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Review Article

Phytochemicals 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 ailment 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.

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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

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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. Table 1.[6] Instead of using whole plants one can also use shoot or root cultures(differentiated organs) for the production of secondary metabolites as they produce the same results as given by the native plants. Those metabolites that are produced in roots of the plants can be generated through hairy root cultures of specific plants.

To further enhance the production of metabolite in plants, *Agrobacterium rhizogenes* mediated transformation has been used as it triggers hairy root formation in plants and also increases *in vitro* secondary metabolite production.[7,8] Proper biological scheme has been devised to increase production of metabolites like propane, nicotine, alkaloids and ginsenosides in plants.[9-11] Secondary metabolite production has many commercial applications therefore consistent production and high yields of these phytochemicals are two important aspects in this field. To increase the construction and yields of secondary metabolites both traditional and metabolic engineering approaches are used nowadays.

Traditional Techniques

Secondary metabolites are produced during primary metabolic reactions taking place in cells. Substrates from primary metabolic pathways are directed to secondary biosynthetic pathways for the production of these metabolites Their synthesis in plant cells depends upon both biotic and abiotic factors like growth, physiology, temperature, light intensity, humidity etc. *In vitro* cultures are dependent upon factors like media composition, inoculum density, pH, temperature, light intensity and duration etc. for the better production of these metabolites.[12] PTC techniques are dependent upon these factors such as choice of suitable culture media having appropriate amount of macro and micro nutrients, carbohydrates/sugars, amino acids, vitamins and plant growth regulators (auxins, cytokinins, gibberellins etc.) for appropriate and enhanced productivity of these metabolites.

Various biotechnological techniques have been used to enhance the production of secondary metabolites using elicitors (they trigger secondary metabolic pathways in plant cells which can be either biotic or abiotic depending upon their sources). Abiotic elicitors are part of inorganic compounds such as salts of heavy metals, metal oxides, metal ions etc.[13] Physical stresses (Osmotic, water stress, UV, cold shock etc.) induce high enzymatic activity during secondary metabolic production pathways.[14,15] Origin of biotic elicitors is from biological sources that could be exogenous 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 alkaloids, flavonoids, terpenoids and phenylpropanoids.[18,19] 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.[20,21]

Few plant pathogens like *Pythium, Fusarium, Trichoderma, Penicillium* etc., are extracted as fungal elicitors to trigger the production of secondary metabolites in plants.[22] *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*.[23] Terpenoid (indole alkaloids) production was increased in *Catharanthus roseus*.[24] using extract of *Aspergillus flavus*. For the production of tropane alkaloids in hairy root cultures of *Scopolia parviflora*.[25] 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.[26] In root cultures of *Laverniera cuneifolia*, glycyrrhizic acid production was increased using *Agrobacterium tumefaciens* and *Rhizobium leguminosarum* as bacterial elicitors.[27]

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.[28] 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, sesquiterpenoids, 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.[29] 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.[30] I-valine, which is an important drug precursor, is also synthesized through metabolic engineering.[30] 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.[31] 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-methyldigoxin 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.[31]

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.[32] 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]

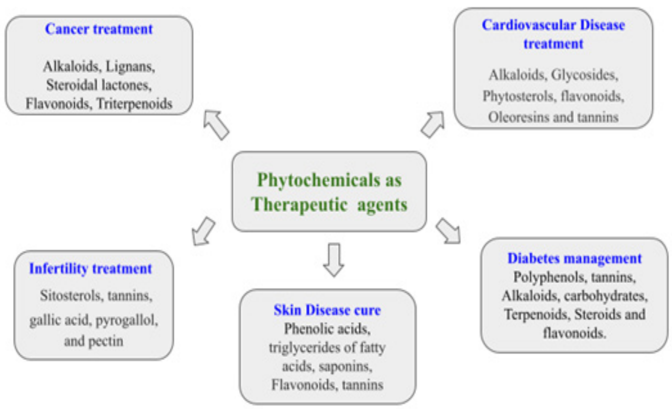

Figure 1: Diagram depicting various phytochemicals used in treatment of diseases.

