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Mini Review

Plant Secondary Metabolites: Natural Antibacterial Agents

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Abstract

Secondary metabolites are produced by the plants and these include alkaloids, phenolics, flavonoids, etc. Unlike primary metabolites which are directly involved in plant growth, development, and reproduction, these secondary metabolites are considered to be defense tools for the plant. In the last decade, much research has been carried out on the antibacterial activity of these plant secondary metabolites. This article discusses several secondary metabolites viz. alkaloids, terpenoids, flavonoids, and phenolics for their antibacterial activities.

Introduction

The metabolites play important role in the physiology and biochemistry of the organisms. Any living organism can't survive without metabolites. The metabolites have role in maintaining the structure, and/ or may work as a source of energy[1]. Besides, certain metabolites also act as signalling molecules[2], effectors for various enzymes[3], co-factor for the enzyme[4, 5],and defense molecules[6]. The metabolites are of two different categories, namely primary and secondary metabolites, depending on their role in the organism. If the metabolite is directly involved in the growth, development, reproduction, etc. of the organism, it is called primary metabolite[7]. When a metabolite is not directly involved in growth, development, reproduction, etc., then it is called secondary metabolite[7]. The secondary metabolites are not the obligate requirement for the survival of an organism. It has been shown that secondary metabolites are involved in long-term impairment of the organism's survivability[8].

Although other organisms also synthesize secondary metabolites, these are mainly synthesized by the plants and these have an important role in plant defense against many pathogens[9]. In recent years, this property of secondary metabolites is being exploited as natural medicines against many diseases[10].The secondary metabolites are found in various amounts in different parts of the plants. The amount depends upon the stage of growth and under different stress conditions like presence of invasive microorganisms, herbivores, etc.[11].

Since last few decades, the side effect of synthetic medicines and resistance being developed in bacteria against many antibiotics has attracted the attention of several researchers towards this field.

The secondary metabolites are of different types such as alkaloids, phenolics, flavonoids, etc. These secondary metabolites have various roles like insect attractants for help in pollination, defense against bacteria, insects, and predators. In addition to the medicinal role, these secondary metabolites have been exploited for flavours, fragrances in food, and cosmetics industries [12-16].

Medicinal plant is a plant when it is as such or some constituent of it is exploited as a medicine for certain disease(s). Nowadays, many plants have been identified as medicinal plants due to the presence of secondary metabolites in them which act as natural antimicrobial agents. The important secondary metabolites which have been identified as natural antimicrobial agents are the following:

Alkaloids

Alkaloids are nitrogenous organic compounds. The word 'Alkaloid' was coined from alkali as mostly these compounds are alkaline in nature. However, some alkaloids have been reported having neutral or acidic property.

Alkaloids have carbon, hydrogen, and nitrogen in their structure. Besides, some of these also have oxygen, sulfur, chlorine, bromine, and phosphorus. Alkaloids are produced by the plants as their defense mechanism[19]. However, few bacteria and fungi have also been reported to produce alkaloids[20]. Alkaloids have been categorized as pharmaceuticals since various alkaloids exhibit activity against many diseases. The most popular alkaloid, quinine, has anti-malarial activity[21]. It has activity against

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Plasmodium falciparum, a microbe responsible for causing malaria in humans. This is transmitted in humans through mosquitoes. Quinine was first isolated in 1820 from the bark of a cinchona tree. Bark extracts are used to treat malaria since centuries. It is on the WHO Model List of Essential Medicines as most important medicine required in a primary health centre. The *Aspidosperma olivaceum* is being used as a medicine against fevers in many parts of the world and its medicinally active ingredients have been reported to be indole alkaloids[22]. The bark and leaves of the plant have also been shown to exhibit antimicrobial activity against *Plasmodium falciparum*[22].

Vincamine is a monoterpenoid indole alkaloid which has been isolated from the leaves of *Vinca minor*. This plant has been reported to be enriched in vincamine which constitutes about 25-65% of the indole alkaloids. Vincamine is a peripheral vasodilator that increases blood flow to the brain[23].

