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Plant Secondary Metabolites (PSMs): Elicitation as a Strategy for Enhanced Biosynthesis in Plant Cell Cultures

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Abstract

Plant secondary metabolites isolated from the whole plants or trees in wild or from the cultivated plants leads to variation in the level of expression of PSMs as wells as there is questionable availability of raw materials for industrial use. Biotechnological production in plant cell cultures is a promising alternative but with limited commercial success due to poor understanding of how these metabolites is synthesized. Recent strategies deployed for enhanced synthesis of them using elicitors, precursors and selection of high yielding clones are bringing more success and is a big hope for using in vitro systems for PSMs production at industrial scale by the pharma companies.

Introduction

Products of plant sources are important part of our routine diet and its nutrient and phyto-constituents are extensively studied for decades. Apart from essential primary metabolites, higher plants produce a wide array of low molecular weight compounds, often referred to as Plant secondary metabolites (PSMs). These PSMs have no specific role in the fundamental life processes of plants but plays an important role in the interaction of the plant with its environment and plays critical role in plant defense and pollination. These secondary metabolites are often low molecular weight compounds with lesser production (< 1% of dry weight) and greatly depend on the physiological and developmental state of the plant.

Plant derived secondary metabolites include drugs such as morphine, codeine, quinine, vincristine, vinblastine, colchicine, reserpine etc. Many of these pharmaceuticals are used till date and often have no synthetic substitutes with same efficacy and pharmacological specificity. Invariably one fourth of all available prescribed pharmaceuticals in developed nations contain compounds that are directly or indirectly, via semi-synthesis are plant derived products.

Continued exploitation of plant containing high-value compounds leads to habitat destruction. Further, chemical synthesis of these plant based compounds is often not economically feasible. An attractive option is to go for *in vitro* production of these valuable secondary metabolites in plant cell or organ cultures. However, these attempts are met with only limited commercial success due to empirical nature of selecting high-yielding clones, and the limited information on the pathways that regulate synthesis of these secondary metabolites. Some of these factors that influence secondary metabolite production include screening high yielding cell

lines, media components optimization, precursor feeding, elicitation, up-scaling through bioreactor systems, hairy root culture, plant cell immobilization, biotransformation among others (Namdeo, 2007).

Elicitors and Elicitation

Elicitation approaches for enhanced secondary metabolites production from medicinal plants is discussed in detail in this article. An 'elicitor' is a substance which, when introduced at lower concentrations to a cell system, improves the biosynthesis of target compounds. Elicitation refers to actively stimulating or inducing or eliciting the plants' response to produce desired chemical response.

Classification of Elicitors

Elicitors can be classified as abiotic or biotic elicitors based on their nature, or as exogenous elicitors and endogenous elicitors based on their supposed origin.

Based on the Nature of Elicitors

Abiotic elicitors are the substances of non-biological origin which includes inorganic salts and other physical factors like UV light, low energy ultra sounds, metal ions including zinc, aluminium, copper, cadmium and calcium ions and high pH whereas the biotic elicitors are substances with biological origin which include plant cell wall derived polysaccharides like pectin or cellulose and microbe derived chitin or glucans and intracellular proteins whose functions are coupled to receptors and acts by regulating several enzymes or ion channels (Veersham, 2004).

Based on the Origin of Elicitors

Exogenous elicitors are substances that originate outside the cell like polysaccharides, polyamines and fatty acids whereas endogenous elicitors originate inside the cell like galacturonide or hepta glucosides etc.

Various elicitors and its biological implications in production of plant secondary metabolites are listed in Table 1.

Table 1: Elicitors and production of plant secondary metabolites

Elicitors	Plant Species	Plant Secondary metabolite synthesized
Abiotic elicitors		
Cu^{2+}, Cd^{2+}	*Atropa belladonna*	Tropane alkaloids
Vanadium sulphate	*Catharanthus roseus (Syn. Vinca rosea)*	Catharanthine
Arachidonic acid	*Capsicum annuum*	Capsidiol, Rishitin
	Taxus spp.	Taxol
Xanthan	*Capsicum frutescens*	Capsaicin
Methyl jasmonate (MeJA)	*Coleus blumei*	Rosmarinic acid
	Coleus forskohlii	Forskolin
	Cupressus lusitanica	Thujaplicin
Copper sulphate	*Hyoscyamus albus*	Phytoalexin
Metal ions: Al^{3+}, Cr^{3+}, Co^{2}+ Ni^{2+},Cu^{2+}, Zn^{2+}	*Datura stramonium*	Sesquiterpenoids
Low-energy ultrasound	*Panax ginseng*	Saponins
Biotic elicitors		
Fungal culture filtrate	*Bidens pilosa*	Phenylheptaryn
Cellulase	*Capsicum annuum*	Capsidol
Fungal elicitor	*Catharanthus roseus*	Indole alkaloids
Pythium aphanidermatum	*Catharanthus roseus*	N-acetyl-tryptamine
Trichoderma viride	*Catharanthus roseus*	Ajmalicine
Fungal spores	*Datura stramonium*	Lubimin
Fungal glucan	*Glycine max*	Glyceollin
Agaropectin	*Lithospermum erythrorhizon*	Shikonin
Vertcillium dahliae	*Papaver somniferum*	Morphine, codeine
Chitosan	*Ruta graveolens*	Rutacridone epoxide
Yeast extract	*Silybum marianum*	Silymarin

