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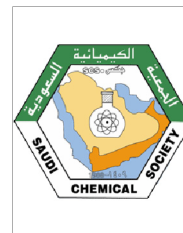

REVIEW ARTICLE

Plant cell culture technologies: A promising alternatives to produce high-value secondary metabolites

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Abstract Plants have been used for its medicinal values since ancient time. The medicinal properties of plants are based on their phytochemical constituent particularly secondary metabolites which are produced in low amounts by plants. Secondary metabolites have been used as medicines, flavors, colors, and fragrances. In recent time, these natural compounds are gaining enormous attention in pharmaceutical, cosmetics, and nutraceutical industries and are regarded economically valuable products. The production of plant secondary metabolites in plant is largely dependent on the plant species, environmental factors and geographical regions. In addition, the main challenges in their mass production is reported to be the quality and quantity issues during their synthesis. Therefore, enthusiasm has grown for increasing the production of secondary metabolites by employing *in vitro* plant cell culture technology and bioengineering methods. Such technological advancement, has led to production of a huge number of medicinal herbs and high-value secondary metabolites that are mostly used in pharmaceuticals, cosmetics and nutraceuticals industries. The current mini-review article focuses on applications of plant cell culture system for the production secondary metabolites and recent techniques used to improve metabolite contents. Furthermore,

Abbreviations: ABA, Abscisic acid; BAP, 6-Benzylaminopurine; IAA, Indole-3-acetic acid; GAE, Gallic acid equivalent; MS, Murashige and Skoog medium; NAA, 1-Naphthaleneacetic acid; PGR, Plant growth regulators; 2,4-D, 2,4-Dichlorophenoxyacetic acid; mg, Milligrams; g, Gram

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our review emphasizes safety issues of plant cell culture derived products.

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1. Introduction

Plant secondary metabolites also referred as phytochemicals are a key source of active compounds that have been used in pharmaceuticals, food, cosmetics, and agrochemicals industries (Krasteva et al., 2021; Maher et al., 2021a,b). Secondary metabolites plays a major role in the adaptation and interaction of the plant with their environment and help them to cope with various biotic and abiotic stresses (Buchanan et al., 2015; Eibl et al., 2018; Abdulhafiz et al., 2020a; Chiocchio et al., 2021; Abdulhafiz et al., 2022). These compounds are usually produced in low amounts in plants, which is why a large amounts of plant material are used to extract significant amounts of the compound of interest. Extraction of these compounds was restricted to only from traditional plant raw materials, and these practice caused over collection and extinction of important plant species. Therefore, plant cell culture technologies were developed for the production of high value metabolites without the need to use the entire plant (Priyanka et al., 2021; Shafi et al., 2021; Abdulhafiz et al., 2020b).

In recent years, plant cell culture technology is gaining enormous attention of pharmaceutical, cosmetics, and nutraceutical industries (Barbulova et al., 2014; Bayraktar, 2019). The growing attention is driven by the search for alternative sources of plant-derived natural compounds. The use of this approach for the production of secondary metabolites involves the optimization of cultivation conditions, as well as the use of methodologies such as metabolic engineering, elicitation, culturing of differentiated cells (organ cultures), and immobilization in order to boost the production of the metabolites of interest (Bulgakov et al., 2018; Yancheva et al., 2019; Valdiani et al., 2019). Large scale secondary metabolite production through *in vitro* culture is multifaceted process. Starting from selecting the cell lines for high yield and quality secondary metabolites, optimizing the media composition, elicitation, controlling environment and good skill and management are crucial in order to get high quality and quantity of natural products (Atanasov et al., 2015; Cabañas-García et al., 2020).

The benefits of plant cell culture is independent of season, producing safe, effective and good quality of plant extracts, production of contaminants and pathogens free bioactive compounds and inducing genetic variability and development of new plant varieties having an important attributes (Haroon and Ghazanfar, 2016; Karuppusamy, 2009). In this review, different alternatives methods for the production of secondary metabolites in plant cell cultures have been discussed and also provides an overview on the important methods used for the secondary metabolite production and their enhancement strategies. Research articles on these area were searched using PubMed, Scopus, ScienceDirect, and Google Scholar with the following keywords: "plant cell culture," "secondary metabolites," "tissue culture," "phytochemicals," "*in vitro* plant cell culture," and "extraction of secondary metabolites form plan cell.".