Chelerythrine, a benzophenanthridine alkaloid, has an antibacterial activity against *Staphylococcus aureus* and many other human pathogens. It has been reported to be present in plants viz. *Chelidonium majus*. It is a potent, selective, and cell-permeable protein kinase C inhibitor *in vitro*. It has also been reported to be efficacious antagonist of G-protein-coupled CB1 receptors[24].

The *Catharanthus roseus* (also known as *Vinca rosea*), a plant belonging to family, Apocynaceae is known for its alkaloids, Vinblastine and vincristine, which have been reported to exhibit anti-cancerous activity[25].

Terpenoids

Azadirachtin, a terpenoid, is a secondary metabolite present in neem (*Azadirachta indica*) seeds. Earlier, it was shown to have inhibitory activity towards the desert locust (*Schistocerca gregaria*). Later, it has been reported to affect nearly 200 species of insect, by acting mainly as an anti-feedant and growth disruptor, and as such it possesses considerable toxicity towards insects. Due to its biodegradable property, Azadirachtin has been considered to be a very good insecticidal. It is degraded within 100 hours when exposed to light and water, and showed very low toxicity towards mammals[26].

Artemisia annua L., a medicinal herb has also been reported to produce secondary metabolites which exhibit antimicrobial activity. This plant has artemisinin, a terpenoid, which is the active ingredient responsible for antimicrobial activity. The secondary metabolites present in this plant are reported to have inhibitory activity against Gram-positive and Gram-negative bacteria. Kim et al.[27] reported anti-inflammatory, antioxidant, and antimicrobial properties of artemisinin derived from water, methanol, ethanol, or acetone extracts of *Artemisia annua* L. They found antimicrobial activity of the extracts against the periodontopathic microorganisms, *Aggregatibacter actinomycetemcomitans*, *Fusobacterium nucleatum* subsp. *animalis*, *Fusobacterium nucleatum* subsp. *polymorphum*, and *Prevotella intermedia*. They recommended the use of *Artemisia annua* L. for dental diseases since these extracts also exhibited the anti-inflammatory and antioxidant activities also.

Flavonoids

Antimicrobial activity of plant flavonoids is known since long time. Mitscher et al.[28] reported isolation of number of isoflavonoids and related compounds from *Glycyrrhiza glabra* L. var. typical and identified them as glabridin, glabrol, glabrene, 3-hydroxyglabrol, 4'-O-methylglabridin, 3'-methoxyglabridin, formononetin, phaseollinisoflavan, hispaglabridin A, hispaglabridin B, salicylic acid, and O-acetyl salicylic acid. They showed that out of these, hispaglabridinA, hispaglabridin B, 4'-O-methylglabridin, glabridin, glabrol, and 3-hydroxyglabrol possessed significant antimicrobial activity *in vitro.* They also reported that hispaglabridin A, hispaglabridin B, 3'-methoxyglabridin, 4'-O-methylglabridi 3-hydroxyglabrol, phaseollinisoflavan, salicylic acid, and O acetyl salicylic acid are newly found in *Glycyrrhiza*sp.; and hispaglabridin A, hispaglabridin B, 3'-methoxyglabridin, 4'-O-methylglabridin, and 3-hydroxyglabrol are new to the literature.

Dastidar et al.[29] studied antibacterial potential of isoflavones. They screened isoflavonoid compounds 'YS11-YS21' for possible antimicrobial property against 12 known Gram-positive and Gram-negative sensitive bacteria. They found that YS11 and YS16 failed to show antimicrobial activity whereas YS12, 13, 14, 15, 17, 18, and 20 had moderate antimicrobial action. However, compounds YS19 and YS21 showed pronounced antimicrobial property. The isoflavones YS19 and YS21 were then tested *in vitro* against 214 strains of bacteria from one Gram-positive and six Gram-negative genera. They determined the minimum inhibitory concentration (MIC) of YS19 and YS21 by agar dilution method and it ranged from 25 to 200 mg/l in most strains. At concentrations of 30 and 60 μg/mouse, these compounds offered significant protection to mice challenged with 50 median lethal dose (MLD) of a virulent strain of *Salmonella typhimurium*.

