Phytoc hemicals in Bifunctional Roles: From Defense Molecules in Plants to Therapeutic Agents in Humans

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ABSTRACT

Medicinal plants have gained a lot of interest in the recent past as healing components in the primary health care system. They possess a multitude property due to the presence of bioactive compounds which include alkaloids, phytosterols, flavonoids, saponins, terpenoids, dietary fibers, peptides, etc. in varied dosages and in different parts of the plant. These phytochemicals are produced by plants for their defense but are extracted by users for their antimicrobial and healing properties. Knowledge about the usage of plant parts in curing ailments and health promotion has been passed orally through indigenous communities for ages. However, in nature, overexploitation of resources has led to the depletion of medicinal plants of high therapeutic value. Introduction of plant tissue culture, metabolic engineering, and other modern techniques have shown mass-scale production of these plants with high concentrations of bioactive components. Thus, an amalgamation of information gathered from local communities along with large-scale production of secondary metabolites through traditional and modern techniques and their utilization in disease treatment is the basis for good health.

Keywords: Bioactive compounds, Traditional techniques, Plant tissue culture techniques, Metabolic Engineering.

INTRODUCTION

Medicinal plants being the important component of traditional medicine have gained popularity among a large number of people as an incredible form of health care with little or no side effects when compared to modern medicine. Increased awareness about usage of biological components that are eco-friendly, safe, cost effective and with maximum bioavailability in animals and humans has led to development of phytomedicines. In the last few decades, it has been observed that the world’s population is more and more believing in traditional or folk medicine, especially drugs from plant origin for their primary health care.[1] Traditionally, this treasure of knowledge has been passed on orally from generation to generation without any written document and is still retained by various indigenous groups around the world. Traditional folk medicine utilizes the knowledge, skills and practices of indigenous people based on the theories, beliefs and experiences indigenous to its cultures for maintenance of health.

Medicinal plants such as tulsi leaves (Ocimum tenuiflorum), neem leaves and stem (Azadirachta indica), ashwagandha berries and leaves (Withania somnifera), giloe stem and leaves (Tinospora cordifolia), sesame seeds (Sesamum indicum) and many others have been used by ethnic groups since time immemorial and their uses have also been mentioned in Traditional system of medicine such as Ayurveda, Unani, Siddha etc.[2] However, the proper documentation of traditional knowledge with regard to their value is still lacking and needs attention.

The medicinal value of plants is attributed to the presence of phytochemicals or bioactive components or secondary metabolites that are produced by plants as a defense mechanism against pathogens and are being exploited by humans as a part of traditional medicine to be used in cure of acute and chronic diseases. These phytochemicals are obtained from different parts of the plant and are present in varied concentrations. The secondary metabolites have the potential to treat several chronic diseases such as liver disorders, cardiac disease, cancer, skin ailments, neurological disorders etc.[3] This review focuses on the phytochemicals which play a dual role in being the defensive molecules for the plants and therapeutic agents in humans. We have tried to give comprehensive insight on the nature and types of phytochemicals, their enhanced production by using different Traditional and modern techniques and their role in treatment of several diseases.

We have used plants since ancient times for curing different ailments, since they have medicinal powers. Plants are a rich source of phytochemicals and these secondary metabolites have
pharmacological properties and act as outstanding source of bioactive compounds. These bioactive compounds are produced when the plant cells are undergoing various kinds of stress while performing different physiological tasks. Since they are used in different industrial units (cosmetics, dietary substances etc.) especially in pharmaceutical industries, various industrial sectors are doing research to increase the production of these metabolites using plant tissue culture techniques and increasing the production of commercial bioactive compounds by using bioreactors. Plant Tissue Culture (PTC) techniques help in sustainable, viable and economical production of secondary metabolites as they are independent of climatic and geographical conditions.

Secondary metabolites / bioactive compounds can be classified into various groups based upon their structure, function and biosynthesis. They can be biosynthesized from various precursors such as Mevalonic acid, Shikimic acid, acetyl coenzyme A etc. via different pathways.[4,5] They are usually categorized as steroids, terpenoids, saponins, terpenes, alkaloids, enzyme cofactors and lipids. Secondary metabolites are usually isolated from naturally growing plants, but due to environmental and regional constraints their commercial production is limited. Conventional methods of propagation are very time consuming and take several years to grow plants and extract desired metabolites from them.