2. Conventional secondary metabolite production strategies

2.1. Callus culture

Plants cells have the ability to develop into a whole plants or organs, this unique characteristics is called "totipotency". Due to this unique characteristics of plant cells, *in vitro* culture are currently used to manipulate the biosynthetic potential of plants (Davies and Deroles, 2014; Cseke et al., 2016). Plants tissue can be cultured in *in vitro* and regenerate into a whole plants/callus depends on the culture medium which contains nutrients and plants growth hormones.

Callus is a growing mass of unorganized plant cell and is produced when explants are cultured in an appropriate plant growth regulators (PGRs). Usually auxin alone or combination with other types of hormones played an important role in inducing callus tissue from excised plants tissue (Cseke et al., 2016). In practice, callus culture involves the growth of a callus (composed of differentiated and non-differentiated cells), which is the followed by a procedure that induces organ differentiation. Based on physical structure, callus divided into three categories such as compact, nodular and friable callus. Friable callus is more prominent and can be obtained upon successive subcultures. This type of callus is suitable for a propagation, establishing a cell suspension culture and production of secondary metabolite. Currently, many kinds of secondary metabolite are successfully produced from callus culture and cells suspension culture (Khafagi, 2007).

2.2. Cell suspension cultures

Plant cell culture technology utilizes a single cell and that can be cultured into a liquid medium (cell suspension) in order to optimize the production of desired natural product (Motolinía-Alcántara et al., 2021). The establishment of cell suspension cultures usually starts by inoculating friable callus (i.e. it can be broken into small piece very easily) into a liquid medium in a flasks and placing on the rotary shaker. As the new cells are formed, the cells disperse throughout the liquid medium to form a cell suspension culture. After two–three weeks, the suspended cells are transferred to a fresh media while a larger pieces are discarded. Cells in suspension can show much higher rates of cell division than do cells in callus culture. Therefore, cell suspension is the most suitable when rapid and many cell generation are required (Bopana and Sanjay, 2007; Namdeo, 2007; Yue et al., 2016; Sahraroo et al., 2016).

Cell suspension can be maintained in the dark condition since most of cells are incapable of sustained autotropic growth (Bopana and Sanjay, 2007). The growth of cell suspension can be monitored by packed cell volume and cell density can be estimated using hemocytometer. There are enormous number of plant cell cultures producing a higher amount of natural product than in the whole plant, however, there still are a problem in the production of secondary metabolite from cell suspension culture resulting from low yields and slow growth, this can be solved by optimizing the growth condition and nutritional requirements of the cells (Rao and Ravishankar, 2002; Lyu et al., 2022).

Numerous important natural product from plants have been produced through plant cell culture technology, whereby majority are produced with plant cell suspension culture such as Teoside 10, Acetos 10P, Teupol 10P, Teupol 50P, and Echinan 4P (Dal Toso and Melandri, 2010; Fremont, 2017). Eibl

et al. (2018), investigated the potential of callus and suspension cell lines of *Theobroma cacao* for the cocoa ingredient in chocolate production. Their result showed that callus cultures had up to 40% higher polyphenol content (epicatechin, procyanidins B1, B2, C1, and cinnamtannin A2) than the source material (*T. cacao beans*) and chocolate taste experiment result confirmed that the cell culture chocolate provided a unique taste experience. Another study had investigated the potential of callus and suspension cell culture of purple yam (*Discorea alata*) for the purple colorant in purple powder production that can be used for the food coloring, textile and printing purposes.

The food biotechnology industries are currently using plant cell culture (cell suspension) to produce bioactive compound which contains polyphenols, vitamins, fatty acids, peptide mixtures, and saccharides (Dal Toso and Melandri, 2010; Fremont, 2017). The benefits of using cell suspension culture is not limited to production and quality aspects but also its cost-effective as the concentration of active molecules in the cells is often higher than in raw plant material (Fremont, 2017). Smetanska (2008) reported that the *in vitro* secondary metabolites production is much higher when compared to conventional method. Apart from high yield and quality products obtained from plant cell culture, many chemicals with complex have been possible to produce through method (Table 1). These plant secondary metabolites include pharmaceuticals, agrochemicals, flavors, and perfumes.

