Review Article

Plant Cell Culture Approach for Secondary Metabolites Production: A Mini Review

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Abstract
Plants are invaluable source of diverse range of metabolites, which are a small organic molecule produced during cellular metabolism. They are grouped into primary metabolite and secondary metabolites on the basis of their functions. Secondary metabolites are functional bioactive compounds that ensures species 'fitness for survival. They play crucial role in defense, adaptation to environmental stress, cell signalling and utilized commercially for production of Pharmaceuticals, insecticides, dyes, flavors and fragrances. The conventional extraction method which relies on cultivation of whole plant is often constrained by environmental variability, seasonal dependency, growth and overexploitation of endangered species. Plant cell culture has emerged as a promising biotechnological approach for consistent and large-scale metabolite production. In this technique the culture is derived from explant under aseptic condition in nutrient media enabling large scale production independent of traditional limitations. Furthermore, the wide scale use of strategies such as elicitation, genetic manipulation, biotransformation, culture optimization has further contributed to improved yield. The present review highlights the significance of plant cell culture as suitable and potential approach for improving yield of secondary metabolites and examine its implementation for modern biotechnology and pharmaceutical industries.

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Statement of Sustainability: The utilization of plant cell culture approach for the production of phytocompounds offers a sustainable option for traditional harvesting of wild population of important plants. This approach helps in the preservation of biodiversity and avoiding the overharvesting of medicinal plants. *In vitro* systems play an important role in minimizing the utilization of natural resources and allow year-round cultivation irrespective of the environmental conditions and provides uniform quality of planting material. Overall, plant cell culture technology could serve as an alternative for enhancing the sustainable production of biologically bioactive compounds for various herbal and pharmaceutical industries uses.

1. Introduction

Plants play a vital role in daily human nutrition, and their dietary importance has been explored for many years. Bioactive compounds present in medicinal plants (cultivated or wild) have been used for centuries in traditional healthcare systems as nutraceuticals and important sources of healing remedies (Davis and Choisy, 2024). In addition to their medicinal value, plant- derived compounds are often favored because of their natural origin, which is generally considered safer and more environmentally sustainable than synthetic alternatives. Furthermore, the traditional knowledge associated with the use of medicinal plants has greatly supported the discovery of new bioactive substances, forming a strong basis for advancements in modern drug development (Dar *et al.*, 2023). For centuries, humans have relied on plants as a major source of food, providing carbohydrates, proteins, and fats, as well as materials for shelter. In addition to essential primary metabolites, higher plants also produce a wide range of secondary metabolites (Smetanska *et al.*, 2008). Secondary metabolites often referred to as natural products, are a wide range of compounds that may act as protective agents against predators and pathogens, or function in communication, competition, symbiosis, and transport of metals (Thirumurugan *et al.*, 2018).

However, medicinal plants generally contain these compounds in higher concentrations and in more active forms compare to common food plants (Bernhoft *et al.*, 2010). These metabolites, such as terpenoids, phenolics, flavonoids, alkaloids, and glycosides, are widely used in nutraceuticals and modern medicines. These compounds also have strong antioxidant activities and can interact with cell membrane, receptors, and genetic material, which contributes to various therapeutic uses (Velu *et al.*, 2018). The extraction of these compounds from natural sources is not always easy, as it is influenced by environmental conditions, variation in crop quality, chances of adulteration, and storage loss. Their chemical synthesis in laboratories is also difficult and expensive due to their complex nature. Due of these limitations, alternative methods of secondary metabolite production have been explored among which plant cell culture has gained considerable importance. Plant Cell culture has been considered to be an effective biotechnological approach for producing valuable secondary metabolites in a more consistent and efficient manner (Wu *et al.*, 2021).

