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Strategies for Secondary Metabolite Production: A Review

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Abstract

This review paper has the details on the production of secondary metabolites through plant tissue culture. It also holds information on the techniques of Plant tissue culture. Biotransformation, the conversion of less useful secondary metabolites into highly used chemical compounds is a very promising technique used to produce secondary metabolites.

Keywords: Plant tissue culture; Biotransformation; Secondary Metabolites; Agar and Agitated Cell Cultures; GC-MS; HPLC

Abbrevations: ABA: Abscise Acid; BA: Benzyl Adenine; NAA: Naphthalene Acetic Acid; 2,4-D: 2,4-Dichloroxyphenoxyacetic-acid; IAA: Indole-3-Acetic Acid; 2-iP: 2-Isopentenyladenine; LS: Linsmaier and Skoog Medium; MS: Murashige and Skoog Medium; GC-MS: Gas Chromatography-Mass spectroscopy; HPLC: High Performance Liquid Chromatography

Introduction

Plant tissue culture

Herbs are used for diabetes treatment from the time immemorial. The plant extracts are used to combat diabetes. Many The growth and multiplication of plant's cells, tissues and organs under controlled environment and aseptic conditions is known as Plant Tissue Culture. The establishment of this culture system has been done by Haberlandt and thereafter, it has been used by various researchers in various plant sciences field. Any part of the plant can be used for the purpose of plant tissue culture known as explants, can be grown in solid or semi-solid or liquid medium. Mostly all the parts of the plants have been used as explants in tissue culturing but axillary buds, stem-tip and meristem-tips are highly used cultures due to their own advantages [1]. The explants taken are to be surface sterilized thoroughly and then they are inoculated on a suitable medium to initiate the culturing process. The basal medium used for majority of the experiments is MS Medium and then the optimization is done according to the mode of the study [2]. The tissue culture MS Basal Medium supplies all the nutrients required for the proper growth of the plant and the stringent light and temperature conditions in the growth room adds an advantage to the entire process. Sometimes, addition of Plant growth Hormones also aids in Plant. Development Once, the mass of cells have grown or divided subsequent sub-culturing is to be done to avoid the accumulation of toxins and replacing the replenished nutrients [3-5].

Micro propagation is another word for plant tissue culture. Micropropagation is the miniaturization process of the clonal propagation [6,7]. Clonal propagation is the asexual process of producing multiple and identical copies of the plant. The process of Micropropagation is divided into five stages. The first step includes selection of the proper explant and the explant source, which should be less contamination prone [8-10].

The second step includes proper and thorough sterilization of the selected explant. The third stage includes incubation

of the sterilized explant into the optimized basal medium. The fourth stage is shooting and rooting of the plant. And the last step is the most crucial and critical stage which is the acclimatization of the plant and hardening of the plant in greenhouse [9-12].

Phytohormones are the hormones in plants with the help of which plants respond to their environment. The main response of the plant takes place through the five plant hormones: Auxin, Cytokinins, Gibberellins, Abscisic Acid and Ethylene [13]. Auxins help in the growth of the plant and they are mostly present on the tip of the plant [14-18].

Cytokinins moreover help in the division of the cells and also prevent ageing. Gibberellins also help in the growth of the plant especially the stem area and it also helps to germinate the buds. Abscisic Acid prevents water loss and put the plant in dormant stage when the conditions are harsh. Ethylene helps in fruit ripening and it also has a role in abscission which is the dropping of fruits, flowers and leaves [19-22]. Auxin aids in rooting while Cytokine aids in shooting process. The ratio of the Auxin Cytokinin is particularly important. High amount of Axim leads to root development while high amount of Cytokinin leads to shoot development. Equal amount of Auxin and Cytokinin leads to callus development, which is just undifferentiated divided mass of cells. If the roots are developed first, the shoots would not develop then. So, the induction and proliferation of the shoots should be done prior to the induction of the roots [23,24].

Plant tissue culture has several applications such as in horticulture, agriculture, improvement of crops, germplasm conservation, study of plant diseases, culture of endangered plants and their preservation. The success of plant tissue culture depends on many factors such as age of the plant, genotype of the plant, the explant type and the position of the explant on the plant since the ability of expressing totipotency is different in different plants [25-28]. Since, the plants have been over-exploited and some there is a threat to some rare species so this way plant tissue culture helps in replenishing those plants [29,30].