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

Secondary metabolite	Type of *in vitro* culture	Plant name
Rosamic Acid	Cell suspension culture	*Salvia officinalis.*
Colchicine	Callus culture	*Gloriosa superba.*
Anthraquinones (Berberine, Nicotine, and Glutathione)	Callus culture	*Morinda citrifollia, Coptic japonica, Nicotiana tabacum.*
Artemisinin	Roots of higher plants	*Agrobacterium rhizogenes* and *Agrobacterium annua.*
Hypericin and Hyperforin	Shoots	*Hypericum perforatum.*
Saponin	Root suspension culture	*Gynostema pentaphyllum.*
Gallotannins	Root suspension culture	*Rhus javanica.*
Anthraquinone	Shoot multiplication	*Frangula alnus.*
Glycyrrhetic acid	Cell cultures	*Glycyrrhiza glabra.*

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, triterpenoic acid, betulinic 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] Brahmamanduki (*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 somnifera*), Deodar (*Cedrus deodara*) etc. with anticancer properties.[35] Several studies have focused on the chemoprotective activity of plants such as anticarcinogenic property of *Abrus precatorius* on Yoshida sarcoma in rats, fibrosarcoma in mice and ascites tumor cells.[38] Dhar *et al.*, (1968) have examined the anticancer properties of *Albizzia 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 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. Procyanins 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 (Ghritkumari) 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), karaviloside 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-amyrins, 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 alleviation of symptoms of atopic dermatitis. *Salvia officinalis* L. (Sage) Sage leaf contain phenolic acids (rosmarinic acid), triterpenoids acids (ursolic and oleanolic acid), essentials oil (monoterpenes) and catechin-type tannins (salviatannin). Sage leaf has astringent, bactericidal and anti-inflammatory properties. Ursolic and rosmarinic acids have been shown to possess anti-inflammatory activity *in vitro* and *in vivo*.[54]

Infertility treatment

There has been an enormous increase in Infertility in the past decade and it is due to the result of a combination of social, environmental, psychological, and nutritional factors.[55] The reasons behind this condition include improper weight, diet, smoking, medical conditions, environmental pollutants, medications and family medical history, infections and thereby might have an effect on conception in couples. Infertility can arise from either of the partners. Infertility is usually because of low numbers or poor quality of sperm in men whereas in women, it occurs when she is not able to produce eggs regularly or because her fallopian tubes are damaged or blocked and the sperm cannot reach her eggs.[56] Infertility itself does not stand alone. It is the result of some other disease. So, the herbs used in the treatment are directed towards eradicating the underlying cause. The most commonly known used herbs include Ashwagandha (*Withania somnifera*), which contain withanolides such as withaferin A, withanosides, sitoindosides, beta-sitosterol, and various amino acids like alanine that have more prominent effect on fertility status.[57] Shatavari (*Asparagus racemosus*) possess various chemical constituents such as Racemoside A, B, C, Shatavarins, Asparanin A which have role in fertility problems,[58] Amalaki (*Emblica officinalis*) contain several secondary metabolites such as emblicanin-A and emblicanin-B. In addition, tannins, gallic acid, pyrogallol, and pectin are also present in significant amounts and play significant role in infertility treatment.[59] The tree is used in preparing extremely useful formulations which help to create the synergistic hormonal balance between the Follicle Stimulating Hormone (FSH) and the Luteinizing Hormone (LH).

No individual herb alone is considered useful for promoting fertility. Therefore, a combination of herbs is used in the treatment of infertility with the purpose of correcting an organic or functional problem that causes infertility.

