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Dr. Arshad H. Rizvi

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Exploring the Biochemical Basis of Plant-Derived Therapeutics: An Overview

Arshad H. Rizvi and Mohd. Zahid Rizvi
Department of Botany, Shia P.G. College, Lucknow, U.P., India

ABSTRACT

Medicinal plants are a dreadful resource for drug development. To date, various plant-derived drugs are used throughout the world. In recent years, great interest in secondary metabolite production has led to the possibility of altering the production of bioactive compounds *via* tissue culture technology. Various medically important secondary metabolites include alkaloids, glycosides, flavonoids, volatile oils, tannins, resins, etc. Due to lack of understanding of how these metabolites are synthesized, biotechnological production through plant cell cultures is an attractive alternative and was introduced at the end of the 1960's as a possible tool for studying as well as producing plant secondary metabolites. Besides this, there are different techniques that have been discussed in the present chapter that are used to enhance the synthesis of secondary metabolites by the plants. The focus of the present chapter is to discuss the application of different technologies for the production of some important medically plant derived bioactive compounds.

Keywords: Medicinal plants; Secondary metabolites; Plant products; Biochemistry; Biochemical pathway.

INTRODUCTION

Throughout the world's population, most mere source of life-saving drugs are medicinal plants. Since the early days, infections, health disorders and illness treatments involve plants having secondary metabolites used by humans. During the last several years, a synthetic drug has replaced natural products. Several of the ergastic phytochemicals such as alkaloids and cardiac glycosides etc have been isolated and are used as remedy against different aliment/disease (Wink et al. 2005). Plants extracted bioactive compounds currently using as fine chemicals, cosmetics and perfumes, pigments, insecticides, dyes, and food additives (Balandrin and Klocke, 1988).

These plants extracted bioactive compounds pertain to a group collectively known as secondary metabolites. These molecules delineate an important source of pharmaceuticals (Rao and Shankar, 2002). In recent years, traditional systems of medicine has become a hot theme for global importance and embolden scientists as well as industries to ponder the possibilities in to cell cultures as an alternative supply for the production of plant phytochemicals. Application of biotechnology into the plant cell cultures provided new way for the commercial purpose of even rare plants. Due to requisition of secondary phytochemicals products as a natural drug, scientist exploring new research methodology to produce large amount of secondary product expression *in vitro*. *In vitro* cultures provide an excellent path for mysterious investigation of metabolic and biochemical pathways and produces only metabolite of interest in specialized plant tissues or glands, for example vanillin and taxol production *in vitro*. Large scale culturing of desired plant cells producing metabolite of interest can be achieved by cell culture technology. Plant cell culture derived extracts can be refer in each of under mentioned general product categories: flavors (onion and garlic, peppermint and spearmint, fruit flavors, chocolate aroma, seaweed flavors, vanilla, celery, coffee, spice, sweeteners, and so on); edible colors for foods and medicines (mainly betalains and anthocyanins); non-food pigments for cosmetics and textiles (shikonin, berberine, and various other products); several examples of fragrances and essential oils; and bioactive natural insecticides and phytoalexins useful in pest management. Phytochemical products include ajmalicine (a drug for circulatory problems) from *C. roseus* and taxol (a phytochemical effective in treatment of ovarian cancer) from *Taxus* species currently produced in large amount via cell cultures techniques. The advantages of cell culture technology can ultimately provide an uninterrupted and faithful source of natural product.