Secondary metabolites

Secondary Metabolites are the components of the plant which are not directly involved in the growth and development of the plant like the primary metabolites [31-34]. There are many types of secondary metabolites in the plant such as alkaloids, terpenes, phenolics, flavonoids, coumarins and stilbenes, tannins, saponins and many more. They have a wide variety of applications such as pharmaceuticals, food additives, drugs and dyes, fragrances, neutraceuticals [35-37]. The amount of secondary metabolites accumulated varies in different species such as Aegle marmelos, Bletilla striata, Cassia acutifolia, Polygonum multiflorum, Zingiber officinale, Moringaoleifera, Ginkgo biloba, Eleutherococcus senticosus and other species [38-41].

This technology of isolating or production of secondary metabolites from higher plants has several advantages:

- It is a simple and straight process
- The isolation process is very efficient
- The compounds isolated work parallel with that of the natural compounds present in plants [42-48].

Plant tissue culture and secondary metabolites

The traditional methods of plant extraction and chemical synthesis of producing secondary metabolites has many flaws which can be improved through the technique of plant tissue culture. Plant tissue culture has been used for production of secondary metabolites has been going on since a long time as described [49-56].

The use of this technology is high since it provides several advantages:

- Controlled laboratory setup
- Less contamination prone if one works carefully
- Closed place where no climatic conditions and soil factors interfere
- Automatic cell growth and metabolite regulation.

The production of secondary metabolites in vitro is a two-step process:

- Biomass production and
- Secondary metabolite production

Strategies for producing secondary metabolites

Classical/conventional methods

Media optimization: The media optimization can be done through removal of some sources, supplementation of some sources or replacement of some sources. Either of these things can be done and standardized according to the feasibility of the experiment. The media can be supplemented with any of these sources such as carbon, nitrogen and amino acids or any of these in varying concentrations. The third variant used is by replacing one element with another in different combinations and checking the results. Different salts can also be added and this way the media can be improved by different techniques [57-59].

Culture condition optimization: The media can be made in duplicates and the culture conditions such as pH, temperature, incubation periods, dark and light conditions and effect of different chemicals on the media can be

checked. Three to four different pH conditions and temperature variants can be checked. Different light and dark photoperiod conditions can be considered and incubation can be set accordingly [60-62].

Strain improvement: Strain improvement is done mostly to improve the metabolic engineering of the strain for biotechnological approaches. It can be done through simple genetics such as exposure to UV light or exposure to some chemical mutagens and then the screening of the improved strain is checked based on the desired genotype [63]. Other technique is advanced molecular genetics where the various biosynthetic pathways can be studied. Various vectors and genes are studied and accordingly transformation studies are done. Gene cloning and analysis can be done by this method and again screening of the strain with improved traits and desired phenotype is selected [64-68].

Somatic embryogenesis: The explants are selected from the plant of interest and is sterilized and kept in growth on MS medium under proper and suitable conditions. Callus culturing is to be done from the explants which will be obtained after 4 weeks approximately. Now, from the callus culture direct secondary metabolite production can be checked or further sub-culturing can be done for 15 days (about 2 weeks) and kept under supervision for somatic embryogenesis after addition of NAA and Kinetin. Then, histology studies can be done for the same and the embryo sections can be checked under electron microscope for the growth check [69-71].

Plant cell cultures: The plant of interest is selected. Then, they are screened for producing secondary metabolites and the best genotype is selected. The genotype is to be stabilized for efficient secondary metabolite production. Next thing is to set up the culture medium for the growth of callus which is to be prompt sub cultured and then the stable genetic line from those callus cultures is selected. Once the genetic stability is achieved further screening of the cell lines is done to produce secondary metabolites. Further from these cell lines various suspension culture studies can be done such as biosynthetic pathways, elicitation studies, immobilization and genetic modifications. Commercial production of these metabolites can also be done with the help of bioreactor systems [72-83].