Ayurvedic herbs used in the treatment for infertility: It has been observed that no single herb can bring about the treatment of fertility but it is always used in combination with others for correcting the underlying problem associated with infertility. Some of the examples of herbs used in combination with other herbs include-

Ovulation disorder - Ashoka, Dashmoola, Shatavari, Ghritkumari, Guggulu etc.

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.

REFERENCES

1. Gijtenbeek JM, van den Bent MJ, Vecht CJ. Cyclosporine neurotoxicity: a review. J Neurol. 1999;246(5):339-46. doi: 10.1007/s004150050360, PMID 10399863.
2. Pathak N, Rai AK, Kumari R, Bhat KV. Value addition in Sesame: A perspective on bioactive components for enhancing utility and profitability. Pharmacogn Rev. 2014;8(16):147-55. doi: 10.4103/0973-7847.134249, PMID 25125886.
3. Chen JT. Phytochemical omics in Medicinal plants. Biomolecules. 2020;10(6):1-7. doi: 10.3390/biom10060936, PMID 32575904.
4. Sandra G, Anabela R. Production of plant secondary metabolites by using biotechnological tools, secondary metabolites – Sources and applications. In: Vijayakumar R, editor. Secondary metabolites Sources and applications; 2018, Intech Open.. doi: 10.5772/intechopen.79766.
5. Hussein R, El-Anssary AA. Plants secondary metabolites: the key drivers of the pharmacological actions of medicinal plants. Herb Med. 2018, Intech Open:11-30. doi: 10.5772/intechopen.76139.
6. Efferth T. Biotechnology applications of plant callus cultures. Engineering. 2019;5(1):50-9. doi: 10.1016/j.eng.2018.11.006.