**Secondary metabolite production-Tissue culture techniques**

Plant tissue culture techniques (micropropagation, cell suspension culture, callus culture etc.) helps us to produce these bioactive compounds within a short duration of time and also helps in bulk propagation of medicinally important plants under controlled conditions without seasonal constraints. For production of secondary metabolites using PTC techniques, differentiated plant structures like shoots, roots, calli and cell suspension cultures etc. are usually used. For callus induction in vitro explants are grown in combinations of auxins and cytokinins or only auxins in high concentrations in the culture media. Callus cultures are widely used material in tissue culture to generate commercially important secondary metabolites of therapeutic use. They can also be used to regenerate new plants through micropropagation techniques and also to develop single cell suspension culture lines using cell suspension cultures one can manipulate the pathways of secondary metabolites synthesis in plants using biotechnological techniques like genetic transformation. Callus cultures of many plant systems have been used for the production of phytochemicals such as ajmaline, serpentine, tropane, alkaloids, α-tocopherol, reserpine, flavonoids, resveratrol etc. as well as endogenous and constituents of microbial cell walls (Chitin, Chitosan) and plant cell wall (polysaccharides or oligosaccharides). Both these can be used as signaling molecules for the elicitation roots as they induce plant defense responses that are similar to pathogen invasion.[16] Specific cell membrane receptors perceive the biotic elicitors and then transfer the stimulus to cell via signal transduction mechanism leading to synthesis of phytochemicals and defensins in plants known as phytoalexins.[17] Plants also produce phytohormones like methyl jasmonates and salicylic acid in response to stress or pathogen invasion and they act as signaling compounds in elicitation leading to increased production of secondary metabolites like oleuropein and tropaeolin A which are used in the treatment of hypertension.[18]
alkaloids, flavonoids, terpenoids and phenylpropanoids. During this process they initiate signal transduction pathways and target secondary signals in the nucleus leading to transcriptional stimulation of various genes and inducing synthesis of multiple proteins involved in secondary metabolite production for the purpose of defense or developing resistance in plants.

Few plant pathogens like Pythium, Fusarium, Trichoderma, Penicillium etc., are extracted as fungal elicitors to trigger the production of secondary metabolites in plants. Saccharomyces cerevisiae and Aspergillus niger cell free extracts were used as fungal elicitors for enhanced production of gymnemic acid through cell suspension cultures of Gymnema sylvestre. Terpenoid (indole alkaloids) production was increased in Catharanthus roseus using extract of Aspergillus flavus. For the production of tropane alkaloids in hairy root cultures of Scopolia parviflora. Gram positive and gram-negative strains of bacteria were used as elicitors, In Ginkgo biloba cell suspension cultures that were raised through PTC techniques ginkgolide and bilobalide biosynthesis was increased by using staphylococcus aureus extract. Coronatine accumulation in Taxus cell cultures increased the taxane production. Coronatine also triggered the synthesis of viniferins in Vitis vinifera cell suspension culture. In root cultures of Lavandera cuneifolia, glycyrrhizic acid production was increased using Agrobacterium tumefaciens and Rhizobium leguminosarum as bacterial elicitors.

Metabolic Engineering

We use different biotechnological tools like genomics, proteomics, and metabolomics for the production of plant metabolites that are commercially important by manipulating biochemical pathways. Using the technique of recombinant biotechnology one can regulate the metabolic pathways that are involved in biosynthesis of enzymes, precursors, regulatory proteins involved in metabolite formation in plants. These pathways can also be reconstituted in different hosts for over production of plant secondary metabolites that are of commercial use. Phenylalanine is the precursor for synthesis of phenolic secondary metabolites in plants via Shikimate biosynthetic pathway. Intermediate of this pathway p-Coumaroyl-CoA forms the origin of metabolites like flavonoids, lignans, catechins, vanillin, Gallic acid, coumarins, etc. Terpenoids pathway is also known as isoprenoid pathway and is used to synthesize terpenoids in plants via two independent pathways (methyl-d-erythritol and mevalonic acid pathway). Secondary metabolites like brassinosteroids, phytosterols, triterpenoids, sesqueriphenoids, and polyphenols are synthesized through the mevalonic acid pathway. Monoterpenoids, diterpenoids, plastoquinone, tocopherols etc. and plant growth regulators like GA3, cytokinins, etc. are synthesized via methyl-d-erythritol pathway.