2.3. Hairy root culture

Hairy root culture is a promising tool in biotechnology to produce high value secondary metabolites by infecting of plant materials by a gram-negative soil bacterium (*Agrobacterium rhizogenes*) produce the similar secondary metabolites as those typically synthesized in parent plant roots with similar or higher yields (Sharma et al., 2011). The great interest in hairy root culture is mainly due to their genetic stability, ability to grow fast without requiring an exogenous application of auxins and proved to be more effective to improve yield of secondary metabolites (Zahra et al., 2012). As reported by Zehra et al. (1999), hairy root cultures improve production of various secondary metabolite and found to be more efficient to increases yield by 1200% in *Brugmansia candida*. In addition, hairy root culture is an attractive platform for the application of biotransformation since they offers genetic and biochemical stability, plant hormone independence and inexpensive culture requirements. In this context, biotransformation of cinnamyl alcohol to rosavins in hairy roots of *Rhodiola kirilowii* yielded more than 95% of the glycosides released to the culture media (He et al., 2015). Notably, biotransformation via hairy root culture can drive the discovery of novel plant secondary metabolites. For example, a new terpenoid indole alkaloid in suspension cultures of *C. roseus* was identified by biotransformation of catharantine (He et al., 2015).

3. Elicitation

Secondary metabolites is produced in plant in response to biotic (attempted pathogens ingress) or abiotic stresses. Elicitors are pathogen signal metabolites that stimulates the defense responses of plants. As a major response of plants to biotic and abiotic stress, the accumulation of secondary metabolites in plant cell culture can be stimulated by the elicitors. Various types of biological origin elicitors have been used including plant cell wall fragments (eg. pectin and cellulose) and polysaccharides from microorganism (e.g. chitin and glucan), plant immune signaling molecules (salicylic acid, methyl salicylate, benzoic acid and methyl-jasmonate. Non-biological origin elicitors include: inorganic salts, heavy metals, Ultraviolet radiation, high salinity and high pressure. The application of the immune-related methyl-jasmonate has been particularly extensively employed. For example, addition of methyl-jasmonate to *Taxus cuspidata* cambial meristematic cells induced the production of the blockbuster anti-cancer drug, paclitaxel, 14, 000% in comparison with control (Lee et al., 2010). Several conditions should be optimized to produce secondary metabolites by elicitors including the concentration, cell age and the stage of the given culture (Lee et al., 2010; Ochoa-Villarreal et al., 2015).

4. Metabolic engineering in secondary metabolite production

Metabolic engineering is an emerging branch of biotechnology that permits altering of specific pathways to improve the production of existing or novel compounds (secondary metabolites) (Bhatia, 2015). The rapid developments of molecular genomics enables the restructuring cellular function to suit specific needs. Metabolic engineering is progressively applied to overproduce secondary metabolites for their potential industrial production. The techniques needs an in-depth understanding of the genes expression involves in the biosynthesis of many plant secondary metabolites through metabolomics study (Zahra et al., 2012). Engineering the biosynthetic pathways allows alteration of secondary metabolite structure to produce novel bioactive compounds having enhanced therapeutic biological activities. This may occur, by overexpressing genes encoding regulatory enzymes involved in a biosynthetic pathways, therefore it is possible to increases the productivity of the *in vitro* plant cell culture. Another approach is to suppress the expression of competitive metabolic pathway (Verpoorte et al., 1999).

Metabolic engineering technology also been used to suppress the production of compounds in plant tissue culture. Tsuda et al. (2004) reported metabolic engineering of the flavonoid biosynthetic pathway to modify flower color by the suppression of endogenous flavonoid biosynthetic genes, the expression of a heterologous flavonoid biosynthetic gene, and the combination of both. Similarly, Katsumoto et al. (2007), engineered the rose flavonoid biosynthetic pathway successfully and generated blue-hued flowers accumulating delphinidin.