The integration of various approaches such as nanotechnology, synthetic biology and microbiome management with plant cell culture could significantly enhance the development of eco-friendly, efficient and commercially viable platform for secondary metabolites production. The use of elicitation and multi-omics approaches, microbial interactions and improvements in bioreactor systems provides a robust platform for controlled growth of plant cells for enhancing sustainable production of high valued phytochemicals for nutraceutical and pharmaceutical applications (Wijerathna-Yapa *et al*., 2025; Sabetpour *et al*., 2025; Nordine, 2025; Manam *et al*., 2026).

2. Natural bioactive compounds present in medicinal plants

Phytocompounds are plant-derived compounds that are not essential for basic growth and development; however, they are important for defense mechanisms and adaptation to environmental factors, helping them to respond to various biotic and abiotic stresses (Aguirre-Becerra *et al*., 2021). Secondary metabolites play a crucial role in protecting plants against herbivores, viruses, bacteria, fungi and other plants that compete for resources. Some of the secondary metabolites present in various plant parts have been depicted (**Figure 1**). Most of these plants utilize these metabolites as a means of communication with symbiotic microorganisms and to attract pollinators and seed dispersers. Secondary metabolites usually have smaller size, lower molecular weight and higher degree of structural complexity compared to primary metabolites (Bottger *et al.*, 2018; Ketehouli *et al.*, 2025).

Structurally secondary metabolites can be classified into phenolics (includes phenolic acids, lignin, lignans, coumarins and tannins), terpenes (includes carotenoids, sterols (and cardiac glycosides), nitrogen-containing compounds (such as cyanogenic glycosides and alkaloids) and sulfur-containing compounds (includes glutathione, lectins, thionins and phytoalexins) (Sengul *et al.*, 2025).

Secondary metabolites obtained from plants demonstrate a broad spectrum of pharmacological effects, which are crucial for drug development and therapeutic use. Plant-based secondary metabolites such as terpenoids, flavonoids, tannins and alkaloids show strong antimicrobial properties against multidrug-resistant (MDR) organisms (Uttam *et al*., 2025). For example, ethanolic and methanolic extracts from *Equisetum telmateia* and *Teucrium polium* demonstrated substantial antibacterial effects against a broad range of MDR bacteria, including extended-spectrum beta-lactamase (ESBL) producing strains and methicillin-resistant *Staphylococcus aureus* (MRSA) (Hanoun *et al*., 2025).

Terpenes are recognized for their ability to reduce inflammation by blocking the production of pro-inflammatory cytokines. In particular, sesquiterpenes such as β-caryophyllene modulate immune responses and lower inflammation. Additionally, ursolic acid triterpene derivatives exhibit a wide range of anti-inflammatory, anticancer, antimicrobial and antioxidant properties (Khanam *et al.*, 2025). Although, there are many treatment options available for cancer, scientists are still searching for new natural molecules that can improve treatment effectiveness or reduce the side effects of existing therapies. Some plant-derived compounds known for their antitumor effects include asiatic acid, lupeol, hypericin, ursolic acid, saidmanetin and indole-3-carbinol (González Mera *et al*., 2019).

Traditional ways of getting bioactive compounds have many challenges and are influenced by various internal and external factors. As a result, researchers have explored plant cell, tissue and organ culture as an alternative technique to study about different biologically active compounds present in plant system. The *in vitro* culture provides a controlled and sterile environment that facilitates the year-round sustainable production of secondary metabolites while ensuring the efficient multiplication of genetically uniform plant materials. The optimization of growth medium composition is essential in regulating plant cell growth and biosynthesis of secondary metabolites, necessitating a balance of macronutrients, micronutrients, amino acids, vitamins, and growth regulators such as auxins, cytokinins, gibberellins and abscisic acid (Sidik *et al.*, 2024).

Plant cell suspension cultures have produced valuable compounds such as carotenoids, polysaccharides, podophyllotoxin, rosmarinic acid, berberine, scopolamine, docetaxel, paclitaxel and shikonin, used in the pharmaceutical industry. The increasing demand of these compounds in the market has motivated researchers to use cell culture methods to produce more high-value products in larger amounts (Bapat *et al.*, 2023). Some of the commercially important plant secondary metabolites have been described (Figure 2).