Organ cell cultures: Organ cell cultures can be done in two ways: Hairy root cultures and Shoot cultures.

Hairy root cultures: The plant of interest is selected and in vitro culturing is done. The infection of the in vitro cultured roots is done with Agrobacterium rhizogenes. Incubation is done and checked for the growth of hairy roots. Hairy roots are isolated and then cultured in solid and suspension medium and plants are regenerated from the same. Further, scale up studies can be done through bioreactors [84,85].

Shoot cultures: Shoots can be developed from any explant or from the callus of the plant. The ratio of auxin to cytokinin is important here. If the focus is on the shoot growth, then the amount of cytokinin should be higher than the auxin. Once, the shoots are grown further elicitation studies can be done to check the increase in the production of secondary metabolites [86,87].

Contemporary/advanced methods

Biotic and abiotic elicitation: Biotic and Abiotic elicitors are another method used for increasing the production of secondary metabolites. Biotic elicitors include carbohydrates, proteins, plant growth promoting bacteria, different fungi and hormones. Abiotic elicitors include Heavy metals, Light, temperature, drought and salinity. Different concentration of chemicals and different combinations will have varying effects on the production of secondary metabolites. In this way, the effect of stress can be checked with these elicitors. Also, detailed biosynthetic pathway of the stress induction in plants can also be checked [88-90]

Metabolic engineering: The genetic or metabolic engineering involves the study of biosynthetic pathways, enzymatic reactions and enzymes involved in them. It also includes the modification studies in the same. The gene expression can be checked at the proteome and transcriptome level. The gene promoters and transcription factors involved in the production of secondary metabolites can also be studied. It is a particularly important technique used for scaling up the production of secondary metabolites in plants [91,92].

Role of endophytes: Entophytes are the organisms which live a considerable time of their lifespan by colonizing the living tissues of their host. Entophytic fungi are known to have symbiotic relation with some plants. During abiotic stresses or any pathogenic attack, these endophytes are known to help plants to produce secondary metabolites in defense by creating oxidative stress [93].

Plant cell immobilization and scaling up technique: The plant cell cultures from the plant of interest are immobilized in calcium alginate and the culturing of the former is done in Murashige and Skoog basal medium with different concentrations of calcium chloride to produce secondary metabolite. The secondary metabolite produced by this is

compared with that of the endogenous level of secondary metabolite. Reports show that it isan important and valuable technique for scaling up the production of secondary metabolites. This also helps in the study of plant-entophytic symbiotic relationship [94-97].

Microbial biotransformation: The microbial biotransformation is carried in the following steps.

- **Preparation of seed culture slants:** The lyophilized culture of the strain is revived by adding it in nutrient broth and keeping it in shaking conditions at room temperature. Through serial dilutions various cultures are prepared and then streaked on petri plates and then the colonies which grow are used to prepare slants.

- **Preparation of seed culture flaks:** The seed flasks are prepared by picking up the colony from the slants and again kept in the shaking condition under suitable conditions.

- **Strain activity test:** The culture from the seed flask is taken and mixed with nutrient broth and kept in shaking conditions. The next day the sample from the flask is taken and checked under microscopy for purity.

- **Biotransformation:** If the culture is pure then it is further kept for incubation in shaking condition for two days after adding the substrate. Then, the biotransformation is checked through HPLC or TLC (Table 1) Figure 1.

Figure 1: Strategies for secondary metabolite production.