5. Safety considerations for plant cell cultures

Plant cell culture technology provides a sustainable production of pathogens-free natural products. Although, plant cell culture products are cultivated *in vitro* in a pathogens-free environment, the raw material produced from plant cell culture may contain many components apart from the desired compounds. In some cases, plant cell culture raw materials may also carry toxic compounds, which may be naturally occurring

Table 1 Secondary metabolites obtained from plant cell culture with their pharmacological applications.

Products	Plant species, culture type and medicinal usage	References
Flavonoids	Callus and cell suspension of *Glycyrrhiza uralensis* Fisch. Culture condition: MS + 1.0 mg L-1 2,4-D, 1.0 mg L-1 NAA, 0.2 mg L-1 BA and 3 % (w/v) sucrose + 2 mM phenylalanine and 5 mg L-1 methyl jasmonate elicitors. Increased flavonoids yield (132.36 mg L-1)	(Guo et al., 2013)
Xanthone	*Gentianella bulgarica* shoot cultures. High concentration of Demethylbellidifolin-8-O-glucoside. Culture condition: MS + BA (1.0 mg l-1).	(Janković et al., 2011)
Ginsenosides	Cell Suspension Cultures of *Panax quinquefolium* L. Culture condition: MS + 1.0 mg L−1 2, 4-D and 0.25 mg L−1 kinetin.	(Gao et al., 2014)
	Cell suspension of *Panax quinquefolium* MS + 1.0 mg L−1 2,4 dichlorophenoxyacetic acid, 0.25 mg L−1 kinetin, 30 g L−1 sucrose, and 7gL−1 agar	Wang et al., 2012
20-Hydroxyecdysone	Cell suspension culture of *Achyranthes bidentate*. Culture condition: MS medium containing 1.5 mg/l 6-BA, 1.5 mg/l NAA and 3% (w/v) sucrose. Methyl jasmonate 0.6 mM increased 20E production in cell cultures (7.5 mg/l) Cell suspension cultures of *Vitex glabrata,* 2.0 mg/L Culture condition: BAP, 1.0 mg/L 2,4-D and 30 g/L sucrose, chitosan at 50 mg/L resulted in 17.16 g/L.	(Wang et al., 2013)
Phenolic compounds	*Panax quinquefolium* cell suspension cultures. 52.57 mg GAE g−1 d.w. of total phenolic compounds. Culture condition: MS + 1 mg L−1 2,4-dichlorophenoxyacetic acid, and 0.1 mg L−1 kinetin. Their biological activities were reported in studies: antioxidant and anti-inflammation	(Kochan et al., 2019)
Vinblastine and vincristine	Cell Culture of Catharanthus roseus (L.). Culture condition: MS + 1.5 mg/L 2,4-D, 0.5 mg/L kinetin and 30 g/L sucrose + 100 mg/L chitosan. Achieved highest quantity of 4.09 µg vinblastine/mg cell dry weight. Biological activity: anti-cancer and antioxidant.	(Pliankong et al., 2018)
Atropine(Alkaloids)	Cell suspension culture of *Hyoscyamus muticus* L. Culture condition: MS + 6-benzyladenine (0.5 mg L-1) + α-naphthaleneacetic acid (1.0 mg L-1). Increased atropine content compared with mother plant (root). Petals, root of *Atropa belladonna*, Control myopia, cardiovascular disorders	(Abdelazeez et al., 2022)
	Petals, root of *Atropa belladonna*, Control myopia, cardiovascular disorders	Raj and Saudagar (2019)
Ginseng	Root; antioxidant and anti-inflammation	Hibino and Ushiyama, 1999
Vinblastine and vincristine	Vincristine plant flower, anti-cancer	Tsuruo et al., 1981
	Cell Culture of Catharanthus roseus (L.). Culture condition: MS + 1.5 mg/L 2,4-D, 0.5 mg/L kinetin and 30 g/L sucrose + 100 mg/L chitosan. Achieved highest quantity of 4.09 µg vinblastine/mg cell dry weight.	(Pliankong et al., 2018)
	Biological activity: anti-cancer and antioxidant.	(Tsuruo et al., 1981)
Atropine	Petals, root of *Atropa belladonna*, Control myopia, cardiovascular disorders	Larkin et al., 2019
Shikonine	*Shikonin Lithospermum,* antimicrobial, anti-inflammatory and anti-tumor purposes	Sun et al., 2018
	Callus culture of *Onosma bulbotrichum*: Culture condition: MS + 0.2 mg.L-1 IAA + 2.10 mg.L-1 kn. Cell suspension culture using SH medium supplemented with different concentrations of sucrose.	(Bagheri et al., 2018)
Quinine	Cinchona tree bark, anti-malaria	Walsh et al., 2007
	Cell culture of *Cinchona ledgeriana*: Culture condition: ABA 3 mgL-1 or with PBZ 7 mgL-1, mixed three weeks after culture. Produced the highest concentration of quinine.	(Pratiwi et al., 2018)
Taxol	*Taxus* spp, Cell suspension cultures, 10–20 mg l–1 and 0.5–1.0 mg l–1 day–1	Hezari et al. (1997)
	T. chinensis, Cell cultures,.3.57 mg l–1 day–1) T. media cell cultures, 7.86 mg l–1 day–1.	Bringi et al. (1995); Yukimune et al. (1996)
	T. canadensis cell cultures, 23.4 mg l–1 day–1.	(Ketchum et al., 1999)
	Taxus chinensis. Cell suspension cultures with methyl jasmonate, 3.2 mg l–1 day–1,	(Wang et al., 2001)
Codeine	*Papaver somniferum* cell culture: high codeine and morphine levels in hormones cultures.	(Siah and Doran, 1991)
Artemisinin	Artemisia annua, anti-malaria	Dondorp et al., 2009
Rosmarinic acid	Lamiaceae family, high anti-oxidant activity	Petersen and Simmonds, 2003
Rutin and quercetin	*Fagopyrum tataricum* Gaertn, TB7 hairy root line in 1/2 MS liquid medium supplemented with 30 g l-1 sucrose. Highest biomass accumulation (13.5 g l-1 fresh weight, 1.78 g l-1 dry weight) and rutin content (0.85 mg g-1).	(Huang et al., 2016)
Amino acids and flavonoids	Hairy root cultures of *Fagopyrum esculentum* Moench Rubra cultivar	(Gabr et al., 2019)
Anthraquinone	Transformed callus cultures of *RubiaCordifolia*. Culture condition: Leaves and stems with bacteria harbouring either *rolB* or *rolC* gene. 0.5 mg l−1 6-benzylaminopurine and 2.0 mg l−1 naphthaleneacetic acid. Cultured 20 °C in the dark.	(Bulgakov et al., 2002)