MAJOR PHYTOCONSTITUENTS

Phenolics

Phenolics are one of the most promiscuous and ubiquitously distributed group of naturally occurring phytoconstituents, all of which having an aromatic ring bearing structure at least one hydroxyl substituent (a phenol). Phenolics commonly found in herbs, fruit, vegetables, grains, tea coffee beans, and red wine. A beneficial biological activity of phenolics in mammals includes antiviral, antibacterial, immune-stimulating, antiallergic, anti hypertensive, anti ischemic, anti arrhytmic, anti thrombotic, hypocholesterolemic, anti lipoperoxidant, hepatoprotective, anti-inflammatory, and anti-carcinogenic actions (Kumar and Pandey, 2013). The medicinal property of phenolics is mostly ascribed to their antioxidant capacity, modulation of gene expression and interaction with the cell signaling pathways. The antioxidant capacity of phenolic compounds is also attributed to their ability to chelate metal ions involved in the production of free radicals (Kumar and Pandey, 2013). Phenolic structures have capability to strongly interact with proteins, due to their hydrophobic benzenoid rings and hydrogen-bonding virtue of the phenolic hydroxyl groups. These exquisite properties of Phenolics gives the ability to act as antioxidants also by virtue of their capacity to inhibit some enzymes involved in radical generation, such as various cytochrome P450 isoforms, lipoxygenases, cyclooxygenase and xanthine oxidase. Phenolics are also capable of acting in redox-sensitive signaling cascades to inhibit DNA damage.

Therefore, phenolics may be beneficial to preventing UV-induced oxygen free radical generation and lipid peroxidation. Phenolics can modulate transcriptional factors such as AP-1 (activator protein-1). It can control the expression of various genes implicated in inflammation processes, cell differentiation, and proliferation. Phenolics may prevent oxidative stress induced mitochondrial transition pore complex opening by decreasing production of Bax and Bad protein (Mandel and Youdim, 2004). Phenolics are also involved in activation of several protein kinases, phase II antioxidant detoxifying enzymes and modulation of several cell survival/cell-cycle genes.

Table 1. List of phytoconstituents having medicinal property

Phytoconstituents	Medicinal property	References
Morphine	Pain killer	Wink et al., 2005
Codeine	Antitussive	Wink et al., 2005
Papaverine	Phosphordiesterase inhibitor	Wink et al., 2005
Ephedrine	Stimulant	Wink et al., 2005
Ajmaline	Antirrhythmic	Wink et al., 2005
Quinine	Antimalarial	Wink et al., 2005
Reserpine	Antihypertensive	Wink et al., 2005
Galanthamine	Acetylecholine esterase inhibitor	Wink et al., 2005
Scopolamine	Travel sickness	Wink et al., 2005
Berberine	Psoriasis	Wink et al., 2005
Caffeine	Stimulant	Wink et al., 2005
Pilocarpine	Glaucoma	Wink et al., 2005
Yohimbine	Aphrodisiac	Wink et al., 2005
Colchicines	Gout	Wink et al., 2005
Capsaicin	Rheumatic pains	Wink et al., 2005

Flavonoids

Flavonoids (a natural substances) mainly presents in fruit, vegetables, grains, bark, roots, stems, flowers, tea, and wine. More than 4000 varieties of flavonoids have been identified (Kumar and Pandey, 2013). The primary flavonoid structure is the flavan nucleus, which consists of 15 carbon atoms grouped in three rings (C6-C3-C6), which are labeled A, B, and C (Figure 1). The various classes of flavonoids (flavones, flavanones, isoflavones, flavonols, flavanonols, flavan-3-ols and anthocyanidins) differ in the level of oxidation and pattern of substitution of the C ring, while individual compounds with in a class differ in the pattern of substitution of the A and B rings (Kumar and Pandey, 2013). They generally occur in plants as glycosylated derivatives. All type of these flavonoids has capability to act as antioxidants. The flavones and catechins are very important and powerful flavonoids for protecting the body against reactive oxygen species (ROS). Flavonoids also chelate metal ion results removal of causal factor for the development of free radicals. The proposed binding sites for trace metals to flavonoids in different rings of their structure are shown in figure 2 (Kumar and Pandey, 2013).

Free metal ions are potential enhancers of ROS formation, as Illustrated by the reduction of hydrogen peroxide with generation of the highly aggressive hydroxyl radical.

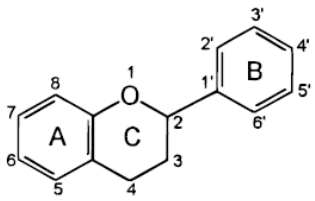

Figure 1. Basic flavonoid structure.

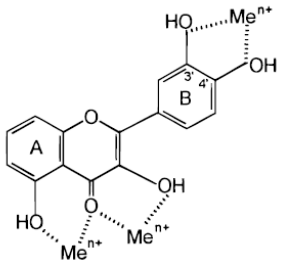

Figure 2. Binding sites for trace metals.