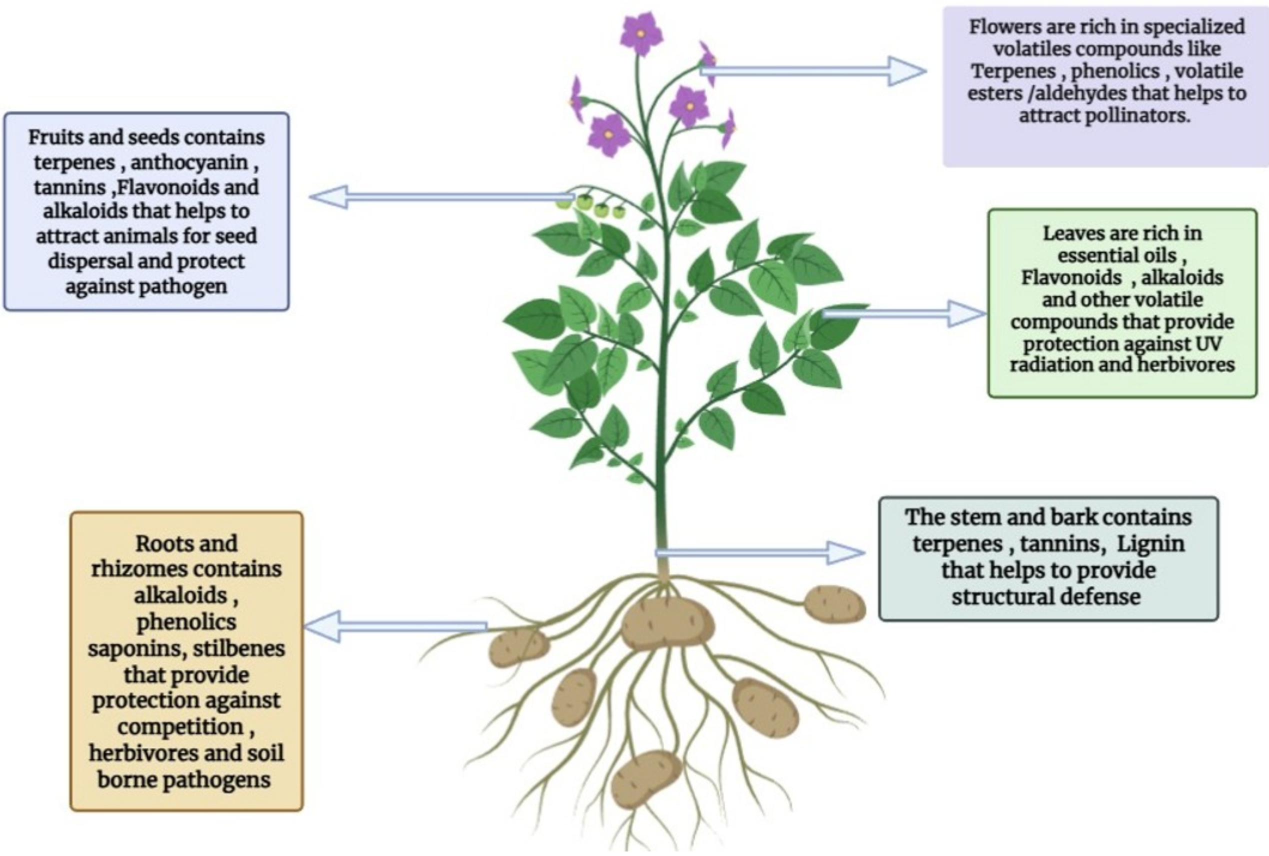

Figure 1. Overview of the various secondary metabolites present in different plant parts.

Taxol: Generally known as paclitaxel, it is a diterpenoid which is derived from *Taxus* sp. (Gallego-Jara *et al.*, 2020). It is an anti-cancer drug that inhibits the mitotic activity further blocking the cancer cell proliferation (Rauf and Ahmad, 2024). Higher production of paclitaxel has been reported when elicitors like salicylic acid, methyl jasmonate, and fungal elicitors are used in combinations to the suspended cell cultures of *Taxus baccata* (Tomilova *et al.*, 2023).