or mount up during the culture process. Therefore, evaluation of the safety of plant cell culture products is, therefore, a priority of the biotechnology industries involved in their production. The analytical methods have been used by various researchers to detect toxic compounds the in plant cell derived products. Friedman et al. (1994) was adopted with modifications to determine the amount of a-tomatine in tomatoes and tomato cell cultures using HPLC. Their results shows a-Tomatine was not detected in either the callus or the cell suspension cultures of *Lycopersicon esculentum* cv. In addition, the use of synthetic phytohormones in the culture medium such as (2.4-dichlorophenoxyacetic acid, 6- bezylaminopurine, N6-furfuryladenine) should be replaced with natural phytohormones such as (indole-3-acetic acid, zeatin). Similarly, phytohormone elicitors such as jasmonic acid, methyl jasmonate, salicylic acid should be used (Murthy et al. 2015; Häkkinen et al., 2020; Gubser et al., 2021; Gry, 1999; Ushiyama, 1999).

6. Conclusion

In this short review, the conventional and latest technology of plant cell cultures and methods used for the production of natural product have been reviewed. Among the techniques such as cell suspension culture offers good prospects for the advancement of commercial biotechnological approaches for the production of valuable natural products. Although extensive work been performed, the application of plant cell culture technology in food biotechnology is not fully adopted. In spite of a lot of advancements, intensive research on the plant cell culture would be crucial to improve low production of natural product in plant cell cultures. In summary, the production of metabolites in plant cell cultures is economically feasible for certain types of compounds. However, the plant cell culture products used as food and cosmetics products are still limited.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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