7. Chen L, Cai Y, Liu X, Guo C, Sun S, Wu C, *et al.* Soybean hairy roots produced *in vitro* by *Agrobacterium rhizogenes*-mediated transformation. Crop J. 2018;6(2):162-71. doi: 10.1016/j.cj.2017.08.006.
8. Palazón J, Piñol MT, Cusido RM, Morales C, Bonfill M. Application of transformed root technology to the production of bioactive metabolites, Recent Res. Dev. Plant Physiol. 1997;1:125-43.
9. Zhang L, Ding R, Chai Y, Bonfill M, Moyano E, Oksman-Caldentey KM, *et al.* Engineering tropane biosynthetic pathway in *Hyoscyamus niger* hairy root cultures. Proc Natl Acad Sci U S A. 2004;101(17):6786-91. doi: 10.1073/pnas.0401391101, PMID 15084741.
10. Yu KW, Murthy HN, Hahn EJ, Paek KY. Ginsenoside production by hairy root cultures of *panax ginseng*: influence of temperature and light quality. Biochem Eng J. 2005;23(1):53-6. doi: 10.1016/j.bej.2004.07.001.
11. Ha LT, Pawlicki-Jullian N, Pillon-Lequart M, Boitel-Conti M, Duong HX, Gontier E. Hairy root cultures of *Panax vietnamensis*, a promising approach for the production of ocotillol-type ginsenosides. Plant Cell Tiss Organ Cult. 2016;126(1):93-103. doi: 10.1007/s11240-016-0980-y.
12. Ochoa-Villarreal M, Howat S, Hong S, Jang MO, Jin YW, Lee EK, *et al.* Plant cell culture strategies for the production of natural products. BMB Rep. 2016;49(3):149-58. doi: 10.5483/bmbrep.2016.49.3.264, PMID 26698871.
13. Isah T, Umar S, Mujib A, Sharma MP, Rajasekharan PE, Zafar N, *et al.* Secondary metabolism of pharmaceuticals in the plant *in vitro* cultures: strategies, approaches, and limitations to achieving higher yield. Plant Cell Tiss Organ Cult. 2018;132(2):239-65. doi: 10.1007/s11240-017-1332-2.
14. Gorelick J, Bernstein N. Elicitation: an underutilized tool in the development of medicinal plants as a source of therapeutic secondary metabolites. In: Sparks DL, editor. Advances in agronomy. Amsterdam, The Netherlands: Elsevier; 2014, 124. p. 201-30.
15. Ramirez-Estrada K, Vidal-Limon H, Hidalgo D, Moyano E, Golenioswki M, Cusidó RM, *et al.* Elicitation, an effective strategy for the biotechnological production of bioactive high-added value compounds in plant cell factories. Molecules. 2016;21(2):182. doi: 10.3390/molecules21020182, PMID 26848649.
16. Zhao J, Davis LC, Verpoorte R. Elicitor signal transduction leading to production of plant secondary metabolites. Biotechnol Adv. 2005;23(4):283-333. doi: 10.1016/j.biotechadv.2005.01.003, PMID 15848039.
17. Tiku AR. Antimicrobial compounds and their role in plant defense in Molecular aspects of Plant Pathogen interaction; 2018:283-307.
18. van der Fits L, Memelink J. Van der Fits L and Memelink J. ORCA3, a jasmonate responsive transcriptional regulator of plant primary and secondary metabolism. Science. 2000;289(5477):295-7. doi: 10.1126/science.289.5477.295, PMID 10894776.
19. Giri CC, Zaheer M. Chemical elicitors versus secondary metabolite production *in vitro* using plant cell, tissue and organ cultures: recent trends and a sky eye view appraisal. Plant Cell Tiss Organ Cult. 2016;126(1):1-18. doi: 10.1007/s11240-016-0985-6.
20. Siddiqui MS, Thodey K, Trenchard I, Smolke CD. Advancing secondary metabolites in yeast with synthetic biology tools. FEMS Yeast Res. 2012;12(2):144-70. doi: 10.1111/j.1567-1364.2011.00774.x, PMID 22136110.
21. Singh A, Dwivedi P. Methyl-jasmonate and salicylic acid as potent elicitors for secondary metabolite production in medicinal plants: a review. J Pharmacogn Phytochem. 2018;7:750-7.
22. Takeuchi C, Nagatani K, Sato Y. Chitosan and a fungal elicitor inhibit tracheary element differentiation and promote accumulation of stress lignin-like substance in *Zinnia elegans* xylogenic culture. J Plant Res. 2013;126(6):811-21. doi: 10.1007/s10265-013-0568-0, PMID 23732634.