Morphine and Codeine: *Papaver somniferum* is propagated for the extraction of alkaloids such as morphine. Codeine is the prodrug of morphine, used as an analgesic (Chen *et al.*, 2022). Embryonic cell cultures are established to obtain higher concentrations of secondary metabolites and disease-free plant in limited amount of time (Rumyantseva *et al.*, 2023).

Bacosides: It is the bioactive compound produced by *Bacopa monnieri* (Brahmi), used in augmenting memory and in treatment of cancer (Banerjee *et al.*, 2021). The plant is over-utilized due to the presence valuable phytoconstituents, therefore, *in vitro* techniques are employed to enhance its production (Sharma *et al.*, 2015).

Shikonin: It is a naphthoquinone obtained from plants of genus *Lithospermum, Alkanna, Arnebia, Anchusa, Onosma, and Echium* (Yadav *et al.*, 2022). It has anti-cancer, contraceptive, wound healing properties etc. It has commercial value in medicine, dye, and colourant industry (Biswal and Biswal, 2024). Shikonin possess cytostatic activity against HIV, anti-tumor and cell-death promoting activity. Therefore, methods like cell/tissue culture are used to derive the therapeutic component from the plant (Bagheri *et al.*, 2018).

Ginsenosides: These are steroidal saponins that are main phytoconstituent of *Panax ginseng*, a perennial plant known to increase life span and acts against nausea, ulcers, vomiting, cancer, stress, and nervousness (Kim *et al.*, 2017). It is excessively exploited due to increasing demands in pharmaceutical industries. It has slow growth rate and cannot be replanted in the same place again. Therefore, to overcome these issues, plant tissue culture techniques are being used. With the help of these techniques' ginseng plants with high concentrations of ginsenosides can be produced (Xu *et al.*, 2023).