Several modern methods are also used for the production of secondary metabolites such as mutagenesis which is mainly used in the fermentation industry. Different strains of micro-organisms are induced in different strains of tobacco for the increased production of phenolics. Another widely used method is the production of transformed roots using biotechnological tools like Agrobacterium mediated transformation of hairy root cultures. A. rhizogenes was used to transform roots of Atropa belladona, it contained vector containing 6-Hydroxylase gene (isolated from Hyoscyamus muticus) for overproduction of scopolamine. L-valine, which is an important drug precursor, is also synthesized through metabolic engineering. Immobilization and bioreactors are the two techniques which help in increasing the production of secondary metabolites. Feed batch, batch and continuous culture are the suitable bioreactor systems used for the large-scale production of secondary metabolites. Cell cultures of Plumbago rosea immobilized in calcium alginate and cultured on MS medium was used in production of plumbagin. Plant cell cultures have been used for a long time for production of secondary metabolites and also for therapeutic purposes to meet industrial demands.

Biotransformation

One of the modern biotechnological techniques that involves production of a new product without adding a whole precursor in the culture media containing plant cells. It involves biotransformation of suitable substrate into a desired product, for example production of digoxin (a cardiac glycoside) that involves biotransformation of beta-methyl digitoxin to beta-methyl-digoxin using D. lanata cells. Another important tissue culture technique is somaclonal variations which are usually seen in cell and protoplast cultures of different plant materials. Variant lines raised from tissue culture help in increasing biomass yield and enhance production of secondary metabolites.

Role of Phytochemicals as therapeutic agents

Botanicals have been used traditionally by herbalists and indigenous healers worldwide for the prevention and treatment of several diseases. Clinical research in this century has confirmed the efficacy of several plants in the treatment of neurological, hepatic, cardiac and skin diseases. Herbal remedies are considered as the oldest forms of health care known to mankind on this earth. Prior to the development of modern medicine, the traditional systems of medicine that have evolved over the centuries within various communities are still maintained as a great traditional knowledge base in herbal medicines.

Traditionally, this treasure of knowledge has been passed on orally from generation to generation without any written document and is still retained by various indigenous groups around the world. Traditional folk medicine uses the knowledge, skills and practices based on the theories, beliefs and experiences indigenous to its cultures for maintenance of health. In this review we have tried to provide the role of the above-mentioned secondary metabolites as effective healing agents of various chronic and acute disorders.
Secondary metabolites role in treatment of diseases

The chemical structure, nature, solubility, bioavailability and the concentration of these phytoconstituents are responsible for their properties such as antimicrobial, anti-inflammatory, anthelmintic, anticarcinogenic, antigenotoxic, antiproliferative, antimutagenic and antioxidative, the metabolites can provide direct or indirect defensive mechanism against pathogens or harmful ailments. These secondary metabolites have been used in treatment of various diseases as shown in Figure 1.[33]

Cancer treatment

Cancer chemoprevention with natural phytochemical molecules is an emerging approach to prevent, delay, or cure cancer.[34] The phytochemicals such as lignans, alkaloids, flavonoids, steroidal lactones etc. have been reported to play an important role as anticancer molecules and the anticancer properties of plants have been recognized for centuries.[35] Lignans extracted from the common mayapple (Podophyllum peltatum) and its derivatives have been reported to be involved in drug development used to treat testicular and lung cancer.[35] Some plants have been reported to be very effective anticancer agents such as guduchi (Tinospora cordifolia) where the most commonly used part of the shrub is the stem, but roots are also known to contain important alkaloids and polyphenols are responsible for anticancer activity, wild jujube (Ziziphus nummularia) contain jujubogenin, a saponin, triterpenoid acid, betulonic acid which shows cancer prevention, kalmegh (Andrographis paniculata). A. paniculata extract contains diterpenes, flavonoids and stigmasterols. The primary medicinal component of Andrographis is the diterpene andrographolide. A. paniculata is a potent chemoprotective agent and is effective against a variety of infectious and oncogenic agents. Andrographolide shows cytotoxic activity against a variety of cancer cells.[36] Brahhammaduni (Centella asiatica) contains centellosides with anticancer property, haldi (Curcuma longa) plant has curcumin (diferuloylmethane, a polyphenol derived from the rhizome of the plant. Turmeric is used for both cancer prevention and treatment. The anticancer potential of curcumin is associated with its ability to inhibit proliferation in a wide variety of tumor cell types.[37] Desai, 2008 suggested plants such as amla (Phyllanthus emblica), Ashwagandha (Withania somnifer) etc. with anticancer properties.[33] Several studies have focused on the chemoprotective activity of plants such as anticarcinogenic property of Abruus precatorius on Yoshida sarcoma in rats, fibrosarcoma in mice and ascites tumor cells.[38] Dhar et al., (1968) have examined the anticancer properties of Albizia lebbeck on sarcoma in mice and Alstonia scholaris on benzo[a]pyrene-induced stomach carcinoma in humans. [39]