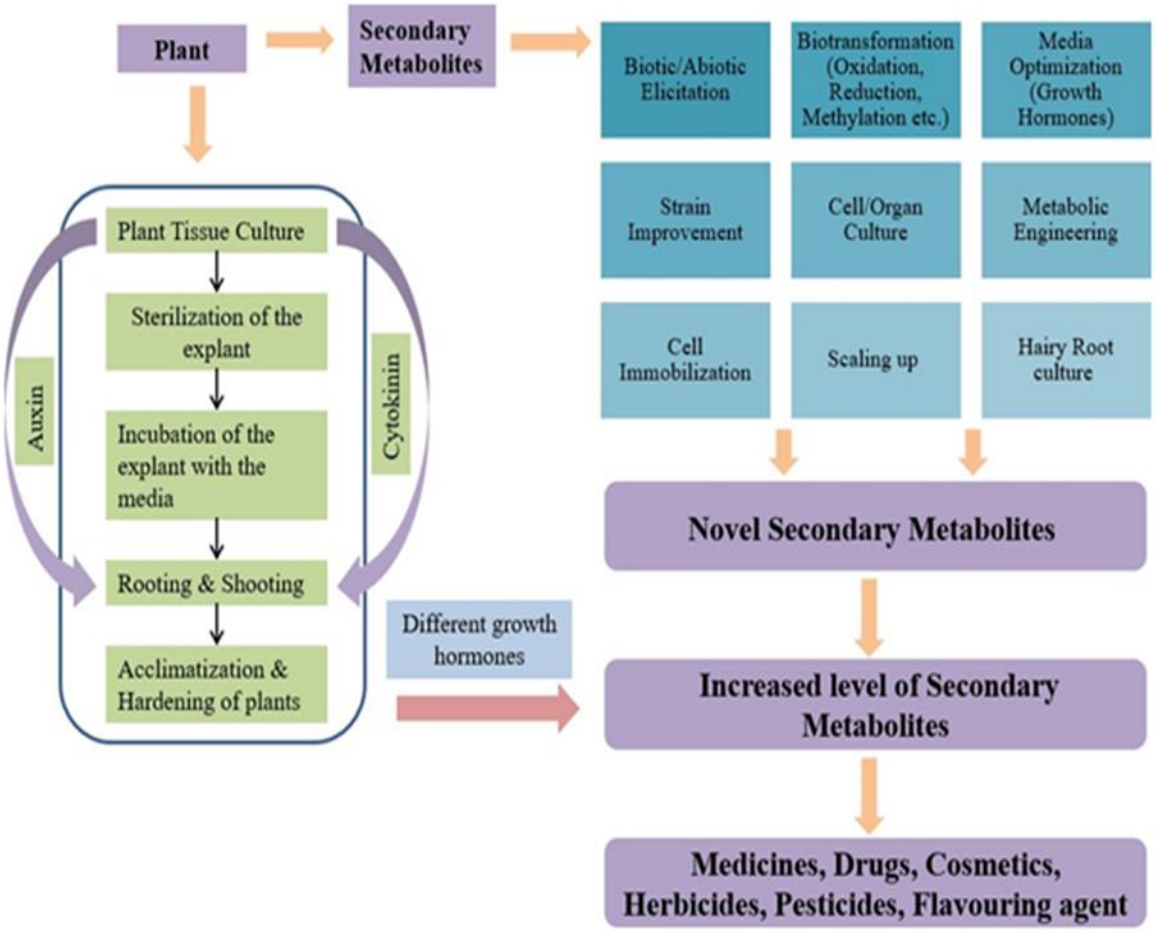


Table 1: Secondary metabolites produced by plant tissue culture in different plant species.