Flavonoids are thermodynamically able to reduce highly oxidizing free radicals such as superoxide, peroxyl, alkoxyl, and hydroxyl radicals by hydrogen atom donation (Kumar and Pandey, 2013) due to their lower redox potentials. The chief determinants for radical-scavenging potency of flavonoids are:

A. Catechol group in ring B is a radical target and has the better electron donating properties.

B. A 2, 3- double bond conjugated with the 4-oxo group, which is responsible for electron delocalization. The presence of a 3-hydroxyl group in the heterocyclic ring also increases the radical-scavenging activity, while additional hydroxyl or methoxyl groups at positions 3, 5 and 7 of rings A and C seem to be less important (Kumar and Pandey, 2013).

Complement activation reduction can be achieved by flavonoids, decreasing the adhesion of inflammatory cells to the endothelium and in general resulting in a reduced inflammatory response. Reduction in the release of peroxidase is another feature of flavonoids. This reduction prevents the origination of ROS by neutrophils. Anti inflammatory and anti thrombogenic properties of flavonoids is due to their inhibitory effect on arachidonic acid metabolism (initiation point for inflammation). Retrogression the creation of inflammatory metabolites occurs due to quercetin, which fend both cyclooxygenase and lipoxygenase activities (Kim et al., 1998). Flavonoids also have potency to prevent cytosolicas well as membranal tyrosine kinase ultimately results into the inhibition of uncontrolled cell growth and proliferation (cancer). Some flavonoids (fisetin, apigenin, and luteolin) may be potent resistor of cell proliferation. Antioxidant systems are frequently insufficient, and damage from ROS is proposed to be involved in carcinogenesis. Herpes simplex virus, respiratory syncytial virus, parainfluenza virus, and adenovirus viruses impressed by flavonoids are reported in literature.

Tannins

The term tannin refers to large polyphenolic compound groups containing sufficient hydroxyls and other suitable groups (such as carboxyls). These groups can form strong complexes with proteins and other macromolecule. Hydrolysable tannins (polymers of ellagic acid, or of gallic and ellagic acids with glucose) and condensed tannins are the two distinct groups of tannin. Formation of tannins includes amalgamation of catechin monomers (called proanthocyanidins) and units of glucose, gallic and/or ellagic acid with ester bond and collectively known as hydrolysable tannins. Important active principles of red latex containing species are proanthocyanidins.

Scavenging free radicals, chelating trace metals and by binding proteins with suppression of their enzymatic activity exerted by their antioxidant activity. The scavenging activity of tannins increases with an increase in the number of galloyl groups and molecular weight and in the existence of an *ortho*-dihydroxy structure: the hydroxyl groups are responsible for the chelating and radical scavenging properties of these compounds (Yokozawaet al.1998). The capacity of tannins to enhance glucose uptake and inhibit adipogenesis have been recently envisaged and being as a potential drugs for the treatment of non-insulin dependent diabetes mellitus. In particular proanthocyanidins aid in lowering plasma cholesterol levels, inhibit LDL oxidation, and activate endothelial nitric oxide synthase to prevent platelet adhesion and aggregation that allow to blood clot formation.

Terpenoids

Terpenes are also one of the important plant secondary metabolites as natural products. The isoprene unit is a five-carbon molecule which can arrange itself in various paths. An isoprene unit bonded with a second isoprene is the expressing characteristic of terpenes. The single isoprene unit delineates the most basic class of terpenes, the hemiterpenes (C5). Monoterpenes (C10), sesquiterpenes (C15), diterpenes (C20), sesquiterpenes (C25), triterpenes (C30), and polyterpenes (>C30) are the different other types of terpenes. Terpenes are the most promiscuous and structurally diverse plant natural products (Figure 3). Based on their numbers and diversity, terpenes offer much potency in an array of industrial and medicinal applications.