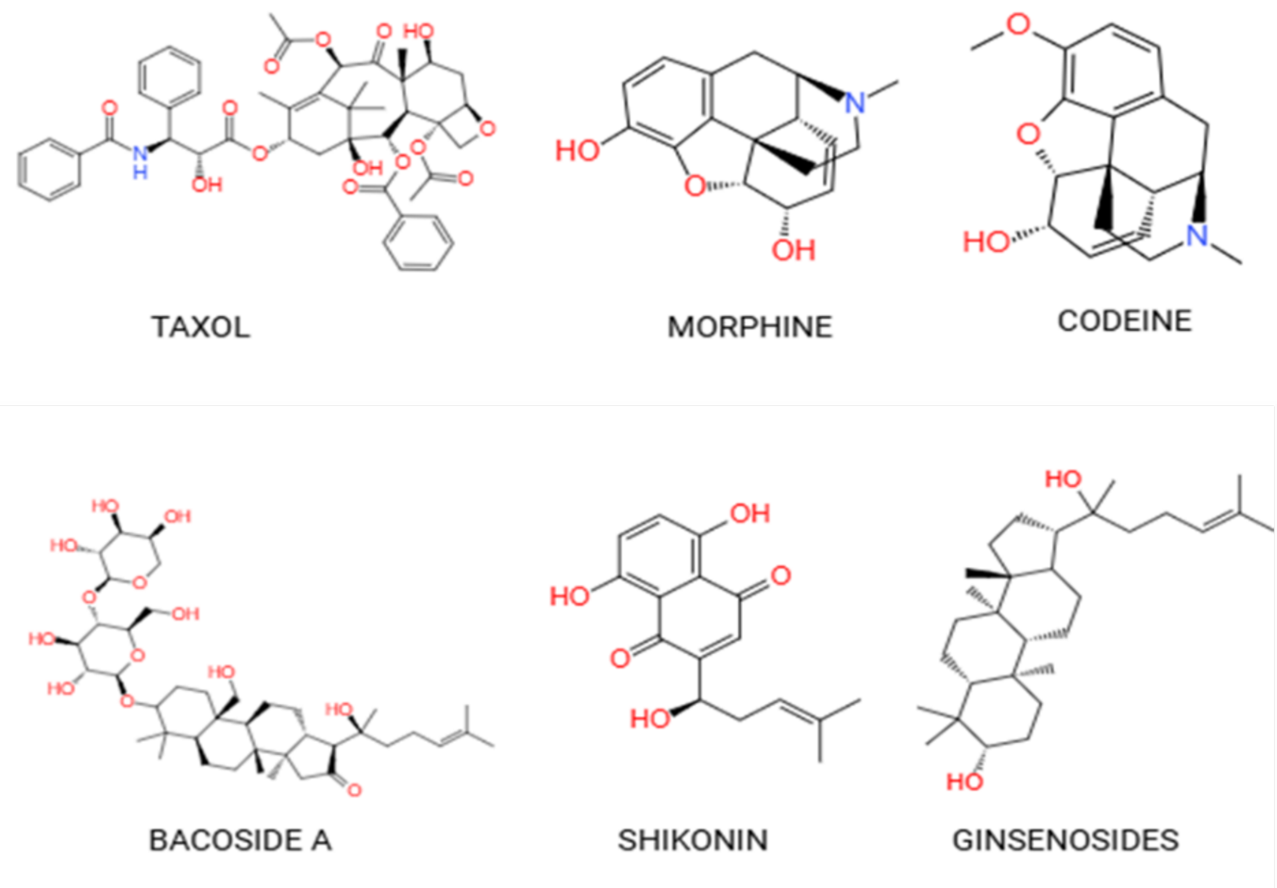

Figure 2. Structure of some of the commercially important secondary metabolites.

3. Biosynthetic pathways of some important secondary metabolites

Secondary metabolites are classified into three major divisions: production of phenolic compounds via shikimate pathway, terpenes in mevalonic pathway, and compounds consisting of nitrogen biosynthesised by tricarboxylic acid pathway (Jan *et al.*, 2021).

3.1. Shikimate pathway

The Shikimate pathway, responsible for biosynthesis of phenolic compounds comprises of seven steps, each leading to formation of an intermediate acting as a precursor for subsequent step. In the first step, phosphoenolpyruvate obtained by glycolysis and D-erythrose 4-phosphate from pentose phosphate pathway are converted into 3-deoxy-D-arabino-heptulosonate-7-phosphate (DAHP) mediated enzyme DAHP synthase (Kabera *et al.*, 2014). This is the entry and rate limiting step of the pathway. Further the seven carbon sugar consisting DAHP is transformed into dehydroquinate catalysed by enzyme Dehydroquinate synthase, which is monofunctional in prokaryotes and pentafunctional in eukaryotes (Jan *et al.*, 2021). Removal of water from dehydroquinate leads to formation of the third number intermediate, 3-dehydroshikimate (Yokoyama *et al.*, 2021). The fourth enzyme in shikimate pathway, Shikimate dehydrogenase helps in NADPH- dependent reduction producing Shikimate, a key intermediate linking early as well as late phases of the pathway (Mir *et al.*, 2015). The hydroxyl group of the third carbon of shikimate is phosphorylated to shikimate-3-phosphate with the use of ATP and this conversion is catalysed by Shikimate kinase (Shende *et al.*, 2024). Shikimate-3-phosphate obtained from fifth step is joined with phosphoenol pyruvate to produce 5-enolpyruvylshikimate3-phosphate (EPSP) and this step is crucial for pathway progression (Mir *et al.*, 2015). In the presence of chorismate synthase, the last step that is conversion of EPSP into chorismate occurs (Ojeda *et al.*, 2021; Yuan *et al.*, 2022). This newly synthesised chorismate not only serves as a precursor for aromatic amino acid biosynthesis, but phenolic compounds like lignin, tannins are also synthesised from chorismate via phenylalanine through phenylpropanoid pathway (Pan *et al.*, 2025; Ninkuu *et al.*, 2025).