23. Chodisetti B, Rao K, Gandi S, Giri A. Improved gymnemic acid production in the suspension cultures of *Gymnema sylvestre* through biotic elicitation. Plant Biotechnol Rep. 2013;7(4):519-25. doi: 10.1007/s11816-013-0290-3.
24. Liang C, Chen C, Zhou P, Xu L, Zhu J, Liang J, *et al.* Effect of *Aspergillus flavus* fungal elicitor on the production of terpenoid indole alkaloids in *Catharanthus roseus* cambial meristematic cells. Molecules. 2018;23(12):3276. doi: 10.3390/molecules23123276, PMID 30544939.
25. Jung HY, Kang SM, Kang YM, Kang MJ, Yun DJ, Bahk J, *et al.* Enhanced production of scopolamine by bacterial elicitors in adventitious hairy root cultures of *Scopolia parviflora*. Enzyme Microb Technol. 2003;33(7):987-90. doi: 10.1016/S0141-0229(03)00253-9.
26. Taurino M, Ingrosso I, D'amico L. Jasmonates elicit different sets of stilbenes in *Vitis vinifera* cv. Negramaro cell cultures. SpringerPlus. 2003, 49.
27. Vithal A, Aniket K, Abhay H. Microbial elicitation in root cultures of *Taverniera cuneifolia* (Roth) Arn. for elevated glycyrrhizic acid production. Ind Crops Prod. 2004;54:13-6. doi: 10.1016/j. indcrop.2013.12.036.
28. DellaPenna D. D. Plant metabolic engineering. Plant Physiol. 2001;125(1):160-3. doi: 10.1104/pp.125.1.160, PMID 11154323.
29. Bertoli A, Ruffoni B, Pistelli L, Pistelli L. Analytical methods for the extraction and identification of secondary metabolite production in '*in vitro*' plant cell cultures. In: Bio-Farms for nutraceuticals. Boston: Springer; 2010:250-66. doi: 10.1007/978-1-4419-7347-4_19, PMID 21520717.
30. Jeong GT, Park DH. Enhanced secondary metabolite biosynthesis by elicitation in transformed plant root system: effect of abiotic elicitors. Appl Biochem Biotechnol. 2006; 129-132: 436-46. doi: 10.1385/abab:130: 1:436, PMID 16915660.
31. Gaspar T, Kevers C, Penel C, Greppin H, Reid DM, Thorpe TA. Plant hormones and plant growth regulators in plant tissue culture. *In vitro* Cell. Dev.Biol.-Plant. 1996;32(4):272-89. doi: 10.1007/BF02822700.
32. Pathak N. Traditional knowledge and its role in biodiversity conservation. J Agroecol Natl Resour Manag. 2022;9(1):39-42.
33. Ogunmefun OT, Chapter 2 Asao T, Asaduzzaman Md, editors. Phytochemicals- God's endowment of curative Power in Plants in Phytochemicals: source of antioxidants and role in disease prevention; 2018:1-19.
34. Wang H, Khor TO, Shu L, Su ZY, Fuentes F, Lee JH, *et al.* Plants vs. cancer: a review on natural phytochemicals in preventing and treating cancers and their druggability. Anti-Cancer Agents Med Chem. 2012;12(10):1281-305. doi: 10.2174/187152012803833026, PMID 22583408.
35. Desai AG, Qazi GN, Ganju RK, El-Tamer M, Singh J, Saxena AK, *et al.* Medicinal plants and cancer chemoprevention. Curr Drug Metab. 2008;9(7):581-91. doi: 10.2174/138920008785821657, PMID 18781909.
36. Varma A, Padh H, Shrivastava N. Andrographolide: a new plant-derived antineoplastic entity on horizon. Evid Based Complement Alternat Med. 2011; 2011:815390. doi: 10.1093/ecam/nep135, PMID 19752167.
37. Aggarwal BB, Kumar A, Bharti AC. Anticancer potential of curcumin: preclinical and clinical studies. Anticancer Res. 2003; 23(1A):363-98. PMID 12680238.
38. Reddy VV, Sirsi M. Effect of *Abrus precatorius* L. on experimental tumors. Cancer Res. 1969;29(7):1447-51. PMID 5799161.
39. Dhar ML, Dhar MM, Dhawan BN, Mehrotra BN, Ray C. Screening of Indian plants for biological activity: I. Indian J Exp Biol. 1968;6(4):232-47. PMID 5720682.
40. Rastogi S, Pandey MM, Rawat AK. Traditional herbs: a remedy for cardiovascular disorders. Phytomedicine. 2016;23(11):1082-9. doi: 10.1016/j.phymed.2015.10.012, PMID 26656228.