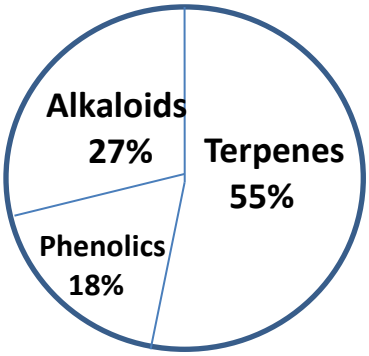

Figure 3. Pie chart representing the major groups of plant secondary metabolites.

Alkaloids

Around 16,000 alkaloids are known to found in many plant families (Solanaceae and Apocynaceae where 60-70% of these species accumulate alkaloids) in which 10,000 alkaloids are known minimally (20-30% of all plant species layup alkaloids). Plants having alkaloids can be used as dyes, spices, and drugs. First alkaloid having its explored structure and to be synthesized was coniine. *Catharanthus* alkaloids and paclitaxel exhibit anticancer properties as well as anti-aging and antiviral perspective. Tubarine, Metubine Iodine, Tubadil and Mecostrin are the different form of tubocurarine alkaloid is available in the market and used as a drug. These drugs are employed as relaxants of skeletal muscles during surgery to control convulsions. Specifically, the alkaloid interferes with the activity of acetylcholine at the surface where it functions, thereby blocking the neuromuscular junction (Dewick, 2002).

Saponins

Massive group of glycosides called saponins are widely dispersed in higher plants. A property having surface activity distinguishes it from other glycosides. Shaking with water, the saponins form colloidal solutions with some foam. Saponins are main ingredient of many plant drugs and folk medicines, and also are amenable for various pharmacological characters. Classification of saponins grouped into two groups (based on the nature of aglycone skeleton). The first group consists of the steroidal saponins, which are merely present in the monocotyledonous angiosperms. The second group consists of the triterpenoid saponins, which are the most common and occur mainly in the dicotyledonous angiosperms (Bruneton, 1995). *Bupleurumfruticescens* (Apiaceae) have Saikosaponins and fruticesaponin B in their root and has been traditionally used to treat inflammation associated disorders. Vindicatory action of saponins present in *Panaxvietnamensis* (Araliaceae) contrary free radical-induced tissue injury depicting their antioxidant activity (Huong et al. 1998). Antimicrobial, antifungal, antiviral, molluscidal, anti-ulcerogenic, wound healing and hepatoprotective activity have been reported in various literatures. Shikimic acid pathway (phenylpropanoids), movalonic acid pathway (quinones), 2-C-methyl-D-erythritol-4-phosphate pathway (quinones), amino acid pathway (alkaloids), acetate-malonate pathway (fatty acid, phenols and quinones) and combined pathways (flavonoids) are the common biosynthetic pathways for secondary metabolite production in numerous plants. Secondary metabolite compounds delineate crucial role in defensing herbivores, insects, pathogens, competing with other plants, and facilitating pollination and reproduction. They act as a defense chemicals.

Table. 2 Classification of secondary metabolite based on nitrogen availability.

Nitrogen-containing	Without nitrogen
Alkaloids	Monoterpenes including iridoids,Diterpenes, Triterpenes, Tetraterpenes
Non-protein amino acids (NPAAS)	Sesquiterpenes
Amines	Steroids, Saponins
Cyanogenic glycoside	Flavonoids, Phenylpropanoids,
Glucosinolates	Tannins, Lignin, Coumarins,
Alkamides	Polyacetylenes, Fatty acid, Waxes, Carbohydrates, Organic acids
Lectins,peptides,polypeptide	Anthraquinones and othespolyketides

Production of secondary metabolites by enzymes

Enhancement the production of secondary metabolite can be achieved by gene cloning and transformation in biosynthetic pathway of secondary metabolites. The biosynthetic pathway and gene regulation research of vinblastin and vincristine, anticancer compounds from *Catharanthusroseus*, is a representative example. Due to the low contents of these two compounds in naturally growing plant, it becomes important to clone and regulate expression of key genes [DXR (1-deoxy-D-xylulose 5-phosphate reductoisomerase), SLS (Secologanin synthase), G10H (Geraniol 10-hydroxylase), STR (Strictosidine synthase)] involved in the pathway, in order to obtain high yield of these two compounds in *in vitro*, which will be based on well understanding of terpenoid indole alkaloids biosynthesis in *C. roseus* (Mei et al.2007).