3.2. Melvonate pathway

The mevalonic acid pathway is necessary for production of an important class of secondary metabolites, terpenoids. Initially two molecules of acetyl-CoA condense to form acetoacetyl-CoA. This acetoacetyl-CoA is changed with the help of HMG-CoA synthase into 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) which is further converted into Melvonate by utilizing NADPH (Duttenhefner and Reindl, 2025). The conversion of HMG-CoA to Melvonate is the first-rate determining step. (Zhang *et al.*, 2021). In the presence of Melvonate kinase and Phosphomevalonate kinase, Melvonate is changed first into Melvonate-5-Phosphate and later into its reversible form Melvonate-5-diphosphate (Miziorko, 2011). Melvonate diphosphate decarboxylase, present in peroxisomes converts Melvonate-5-diphosphate into IPP. IPP forms its reversible isomer which is DMAPP. One molecule each of DMAPP & IPP is joined by GPPS to produce GPP, which occur in mitochondria and plastid. For elongation of chain & terpenoid formation, FPPS add an extra IPP to GPP to form FPP. Further addition one DMAPP to three IPPs, producing GGPP, which acts as a precursor for monoterpenes(C10), Sesquiterpenes(C15), Diterpenes(C20) (Cheng *et al*., 2025).

4. Approaches employed for enhancing productivity in cultured plant cells

A number of efforts have been made by various researchers for increasing the production of important biologically active metabolites in cell culture system for nutraceutical, pharmaceutical and industrial applications (Kamra *et al*., 2025; Wijerathna-Yapa *et al*., 2025).

One of the most effectively used strategies for secondary metabolite production is elicitation which is a common technique that involves elicitors. Elicitors are categorized as biotic and abiotic according to their nature and exogenous and endogenous based on their origin (Garciglia *et al*., 2026). Biotic elicitors such as cellulase, hemicellulose, chitosan, fungal & yeast elicitors whereas salicylic acid, metal ions like Al^{3+}, Zn^{2+}, and oxidative & UV stress (Fazili *et al.*, 2022). The amount of elicitor required for production of secondary metabolites varies with the interest of metabolite to be obtained. For example, in adventitious roots of *Scopolia parviflora,* the concentrations of valuable metabolites, such as scopolamine and hyoscyamine, varied with different concentrations of the elicitor methyl jasmonate (MeJA) (Narayani and Srivastava, 2017). Salicylic acid and jasmonic acid treatment enhance alkaloid accumulation and increased tropane alkaloid (TA) production, possibly through upregulating key biosynthetic genes and enzymes. (Wen *et al*., 2023). The earlier study reported a significant increase in phenylpropanoid and flavonoid biosynthesis in methyl jasmonate treated apple suspension culture and metabolite accumulation due to the activation of triterpene pathways (Xu *et al*., 2025).

Nanoparticles (NPs) have recently emerged as novel elicitors for enhancing the production of secondary metabolites in cell culture due to their physicochemical properties that enables the activation of specialized metabolic pathways. The iron oxide NPs have been shown to enhance the phenylethanoid glycosides accumulation in *Scrophularia striata* cell cultures by activating the shikimate and phenylpropanoid pathways without inducing oxidative damage at optimal concentration. However, exposure to higher NPs concentration caused cellular stress and negatively affect metabolic biosynthesis, highlighting the importance of precise dose optimization (Sabetpour *et al*., 2025).

Precursor supplementation to plant culture media is another important strategy for enhancing secondary metabolite production in *in vitro* cultures by increasing the availability of key substrate required for biosynthetic pathways (Cheng *et al*., 2024). Precursor feeding and elicitation represent effective strategy can substantially enhance TAs biosynthesis and accumulation in Solanaceae species, including *Atropa belladonna* and *Erythroxylum novogranatense* (Parks *et al*., 2022; Wang *et al.*, 2022). The plant hormones such as brassinolide have been shown to stimulate alkaloid production by upregulating genes linked to tropane, indole, and other alkaloid pathways (Guo *et al.*, 2022).