S.no.	Plant name	Secondary metabolite	Medium	Reference
1	*Agave amanuensis*	Saponin	MS+Kinetin+2,4-D	Andrijany
2	*Hylotelephium tatarinowii* (Maxim.)	Flavonoid	MS+6-BAP+NAA+2,4-D	Wang
3	*C. auranctium*	Orange Flavonoids	MS+IAA+Kinetin	Brunet and Ibrahim
4	*Saussurea medusa*	Flavonoids	MS+NAA+6-BA	Gao
5	*Ginkgo biloba*	Flavonoids and Terpene Lactones	MS+NAA+6-BA	Cheng
6	*Aegle marmelos*	Kaempferol	MS+GrowthHormones	Talreja
7	*Moringa oleifera*	Quercetin	MS+GrowthHormones	Talreja
8	*Zingiber officinale*	Phenolic acid and Flavonoid	MS+Zeatin+NAA	Zahid
9	*Polygonum multiflorum*	Jasmonic Acid	MS	Ho
10	*Scutellaria lateriflora*	Flavones	Hormone-free MS	Barska
11	*Bletilla striata*	p-hydroxybenzyl alcohol	MS+6-BA+2,4-D	Pan
12	*Hypercium perforatum L.*	Phenolics and Flavonoids	MS+IAA	Cui
13	*Ammi majus L.*	Scopoletin	MS+NAA+BAP	Staniszewska
14	*Rhodiola imbricateEdgew.*	Phenolics and Flavonoids	MS+NAA+BAP	Kapoor
15	*Artemisia annua L.*	Salicylic Acid and Phenolics	MS (Hormone-free)	Kumari
16	*Fagonia indica*	Phenolics and Flavonoids	MS+TDZ	Khan
17	*Stevia rebaudiana*	Steviol glycoside	MS	Ghaheri
18	*Polygonum multiflorum*	Phenolic and Flavonoid	MS+IBA	Ho
19	*Echium vulgare L.*	Phenolic and Flavanoid	MS	Dresler
20	*Phoenix dactylifera L.*	Kaempferol	MS+NAA+2,4-D,2 iP	Naik and Al-Khayri
21	*Dendrobium fimbriatum*	Phenolic, Alkaloid, Tanninand Flavonoid	MS+BAP	Paul and Kumaria
22	*Azadirachta indica*	Mevalonic acid, squalene andazadirachtin	MS+Picloram+Kinetin	Farjaminezhad andGaroosi
23	*Withaniasomnifera L.*	Withanolide A	Hormone-free MS	Nagella andMurthy
24	*Lallemantia iberica*	Flavonoids and Phenolics	MS+TDZ+NAA	Pourebad
25	*Artemisia annua L.*	Artemisinin	MS (Hormone-free)	Wang
26	*Cnidium officinale*	Phthalide and 3-butylidenephthalide	MS+2,4-D+BA	Adil
27	*Eleutherococcussenticosus*	Eleutherosides andChlorogenic acid	MS+2,4-D	Shohaelet
28	*Tripterygium wilfordii*	Triptolide, Wilforgine andWilforine	MS+2,4-D+Kinetin	Miao
29	*Zataria multiflora*	Phenolics and Flavonoids	MS+Cytokinin+Auxin	Mosavat
30	*Hyperciumhirsutum andHypercium maculatum*	Hypericin and Hyperforin	MS+NAA+Kinetin	Coste
31	*Lavandula* spp.	Monoterpenes andSesquiterpenes	MS+Auxin+Cytokinin	Goncalves and Romano
32	*Polygonum minus*	Essential oils: decanal	MS+NAA+2,4-D	Shukor

		anddodecanal		
33	*Mentha pulegium*	Pulegone and Menthol	MS+2,4-D	Darvishi
34	*Eurycoma longifolia*	Beta-carboline and Canthin-6-one	MS+2,4-D	Natanael
35	*Salvia miltiorrhiza*	Tanshinone	MS+2,4-D, 6-BA	Zhao
36	*Ruta graveolens*	Phenols and Flavonoids	MS+NAA	Sharifi
37	*Corylus avellana* L.	Taxol	MS+6-BA	Rezaei
38	*Silybum marianumtissue*	Silymarin	MS+2-IPA	AbouZid
39	*Catharanthus roseus*	Indole Alkaloids	MS+2,4-D+NAA+Kinetin	Zhao
40	*Capsicum annuum* L.	Capsaicinoids and Lignin	MS+6-BA+2,4-D	Palenius and Alejo
41	*Coffea arabica*	Caffeine	MS+2,4-D	Waller
42	*Eriobotrya japonica*	Triterpenes	LS+NAA+6-BA	Taniguchi
43	*Cornuskousa*	Polyphenol	MS+NAA+BA	Ishimaru
44	*Eucommia ulmoides*	Chlorogenic acid	MS+2,4-D+6-BA+Kinetin	Wang
45	*Rubia peregrine*	Anthroquinone	MS+NAA+BA	Lodhi andCharlwood
46	*Chaenomeles japonica*	Pentacyclic triterpenoids and Polyphenols	MS+IAA+BA	Kikowska
47	*Nothapodytesnimmoniana*	Camptothecin	MS+IAA+BAP	Isah and Mujib
48	*Ailanthus altissima*	Alkaloid	MS+2,4-D+Kinetin	Anderson
49	*Cassia acutifolia*	Anthroquinone	MS+2,4-D+Kinetin	Nazif
50	*Rheum franzenbachii*	Rhaponticin	MS+6-BAP+NAA	Wang
51	*Camptotheca acuminate*	Camptothecin and 10-hydroxycamptothecin	MS+NAA+Kineti n	Wiedenfeld
52	*Angelica dahurica*	Imperatorin	MS+BA	Tsay
53	*Citrus foliage*	Glycoproteins	MS+NAA+ABA	Witt
54	*Cinchona ledgeriana*	Alkaloid	MS+2,4-D+Kinetin	Anderson
55	*Stephania cepharantha*	Biscoclaurine	MS+2,4-D+IAA	Akasu