Rapid amplification of complementary DNA (cDNA) ends polymerase chain reaction (RACE PCR) and Reverse transcription polymerase chain reaction (RT-PCR) needs at least partial gene sequence information from other plant species to synthesize degenerate primers. Reported reference is important to able to be work well. Underneath this condition, library based method can be selected for gene cloning however, the library based methods are non specific enough like bacterial artificial chromosome (BAC) library and cDNA library because of the low proportion of genes involved in secondary metabolism in total mRNAs expression. Functional genomics provides useful methods incloning the particular genes involved in the secondary metabolism, such as Subtractive hybridization 'Differential screening' Microarray assay and Serial Analysis of Gene expression. Functional genomics focused on the selection of treatment responsive genes and to clone genes involved in the biosynthetic pathways, the treatments need to be specific enough to result in the improvement of target secondary metabolites.

Introduction of common elicitors in the biosynthetic pathway

In plant cells hypersensitive reaction can be triggered by Elicitors. They are used widely in medicinal plant cell and tissue culture to maximize the production of target compounds. Elicitors may be either biotic or abiotic. Juxtaposition to abiotic, biotic elicitor attracted much more meditation due to their advantages of low cost, little side effects, strong elicitation effects and easy manipulation. The former one includes fugal polysaccharides, proteins, cell debris and conidium (Table 3). These kinds of elicitors are made from cultured fungi and some species are specific for specific kinds of secondary metabolites accumulation. In plant cell/organ culture, it is believed that, treated cells/organs with elicitors at the stabilization stage can increase the accumulation of secondary metabolites.

Table 3. Brief introduction of common elicitors.

Common elicitors	Description	Secondary Metabolite	References
Lipopolysaccharides	Found on the surface of gram-negative bacteria cell wall	Pseurotin A, A_1 and A_2, Shornephine A, Neoasterriquinone	Meyer et al. 2001
Elicitins	Secreted by phytopathogenicmicroorganisms belonging to the *Phytophthora* and *Pythium* species	Phytoalexins	Ricci et al. 1989
Flg22	Hollow cylinder arrangements of Flg22 proteins to form the filament in bacterial flagellum	Glucosinolate	Gomez et al. 1999

Oligogalacturonides	Oligomers of α-1,4-linked galacturonosyl residues released from plant cell walls upon partial degradation of homogalacturonan	Phytoalexins and lignin production	Hahn et al. 1981
Pep-13	Pep-13 compose a surface-exposed fragment within a novel Ca^{2+}-dependent cell wall transglutaminase (TGase) from *Phytophthorasojae*	Phytoalexin induction	Brunner et al. 2002
β-glucan	β-glucan, non-starch polysaccharides composed of glucose molecules in long linear glucose polymers with mixed β-(1→4) and β-(1→3) links.	Glyceollins, Apigenin, Genistein, Luteolin	Modolo et al. 2002
Chitosan	A linear polysaccharide composed of randomly distributed β-(1-4)-linked D-glucosamine(deacetylated unit) and N-acetyl-D-glucosamine (acetylated unit).	Rutacridone epoxide	Eilert, et al. 1984
Salicylic acid	Medicinal properties having fever relief, and used as an anti-inflammatory drug.	Chitinase	Muller et al. 1994
Xylanase	It is an enzyme that catalyzes the hydrolysis of 1,4-beta-D-xylosidic linkages in xylans that are constituents of hemicellulose, a structural component of plant cell walls	Xylan	Lotan et al. 1990
Sacharomycescerevisiae	Promote accumulation of specific kind of secondary metabolites in target plant	Berberine	Jeong et al. 2006

Yeast extract	Promote accumulation of specific kinds of secondary metabolites in target plant	Capsidiol, debneyol, scopoletin,Nicotine, Ajmalicine,Diterpenoid, tanshinonesSilymarin, Beta-amyrin,Diterpenoid, tanshinones	Wibberley et al. 1994
Verticillium dahlia	Promotes accumulation of specific kinds of secondary metabolites in target plant	Dopamine	Cline et al.1993
Pythiumaphanidermatum	Promotes accumulation of specific kinds of secondary metabolites in target plant	Alkaloids (indole)	Moreno et al. 1993
Copper sulphate	-	Phytoalexin	Mader et al. 1993