Cardiovascular disease treatment

Cardiovascular disease has been the leading chronic disorder observed for the highest death rate in the world. People are now looking for traditional or alternative system of medicine in treating various medical conditions observed in cardiac disease such as congestive heart failure, Hypertension, Angina pectoris, Atherosclerosis, Cerebral and peripheral vascular disease and Venous insufficiency.[40] The condition known as Venous insufficiency is treated by intake of saponin glycoside, Aescin from Aesculus hippocastanum.[40] Toma et al. (2020) have suggested

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Table 1: Some of the important in vitro grown cultures producing secondary metabolites.

<table>
<thead>
<tr>
<th>Secondary metabolite</th>
<th>Type of in vitro culture</th>
<th>Plant name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosamic Acid</td>
<td>Cell suspension culture</td>
<td>Salvia officinalis.</td>
</tr>
<tr>
<td>Colchicine</td>
<td>Callus culture</td>
<td>Gloriosa superba.</td>
</tr>
<tr>
<td>Anthraquinones</td>
<td>Callus culture</td>
<td>Morinda citrifolia, Coptic japonica, Nicotiana tabacum.</td>
</tr>
<tr>
<td>(Berberine, Nicotine, and Glutathione)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Artemisinin</td>
<td>Roots of higher plants</td>
<td>Agrobacterium rhizogenes and Agrobacterium annua.</td>
</tr>
<tr>
<td>Hypericin and Hyperforin</td>
<td>Shoots</td>
<td>Hypericum perforatum.</td>
</tr>
<tr>
<td>Saponin</td>
<td>Root suspension culture</td>
<td>Gynostema pentaphyllum.</td>
</tr>
<tr>
<td>Gallotannins</td>
<td>Root suspension culture</td>
<td>Rhus javanica.</td>
</tr>
<tr>
<td>Anthraquinone</td>
<td>Shoot multiplication</td>
<td>Frangula alnus.</td>
</tr>
<tr>
<td>Glycyrrhetic acid</td>
<td>Cell cultures</td>
<td>Glycyrrhiza glabra.</td>
</tr>
</tbody>
</table>
the role of phenolic compounds as effective lipid regulatory and anti-inflammatory agents in treating cardiovascular disease.[41]

Several plants such as Digitalis purpurea containing digitoxin, digoxin have been reported to treat congestive heart failure in proper dosage form. The roots of Rauwolfia serpentina containing alkaloid, reserpine and others are used in treatment of hypertension. It slows down the activity of the nervous system which in result decreases heart rate and dilates blood vessels. Rauwolfia consists of indole alkaloids as major phytochemicals with others including fatty acids, alcohols, sugars and glycosides, steroids, phytosterols, flavonoids, oleoresins and tannins. Procytanins in fruits, flowers and seeds of Crataegus oxyacantha have been researched upon to treat Angina pectoris condition. Atherosclerosis treatment include use of Allium sativum bulbs which contain organo sulphur compounds containing allinin, ajoene, S-allyl-L-cysteine, Diallyl Disulfides (DADS), methyl thiosulfonate and diallyl trisulfides etc. which are responsible for the pharmacological activities. Ginkgo biloba which contains flavone glycoside and terpene lactone is used in treatment of cerebral and peripheral vascular disease. The study and research made by different scientific groups on these plants have provided a way to manufacture phytomedicines and to include them in the mainstream of the healthcare system.

Diabetes management

Diabetes is considered to be an important metabolic ailment in humans due to insulin imbalance and acts as a trigger for causing more severe health disorders. Over several decades, usage of herbal remedies to cure Diabetes have gained importance when compared to modern medicine due to lesser side effects and cost-effective nature. There are many herbal formulations suggested for diabetes and diabetic complications of which the most important component is medicinal plants.