Biotransformation or Biochemical modifications is a process in which added substances are changed into useful products with the help of plant cells or their enzymes. It is commonly used in biotechnology and can also be used as an alternative to precursor feeding. Plant cell cultures and even microorganisms can convert simple compounds into more complex and useful substances like alkaloids and steroids. This process mainly depends on the enzymes present in the cells and is useful for making compounds that are not easy to produce in the laboratory (Karuppusamy, 2022; Bapat *et al.*, 2023). The plant associated endophytic bacteria and fungi contribute to host stress tolerance and influence secondary metabolism. The co-culturing plant cells with beneficial endophytes can enhance metabolite production by activating immune response and altering metabolic networks. The inoculation of *Salvia hispanica* with Actinobacteria markedly enhances plant growth and biosynthesis of flavonoids, phenolics and saponins under saline conditions, highlighting their potential for sustainable plant bioproduction in changing environmental conditions (Nikalje *et al.*, 2026; Elhosary *et al.*, 2026).

Liquid culture media has emerged as an efficient approach to overcoming the limitations associated with the use of semi-solid media. One can utilize vessel of various extents, replace media without shifting container and simplify clean the container after using it. Use of liquid culture media in culture systems, such as plant bioreactor, results in effective assimilation of nutrients by tissues, rapid growth, and enhanced metabolic production (Nirmal *et al.*, 2023). A bioreactor is a container which maintains constantly stable environment to plant cells so that they can grow faster and in larger amounts by providing automated controlled conditions like pH, temperature, nutrients, oxygen levels (Ozyigit *et al.*, 2023). Bioreactor systems have completely changed production of secondary metabolites enabling the transition from small-scale cultures to industrial-scale production. Different type of bioreactor used to grow plant cells are stirred tank, air-lift, bubble column, varying in their ways of mixing liquid culture media.

The production of valuable phytocompounds, such as pentacyclic triterpenes from apple cell suspension, crocin (carotenoid) from saffron cell biomass, and significant biologically active compounds from *Viola odorata*, is made possible by *in vitro* plant cell bioreactor systems, especially stirred-tank and bubble column bioreactors (Lillberg *et al.*, 2026; Xu *et al.*, 2025; Amini *et al.*, 2022; Babu *et al.*, 2025). Moreover, bubble column bioreactor also provides a controlled approach for producing lipids and carbohydrates rich microalgal biomass and microbial systems that induces fatty acids and hydrocarbons production (Marra *et al.*, 2025). Air-lift bioreactors are useful for shear-sensitive plant cells and have been utilized for a number of medicinal plants for enhancing the production of secondary metabolites, including terpenoids, phenolics, and alkaloids (Verdú-Navarro *et al.*, 2023).

5. Conclusion

Medicinal plants are known for their therapeutic value due to the presence of various secondary metabolites. However, obtaining these compounds directly from natural sources is not always easy because of low abundance, environmental conditions, plant growth stage, and other external factors. In this context, plant tissue culture has emerged as a useful method for producing these compounds under controlled and stable conditions. Different strategies such as precursors supplementation, elicitor treatment, and the use of liquid culture and bioreactors can enhance the production of secondary metabolites. Furthermore, advancements in plant tissue culture techniques can facilitate the efficient, consistent, and large-scale production of these valuable bioactive compounds. As research progresses, these methods are expected to become increasingly accessible and widely implemented. Consequently, this technique offers promising opportunities for future research and practical applications in this field.

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Author Contributions

Conceptualization, Methodology, Data curation, writing original draft, BioRender Software: Anshika Bhardwaj, Sumedha Sharma, Arti Thakur, Konika Nagyal, Riya Sharma Conceptualization, Reviewing, editing and Supervision: Munish Sharma. All authors reviewed, edited, and approved the final version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

Institutional/Ethical Approval

Not applicable.

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