41. Toma L, Sanda GM, Niculescu LS, Deleanu M, Sima AV, Stancu CS. Phenolic compounds exerting lipid-regulatory, anti-inflammatory and epigenetic effects as complementary treatments in cardiovascular diseases. Biomolecules. 2020;10(4):641. doi: 10.3390/biom10040641, PMID 32326376.
42. Kamalakkannan N, Stanely Mainzen Prince P. Effect of *Aegle marmelos* Correa. (Bael) fruit extract on tissue antioxidants in streptozotocin diabetic rats. Indian J Exp Biol. 2003;41(11):1285-8. PMID 15332498.
43. Panaskar SN, Joglekar MM, Taklikar SS, Haldavnekar VS, Arvindekar AU. *Aegle marmelos* Correa leaf extract prevents secondary complications in streptozotocin-induced diabetic rats and demonstration of limonene as a potent antiglycating agent. J Pharm Pharmacol. 2013;65(6):884-94. doi: 10.1111/jphp.12044, PMID 23647682.
44. Mathew PT, Augusti KT. Hypoglycaemic effects of onion, *Allium cepa* Linn. on diabetes mellitus – a preliminary report. Indian J Physiol Pharmacol. 1975;19(4):213-7. PMID 1223000.
45. Ajabnoor MA. Effect of aloes on blood glucose levels in normal and alloxan diabetic mice. J Ethnopharmacol. 1990;28(2):215-20. doi: 10.1016/0378-8741(90)90031-n, PMID 2109811.
46. Khanna P, Jain SC, Panagariya A, Dixit VP. Hypoglycemic activity of polypeptide- p from a plant source. J Nat Prod. 1981;44(6):648-55. doi: 10.1021/np50018a002, PMID 7334382.
47. Tan MJ, Ye JM, Turner N, Hohnen-Behrens C, Ke CQ, Tang CP, *et al.* Antidiabetic activities of triterpenoids isolated from bitter melon associated with activation of the AMPK pathway. Chem Biol. 2008;15(3):263-73. doi: 10.1016/j.chembiol.2008.01.013, PMID 18355726.
48. Stanely Mainzen Prince P, Menon VP. Antioxidant action of *Tinospora cordifolia* root extract in alloxan diabetic rats. Phytother Res. 2001;15(3):213-8. doi: 10.1002/ptr.707, PMID 11351355.
49. Prince PS, Menon VP. Antioxidant activity of *Tinospora cordifolia* roots in experimental diabetes. J Ethnopharmacol. 1999;65(3):277-81. doi: 10.1016/s0378-8741(98)00164-0, PMID 10404427.
50. Ikeda Y, Murakami A, Ohigashi H. Ursolic acid: an anti- and pro-inflammatory triterpenoid. Mol Nutr Food Res. 2008;52(1):26-42. doi: 10.1002/mnfr.200700389, PMID 18203131.
51. ESCOP Monographs. Matricariae flos. 2nd ed. New York: Thieme; European Scientific Cooperative on Phytotherapy; 2003:312-9.
52. EMEA, European Medicines Agency. London: *Calendula officinalis* L., Flos; 2008.
53. Schulz V, Hänsel R, Blumenthal M, Tyler VE. Rational phytotherapy. Berlin, Heidelberg: Springer-Verlag; 2004:335-47.
54. Blumenthal M, Goldberg A, Brinckann J. Sage leaf. Newton: American botanical council. Expanded Commission E Monographs. Herb Med. 2000:330-3.
55. Oberoi A, Lal PR, Rishi P. Ayurvedic concepts of female fertility-A Review. Int. J. Ayurvedic. Herb Med. 2016;6:2313-20.
56. Walker MH, Tobler KJ. Female infertility. StatPearls [Internet]. 2022; 2023.

57. Ambiye VR, Langade D, Dongre S, Aptikar P, Kulkarni M, Dongre A. Clinical Evaluation of the Spermatogenic Activity of the Root Extract of Ashwagandha (*Withania somnifera*) in oligospermic Males: A Pilot Study. Evid Based Complement Alternat Med. 2013; 2013:571420. doi: 10.1155/2013/571420, PMID 24371462.
58. Thakur S, Kaurav H, Chaudhary G. Shatavari (*Asparagus racemosus*) – The best female reproductive tonic. Int J Res Rev. 2021;8(5):73-84. doi: 10.52403/ijrr.20210511.
59. Gantait S, Mahanta M, Bera S, Verma SK. Advances in biotechnology of *Emblica officinalis* Gaertn. syn. *Phyllanthus emblica* L.: a nutraceuticals-rich fruit tree with multifaceted ethnomedicinal uses. Biotech. 2021;11(2):62. doi: 10.1007/s13205-020-02615-5, PMID 33489680.

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