Precursor feeding

In a biosynthetic pathway there is a series of events where one substrate is used as precursor to produce next product, which in turn act as precursor for the subsequent product of the target compound pathway. Precursor's amount will decide the rate of reaction. At higher concentration, the reaction speed isusually higher than that when precursor concentration is lower. Precursor also can inhibit cell growth and enzyme activity if concentrationis too high even sometimes toxic for cells. Precursors can be fed in the media and as the cell grows secondary metabolites synthesized.

Inhibitors of undesired metabolites of particular biosynthetic pathway

In most medicinal plants there are severaltypes of secondary metabolites accumulated. For example, there are about 50 terpenoids, 15 flavonoids, 20 phenylpropanoids, 15 fatty acid and 35 glucosinolates have been reported in *A. thaliana* (Auria et al. 2005). Genetic transformation scheme have been used to renovate the accumulation of one specific kind of compounds having relevant medicinal property and blocking the other biosynthetic routes. Treatments of cells with specific enzyme inhibitors, the enzyme activity will be specifically inhibited, and result in the corresponding consequences. Correlation analysis between enzyme activityand target compounds accumulation can show the contribution of specific enzyme in the biosynthetic pathway of target compounds. Specific inhibitor treatment blocking the competitive branch, more carbon flux will be channeled to the biosynthesis of target compounds, and result in the improved accumulation. Furthermore, if the cells are treated with specific inhibitors, the enzyme activity will be inhibited, and the upstream compounds can be consequently accumulated at higher concentration which will facilitate the identification and characterization of key intermediates.

Techniques involved in the biochemical pathway

To date, there are agglomerations of plant species whose genome has been sequenced, such like *Arabidopsis thianalia*, *Oryza sativa*, *Artemisia annua* and so on. Various genetic techniques *viz.,* Expressed Sequence Tag (EST), RACE PCR, transformation, transfer DNA (T-DNA) tagging, Small (or short) interfering (siRNA), micro RNA etc. have been carried out to enhance the production of required secondary metabolites in different medicinal plants, like *Panaxgiseng* and *Saussurea involucrate* etc.

Scientists proposed a flavonoid 3'5' hydroxylase gene into rose plant with red flowers, and thetransgenic plant showed blue-purple flowers (Yukihisa et al. 2007). In *Saussurea involucrate* hairy root culture, a chalcone isomaerase gene was introduced and over expressed, which resulted in 12 times production of apigenin of that in control hairy root. Tyrosine decarboxylase gene isolated from parsley, was introduced in potato, and in transgenic plant, salidroside was detected (Jorn et al. 2002). Salidroside is a phenylethanoid compound with significant adaptive effects and is the main active compound in *Rhodiola sachalinensis*. Thus literature showed the potential of above mentioned techniques in the production of pharmaceutically important compounds besides original medicinal herb.