Mechanism of Elicitation in Plant Cells

The exact mechanism of elicitation is poorly understood. However, various mechanisms are hypothesized like messenger Ca^{2+} ions affects cell membrane integrity and alter intracellular pathways and changes in osmotic stress etc. Also there are possibilities of rapid changes in protein phosphorylation patterns and protein kinase activation as mechanism of elicitation.

Accumulation of defence-related proteins pathogenesis related (PR) proteins such as chitinases and glucanases, endopolygalacturonases contributes to the release of signalling pectic oligomers (endogenous elicitors) and protease inhibitors. On the gene expression regulation, transcriptional activation of the corresponding defense response genes for elicitation process has been reported. However, the exact mechanism of elicitation and their network between them is highly complex and is being investigated by several researchers. The mechanism of action varies with their origin, elicitor specificity, concentration of elicitors, physio-chemical environment, stage of their growth cycle, nutritional uptake pattern etc.

These secondary metabolites are basically integrated components of metabolic networks which are exerted as a result of environmental selection pressures and understanding their mechanism will improve our understanding of how plants respond to environment cues (Erb and Kleibenstein, 2020).

Elicitation and Production of Secondary Metabolite by Plant Cell Cultures

Plants serve as biochemical factories for the production of primary metabolites and secondary metabolites of pharmaceutical significance. These products are sometimes considered to be waste or secretary products of plant metabolism.

Extraction of secondary metabolites from plants gains considerable importance commercially and in most cases synthesizing them at industrial scale is a herculean task and is uneconomical for several reasons. This necessitated deployment of cell culture system for the production of plant secondary metabolites. Advent of recombinant DNA technology has added benefits to the use of cell culture system, where metabolic pathways are engineered leading to production of specific compounds and hairy root culture systems are used for production of secondary metabolites at larger scale.

Different plant species produces various secondary metabolites on elicitation with different elicitors. Several parameters were considered to be significant leading to enhanced product accumulation *viz.,* elicitor specificity and concentration, duration of contact and quality of cell wall materials. The effect of elicitors in improved production of secondary metabolites is compared and furnished in Table 2.

Table 2: Effect of elicitation on the production of secondary metabolites under in plant cell and organ cultures

Sl. No.	Plant species	Culture type	Elicitor	Plant Secondary Metabolites (PSMs)	Product Concentration in control	Product concen-tration after elicitation
1.	*Capsicum annum* (cells)	Cells	*Trichoderma viride* (crude)	Capsidiol	0	1 mg per flask
2.	*Cupressus lusitanica*	suspension cultures	fungal elicitor	Beta-thujaplicin	0	187 mg/g dry weight
3.	*Dioscorea deltoida*	Cells	*Rhizopus arrhizus* (crude)	Diosgenin	134 mg/L	230 mg/L
4.	*Carthamus tinctorius*	Cells	*Blue green algae (crude)*	Kinobeon A	0.6 mg/L	5.78 mg/L
5.	*Lotus corniculatus*	Hairy roots	Glutathione (abiotic)	Isoflavonoids	0	160 µg/gm fresh weight
6.	*Nicotiana tabacum*	Hairy roots	Yeast extract	Sesquiterpenes	1 µg/gm	87 µg/gm fresh weight
7.	*Catharanthus roseus*	Hairy roots	*Penicillium* sp. (crude)	Indole Alkaloids	3 mg/gm dry weight	9 mg/gm dry weight
8.	*Papaver bracteatum*	Cells	*Dendryphion* (crude)	Sanguinarine	50 µg/gm fresh weight	450 µg/gm fresh weight
9.	*Thalictrum rugosum*	Cells	*Saccharomyces cerevisiae* (crude)	Berberine	0.5% of dry weight	2% of dry weight
10.	*Catharanthus roseus*	Cells	*Pythium* sp. (crude)	Ajmalicine	0	400 mcg/L

Conclusion

Plant secondary metabolites (PSMs) produced by the pharma based industries are met with limitations with respect to yield and availability of raw materials. Plant tissue culture approaches aids in production of PSMs in large scale by deploying strategies for enhanced accumulation of secondary metabolites by using high yielding cell lines, precursor feeding, elicitation and media modification. Elicitation of plant cell culture system is found to be promising with favorable results in triggering the production levels completed to control. This paves way for interdisciplinary approaches to exploit the maximum potential of plant cells for the production of plant secondary metabolites.

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