Biotransformation

Biotransformation of secondary metabolites is a process in plant which can be defined as conversion of the chemical compound into some new chemical compound which is of potential importance by biological means. Methylation, Oxidation, Esterification, Reduction, Glycosylation, Isomerization and [98-105].

Hydroxylation are some of the reactions through which biotransformation can be carried out. There is an alternative for the production of secondary metabolites and that is the production of secondary metabolites through plant cell cultures. Hydroxylation is possible in compounds which have oxygenated positions in it and can be exploited for conversion into some valuable products. Oxidation and Reduction can also take in some selected group of plants and is an important reaction of the biotransformation process where the hydroxyl groups are oxidated [106,107].

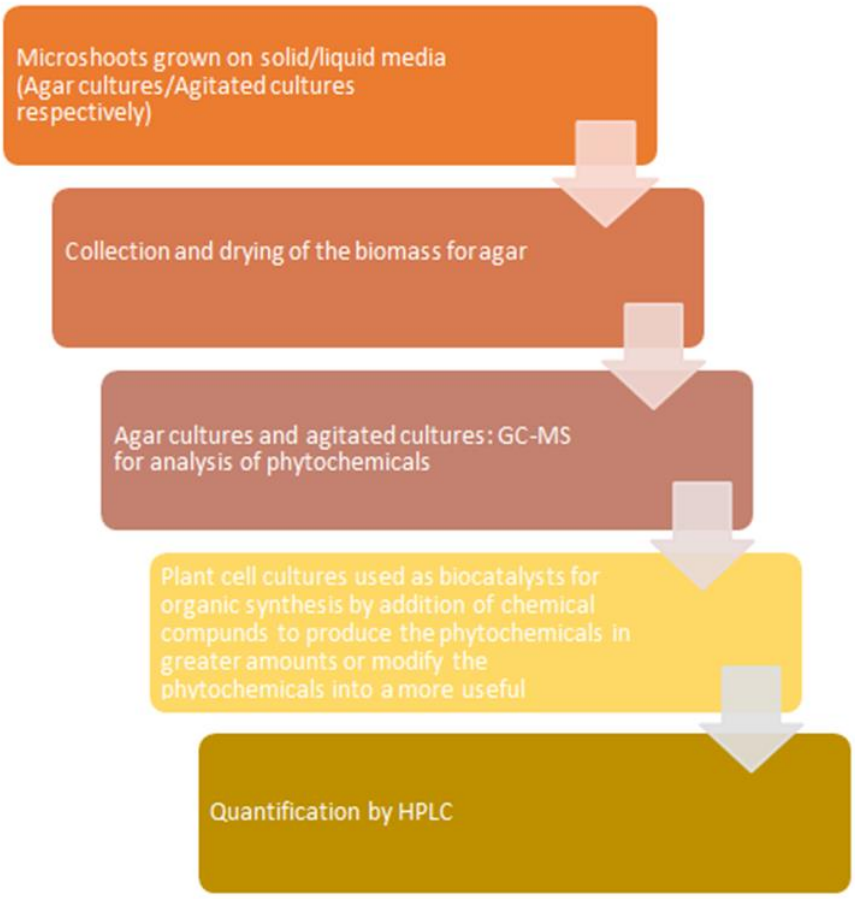
The alcohol is converted to ketones by the plant cell cultures and the corresponding aldehydes and ketones can also get converted to alcohols back by the plant cell cultures. Glycosylation is another reaction which occurs in plant cell cultures during low substrate concentration. It also takes place during toxicity by converting one compound to another less toxic compound and thereby helps in medicine sector. In a layman's language Esterification is the reaction where at least one ester group is formed when two compounds react. If the compound has one hydroxyl group on the steroid, then it can react and form a conjugate with the fatty acid and as a result esterification can take place. Acetylation is the reaction where the hydrogen atom is substituted or replace by the acetyl group and the same mechanism applies during biotransformation too [108-110]. The reaction has been known to have many applications in producing useful secondary metabolites. Isomerization, another reaction for biotransformation is an incomplete reaction which leads to the formation of different substrates and products due to thermodynamic equilibrium. The amount of productaccumulated by different enzymatic reactions depends on the capacity of the cells, variation and the stability of