Processing and biochemistry of medicinal plant compounds

Research in the area of plant tissue culture technology has resulted in the production of many pharmaceutical substances for new therapeutics. Advances in the area of cell cultures for the production of medicinal compoundshas made possible the production of a wide variety of pharmaceuticals like alkaloids, terpenoids, steroids, saponins, phenolics, flavanoids and amino acids. Taxol (plaxitaxol), a diterpene alkaloid found in the bark of the *Taxus* tree, is one of the most promising anticancer agents known due to its unique mode of action on the micro tubular cell system (Jordan and Wilson, 1995). Morphine and codeine, well known analgesics isolated from the latex of opium poppy (*Papaver somniferum)*. The root of *Panax ginseng (*ginseng) is a highly prized medicine since ancient times. In recent years ginseng cell culture has been explored as a potentially more efficient method of procreate ginsenosides. L-3, 4-dihydroxyphenylalanine (L-DOPA) is a precursor of catecholamines in animals and is being used as a potent drug for Parkinson's disease, a progressive disabling disorder associated with a deficiency of dopamine in the brain. The prevalent application of this therapy led to the involvement of cell cultures for the enriched production. Berberine is an isoquinoline alkaloid found in the roots of *Coptis japonica* and cortex of *Phellondendron amurense*. Diosgenin (steroid sapogenin) is the product of saponins, extracted from thetubers of Dioscorea wild yam, such as the Kokoro. The search for high-producing cell lines coupled to recent developments in immobilized cultures and the use of extraction procedures, which convert furostanol saponins to spirostanes such as diosgenin, should prove useful in increasing productivity in the years to come. Capsaicin, an alkaloid is used mainly as a pungent food additive in formulated foods. It is obtained from fruits of green pepper (*Capsicum* spp.). Camptothecin, a potent antitumor alkaloid was isolated from *Camptotheca acuminata.* 10-Hydroxycamptothecin, a promising derivative of camptothecin is in clinical trials in the US. The dimericindole alkaloids vincristine and vinblastine have become valuable drugs in cancer chemotherapy due to their potent antitumor activity against various leukemias and solid tumors. These compounds are extracted from large quantities of *Catharanthusroseus*. Vinblastine is composed of catharanthine and vindoline. Since vindoline is more abundant than catharanthin in intact plants, it is less expensive. Tanshinones are a group of quinoid diterpenoids believed to be active principles of danshen (*Salvia miltiorrhiza*), a well known traditionary Chinese medicine. Tanshinone I and crypto-tanshinone inhibit complications of myocardial ischemia. Podophyllotoxin is an antitumor aryl tetralin lignan found in *Podophyllum peltatum* and *Podophyllum hexandrum*. Successful attempts for the production of above mentioned valuable secondary metabolite pharmaceuticals in relatively large quantities by cell cultures have been tabulated in table 4.

Table 4. Endeavors to eke secondary metabolite production.

Metabolite	Studies to enhance the production	References
Taxol	Effect of nutrients and other factors on paclitaxel production by *T. cuspidate* cell cultures (0.02% yield on dry weight basis).	Fett-Neto et al. 1995
Morphine and Codeine	Production of morphine and codeine in morphologically undifferentiated cultures.	Yoshikawa and Furuya, 1985
Ginsenosides	Jasmonic acid improves the accumulation of gensinosides in the root cultures of ginseng.	Yu et al. 2002
L-DOPA	Induced callus tissues of *Mucuna hassjoo*, *M. Pruriense*, and *M. deeringiana* and optimized the culture conditions.	Teramoto and Komamine 1988
Berberine	The productivity of berberine was increased in cell cultures by optimizing the nutrients in the growth medium and the levels of phytohormones.	Morimoto et al. 1988
Diosgenin	Use of cell cultures of *Dioscorea deltoidea* for production of diosgenin and found that carbon and nitrogen levels greatly influenced diosgenin accumulation in one cell line	Tal et al. 1983
	Able to obtain diosgenin levels as high as 8% in batch-grown *D. deltoidea* cell suspensions. However, the daily productivity was only 7.3 mg/l.	Tal et al. 1983
Capsaicin	Suspension cultures of *Capsicum frutescens* produce low levels of capsaicin, but immobilizing the cells in reticulated polyurethane foam can increase production approximately 100- fold.	Lindsey and Yeoman, 1984
	Improvements in productivity can be brought about by supplying precursors such as isocapric acid.	Lindsey and Yeoman, 1984
Camptothecin	Established an economically feasible process consisting of production of catharanthine by plant cell fermentation and a simple chemical or an enzymatic coupling.	Misawa et al. 1988
Tanshinones	Diterpenoid production in Ti-transformed root or hairy root cultures of *S. miltiorrhiza*	Hu and Alfermann 1993
Podophyllotoxin	To increase the yield of podophyllotoxin, used a complex of a precursor, coniferyl alcohol, and b-cyclodextrin to *P. hexandrum* cell suspension cultures	Woerdenberg et al. 1990

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Corresponding author: Dr. Arshad H. Rizvi, Associate Professor of Botany, Department of Botany, Shia P.G. College, Lucknow, U.P., India
Email: rizviarshadhasan@gmai.com