cell wall overcome obstacle to penetrate the hydrophobic and hydrophilic compounds which are found a majority of essential oils may disrupt essential cellular metabolic pathway of fungi. In overall, whole essential oils have exhibited greater antimicrobial activity due to a synergistic effect with some active components rather than single compound(s). Penetration of phytochemicals into this phospholipid bilayer will have a profound effecton a wide range of essential cell functions. Induction of phyto chemicals into the membrane of microorganisms and disrupt solute equilibration across the bilayer, resulting incell death, but more subtle interactions at subinhibitory concentrations induce re-organization of membrane architecture with implications for the capacity of the target bacteria to cause disease in the susceptible host [3].

Conclusion

In summary, several natural components act very important role to combat against harmful microbes. Numerous compounds have been identified and characterized from various sources of nature which need biological activities not only against microbes but also other diseases. Several plants and their isolated compounds have been screened for bioactivities against pathogens, but the other natural sources *viz.*, marine flora and endophytes are poorly investigated. Endophytes are capable to synthesizing bioactive compounds that can be used to combat numerous pathogens and which can supply the demand of the drug and can be the option for potential renewal sources for the sustainable production of bioactive natural compounds.

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