Mukne et al.[30] reported that flavonoids and related compounds possessed potent antimicrobial activities. Most of the flavonoids are considered as constitutive antimicrobial substances termed as "Phytoanticipins," especially those belonging to prenylated flavonoids and isoflavones. They highlighted the structural prerequisites for isoflavones as antibacterial agents and drew Structure–activity relationship (SAR) conclusions by comparing the reported minimum inhibitory concentration values for the various isoflavones against *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* (MRSA). They also formulated a significant co-relationship between the presence of certain functional groups viz. prenyl and phenolic hydroxyl at particular positions and antibacterial activity of the compounds. They postulated these trends with a view of assisting better drug designing of future next-generation anti-infectives,

particularly against the bothersome multidrug-resistant microbes. They showed that SAR of these isoflavones also proved to be a basis to explore the mechanism of antibacterial action. They hoped that their study would prove extremely useful to synthesize antibacterial isoflavones in future, which would eventually be beneficial for optimizing the lead molecule for the antibacterial action.

Praveen and Ghalib [31] showed that methanolic extract of the leaves of *Xylosma longifolium* has a new flavonodic compound, Kaempferol-3-β-xylopyranoside-4'-α-rhamnoside, along with Kaempferol, Quercetin, Kaempferol-3-rhamnoside, and Quercetin-3-rhamnoside. They checked the *in vitro* antimicrobial activity of the aqueous and methanolic extract against *Escherichia coli, Staphylococcus aureus, Salmonella typhimurium,* and *Bacillus subtilis*. They tested *Candida albicans, Fusarium oxysporum, Penicillium notatum, Aspergillus niger*, and *Trichoderma viridae* for the *in vitro* antifungal activity. They found that these extracts had antimicrobial activity against Gram-positive bacteria and fungal strains. The aqueous extract exhibited high antimicrobial activity against *Staphylococcus aureus* and *Candida albican*, and moderate activity against *Bacillus subtilis* and *Trichoderma viridae*. The methanolic extract exhibited antimicrobial activity against *Staphylococcus aureus* and *Candida albican*, and moderate activity against *Bacillus subtilis*, *Salmonella typhimurium*, and *Aspergillus brassicola*.

Phenolics

Phenolics are the well-known antibacterial agents. These are synthesized by the plants and are considered to be as secondary metabolites. Phenolics protect the plants from pathogenic bacteria. It has been shown that the growth of *Xyletta fastidiosa*, a pathogenic bacteria which infects many crops, gets inhibited by phenolic acid as shown using low minimum inhibitory concentrations [32]. Maddox et al. [32] also showed that phenolics with different structural features viz. catechol, caffeic acid, and resveratrol exhibited strong antibacterial activity against different strains of Xytella fastidiosa isolated from grape and almond. Papuc et al. [33] reviewed plant polyphenolics as antibacterial agents.The phenolics are used as preservative for increasing the shelf life of meat and meat products [34, 35]. It is shown that polyphenols interact with the cell wall components of the bacteria and bacterial cell membrane control biofilm formation. Besides, phenolics are known to inhibit microbial enzymes. They also influence the regulation of protein biosynthesis. The phenolics may also deprive the bacterial cell enzymes of substrates and metal ions.

Ouerghemmi et al. [36] isolated phenolics from the leaves and flowers of Tunisian *Ruta chalepensis* L and identified vanillic acid and coumarin mainly in the extract. They extracted from cultivated as well as wild grown Tunisian *Ruta chalepensis*, and found no significant difference in the efficiency of the extract for antibacterial activity.They showed it as a potent antibacterial agent in the food industry.

Mahmoudi et al. [37] extracted phenolics using methanol from the leaves of different varieties of fig (*Ficus carica* L.). They showed that this methanolic extract had bactericidal activity against Gram-negative and Gram-positive bacteria. They tested *Bacillus cereus* and *Staphylococcus aureus*. They also found that this methanolic extract also exhibited moderate antifungal activity against *Aspergillus brasiliensis* and *Candida albicans*.

Conclusion

Secondary metabolites are important defense tools against many pathogenic microbes. Plants being enriched in these secondary metabolites have high possibility to be used for cure against pathogenic microbes. These may be exploited using biotechnological tools.

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