the cells. Numerous factors affecting the process of biotransformation are Media composition especially Carbon, Nitrogen and Phosphorus, Growth Regulators and Light [110-117].
The Table 2 given below depicts the secondary metabolites produced by various plant species through plant cell cultures by Biotransformation Figure 2.

Table 2: Biotransformation of secondary metabolites in different plant species.

S. No.	Plant species	Secondary metabolite	Reference
1	*Atropa belladonna*	Hyoscyamine and Scopolamine	Subroto
2	*Duboisia* spp.	Hyoscyamine	Subroto
3	*Eucalyptus*	Beta-Thujaplicin	Furuya
4	*Scutellaria lateriflora* L.	Flavonoids and Verbascoside	KawkaB
5	*Hypercium perforatum*	Phenolic Acid	Kwiecien
6	*Scutellaria baicalensis*	Flavonoids and Verbascoside	Kawka
7	*Aronia arbutifolia*	Hydroquinone and Arbutin	Szopa
8	*Cistus x* incanus *L.*	Gallic acid, Catechins andFlavonoids	Kubica
9	*Eryngium alpinum L.*	Phenolic Acid and Flavonoids	Kikowska
10	*Cistus x incanus*	Phenolic Acids, Catechins and Flavonoids	Dziurka
11	*Verbena officinalis*	Phenolic Acids and Phenylethanoid glycosides	Dziurka
12	*Scutellaria baicalensis*	Phenolic Acids, Flavonoids and Phenylethanoid glycosides	Dziurka
13	*Scutellaria lateriflora*	Phenolic Acids, Flavonoids and Phenylethanoid glycosides	Dziurka
14	*Schisandra chinensis* (Turcz.)	Phenolic Acids and Flavonoids	Szopa
15	*Schisandra chinensis* (Turcz.)	Dibenzocyclooctadiene lignans	Szopa
16	*Schisandra chinensis cv.*	Phenolic Acid and Flavonoid	Szopa
17	*Capsicum frutescens*	Phenyl propanoids	Suresh and Ravishankar
18	*Origanum majorana L.*	Hydroquinone	Pietraszek
19	*Lavandula augustifolia*	Monoterpenoids	Lappin
20	*Micrococcus luteus*	Oleic Acid	Boratynski
21	*Bacillus safensis*SMS1003	Eugenol	Singh
22	*Melittis melissophyllum L.*	Harpagide and 8-O-acetyl harpagide	Pietraszek
23	*Pseudomonas aeruginosa*	Melanin	Bolognese
24	*Leptosphaerulina* sp.	Cephadroxyl	Perez-Grisales
25	*Schisandra chinensis*	Hydroquinone and 4-hydroxybenzoic acid	Szopa

Figure 2: The Figure describes the process of biotransformation of secondary metabolites by Plant tissue culture.



Conclusion

There are numerous numbers of methods which can be used for producing secondary metabolites and the elicitation for the same. The appropriate method to be used depends on the plants and their characteristics.

Different methods have different effect on the plants and accordingly the best technique suitable for the plants can be manipulated, combined and applied. The choice of technique used for enhancement of these metabolites needs to be explored in more plants to understand its efficacy in a better way.

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Author Contribution

"All the authors have contributed in the work and have gone through the final work. All the authors take equal responsibility for the integrity and publication of the work."

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