Some of the important medicinal plants which have been studied for treatment of diabetes include Aegle marmelos (Bael), experimental studies reported that the administration of aqueous extract of leaves improves digestion and reduces blood sugar and urea serum cholesterol in alloxanized rats as compared to control.[42] Limonene has been proposed to be an antiglycating agent in bael.[43] Allium cepa (onion) is another plant which shows antidiabetic properties where various ether soluble fractions as well as insoluble fractions of dried onion powder have shown anti-hyperglycemic activity in diabetic rabbits.[44] Aloe vera (Ghritikumari) gel has also shown hypoglycemic effect in diabetic rats. This property of Aloe vera and its bitter principle is through stimulation of synthesis and/or release of insulin from pancreatic beta cells,[45] and thereby cure of Diabetes. Momordica charantia (Karela) extract of fruit pulp, seed, leaves and whole plant was shown to have hypoglycemic effect in various animal models.[46] The potent antiglycating agents include cucurbitane-type triterpenoids charantin (a steroidal glycoside), karavilose IX, momordicoside S etc.[47] The plant has been used as an antidiabetic and antihyperglycemic agent in India as well as other Asian countries for a long time. Tinospora cordifolia (Giloe) is widely used in Indian ayurvedic medicine for treating diabetes mellitus.[48] Studies have reported that oral administration of an aqueous T. cordifolia root extract to alloxan diabetic rats caused a significant reduction in blood glucose and brain lipids.[49] Therefore many combinations and polyherbal formulations are being used in treatment of Diabetes but the most important thing to be considered is proper identification, and authentication of the active ingredient in these formulations. This aspect is of much importance in determining the efficacy of the product.

Skin disease cure

Skin is the exposed and diverse organ of the human body. Skin features determine the internal health of an individual. Its appearance in the form of redness, itching, and inflammation can affect the psychic condition of the patient, and it is imperative to cure it by observing the underlying cause of chronic skin diseases. Inflammation, one of the responses, is provoked by pathogens, noxious mechanical and chemical agents, and autoimmune responses, and it is a complex process during which the body repairs tissue damage and defends itself against harmful stimuli.[50] One of the typical inflammation-based conditions is atopic dermatitis (atopic eczema), which is a chronic disease affecting people genetically inclined to overreact to external factors. It has been widely studied that plants can have an anti-inflammatory action affecting various stages of the process of inflammation. They inhibit formation of cytokines and eicosanoids, prevent the inflammatory reaction cascade from starting, and diminish skin flare, itching or excessive exfoliation.

Some of the plants widely used for treatment of skin disease include- Matricaria recutita L. (German chamomile) is the most known and commonly used medicinal plant. It contains the essential oil (the major components of which are α-bisabolol and its oxides A, B and C, matricin, which is converted to chamazulene by distillation and en-yn-dicycloethers) and flavone derivatives: apigenin, luteolin, and apigenin-7-glucoside.[51] These metabolites are responsible for treating eczema, dermatitis etc. Calendula officinalis L. (Marigold), is native to the Mediterranean countries. It has characteristic yellow-orange flower heads. The active ingredients of the calendula flower are triterpene saponins (oleanolic acid glycosides), triterpene alcohols (α-, β-amyrrins, faradiol), and flavonoids (quercetin and isorhamnetin).[52] and these are responsible for reducing inflammation conditions. Another important plant is Oenothera biennis L. (Evening primrose). The active ingredients of evening primrose oil are triglycerides of fatty acids, mainly γ-linolenic and linoleic acid.[53] Oenothera oil is administered internally in treatment and...
Premature Ovarian Failure (POF) - Ashoka, Dashmoola, Shatavari, Guduchi, Jeevanti etc.

Blocked fallopian tubes, adhesions (scar tissue) and pelvic inflammatory disease - Guduchi, Punarnava etc.

CONCLUSION

Secondary metabolites have gained a lot of interest among people for their effectiveness in control of chronic conditions, role in health promotion and their minimal side effects. These compounds are nowadays being produced at a large scale in industries in bioreactors to meet the increased demand of the masses. The high yield of these metabolites is being met by various traditional and modern techniques, including genetic engineering, use of elicitors, biotransformation etc. Usage of such techniques have enabled consistent production of these metabolites and their distribution in different health sectors. These bioactive compounds in minimal concentrations have shown to possess effective therapeutic properties in curing cancer, treatment of diabetes, skin care problems, infertility etc. In essence, invention of modern-day tools and techniques have resulted in enhanced production of these bioactive components with multifunctional roles.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

PTC: Plant tissue culture techniques; UV: Ultraviolet radiation; DADS: Diallyl disulphides; FSH: Follicle stimulating hormone; LH: Luteinizing hormone.

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