University of Thi-Qar Journal of agricultural research

Thi-Qar Journal of agricultural research

ISSN Onlin:2708 -9347, ISSN Print: 2708 -9339 Volume 15, Issue 1 (2026)

https://iasj.rdd.edu.iq/journals/journal/issue/20226 https://doi.org/10.54174/utjagr.v13ii 56.

"Smart Cellular Factories": How does biotechnology use plant cells to produce the medicines of the future?

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I. Abstract

The transformation of plant cell cultures from basic research tools into industrial pharmaceutical production platforms represents one of the most significant achievements in modern biotechnology. This comprehensive review examines the multifaceted biotechnology strategies employed to optimize plant cell cultures as cellular factories for high-value pharmaceutical compounds. We analyze the integration of genetic engineering, metabolic pathway reconstruction, cellular process optimization, and bioprocess engineering that colle-ctively enable sustainable, scalable production of complex natural products. The review addresses fundamental challenges including low productivity of wild-type cultures, genetic instability, metabolic burden, and pathway complexity, while presenting innovative solutions through CRISPR-based genome editing, synthetic biology approaches, systems metabolic engineering and advanced technologies.

Keywords- Biotechnology, metabolic engineering, CRISPR, Plant cell, pharmaceutical production

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II. INTRODUCTION

The plant kingdom is a rich natural source of chemical compounds with vital value, which have been used throughout history to treat diseases and promote human health. Plants contain a vast array of secondary compounds (metabolites), estimated to number around one million in total, with a single plant species potentially containing more than 5,000 of these compounds [1] **[2]**. Due to their unique properties, these compounds are used in up to 85% of traditional medicine reparations, making them a cornerstone of health sciences and drug development. A large part of the healthcare industry relies primarily on wild plants as a source of raw materials for the extraction of therapeutic compounds. With rapid population growth and increasing demand for natural resources for food and medicine, there is an urgent need to develop sustainable biotechnological solutions to ensure a continuous supply of these vital compounds [3] [4].

In this context, biotechnologies represent a paradigm shift in the production of high-value pharmaceutical compounds, transforming plant cell cultures into sustainable production platforms capable of meeting growing demand. This cultivation provides controlled laboratory conditions for the production of valuable plant secondary metabolites [5]. It has achieved remarkable early successes, such as the production of the drug shikimic acid from the plant *Lithospermum erythrorhizon* [6] and the an.ti-cancer drug paclitaxel from the yew tree [7], both of which are currently produced on an industrial scale through cell fermentation[6].

Plant cell suspension culture provides several advantages such as the capability of constant year-round production independent of climatic conditions, and the ability to produce compounds that are difficult or impossible to chemically synthesize under sterile environment [8]. In addition to other advantages, this technology may contribute to relive survival pressure in the case of endangered species [9]. Moreover, laboratory manufacturing guarantees quality and produces in accordance with Good Manufacturing Practices (GMP) standards[10]. Research has demonstrated that cell-cultured products are just as pure and efficacious as their plant-derived counterparts. For instance, paclitaxel made in this way was approved by the FDA after being demonstrated to be therapeutically equivalent to a natural product. In spite of these potential benefits, the industrial use of plant cell culture in pharmaceuticals is not widely used commercially [11]. This is mainly attributed to the low productivity and heterogeneity of cell culture, which cannot compete with chemical or agricultural origin[12]. However, with the advent of contemporary biotechnological techniques in the production process, a breakthrough is within reach [13], which putatively provides for a systematic optimization of cell strains and thus enhanced productivity. The revival of plant cell culture as a viable production platform for active pharmaceutical ingredients is enabled by the development of multigenomic approaches, precise genome editing (e.g., CRISPR) and synthetic biology. Such tools would allow "re-designing" of the "cell factories" to enhance their productivity, emulating similar to what has been achieved in microbial fermentation [5]. This document deals with this subject from the industrial application point of view, on how bio-technological tools may be used to enhance plant cell lines. The practical approach to convert these farms into sustainable and efficient specialized commercial production centers for bioactive compounds is also discussed.

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II. **Plant cell farming: concept and strategic importance**

Plant cell culture is defined as an advanced biotechnology based on the cultivation of plant cells or tissues in a sterile, controlled environment in a laboratory .This system relies on specific nutrient media supplemented with plant growth regulators[14], enabling targeted propagation and biomass production.

The strategic importance of this technology lies in transforming plant cells into a closed production system that is independent of external environmental conditions [15]. It enables the sustainable production of high-value secondary metabolites that are rare in nature or difficult to synthesise chemically, such as cardiac glycosides[16], They also overcome the limitations of direct extraction from wild plants, which often yields low returns. Their applications include the production of a wide range of bioactive compounds such as antitumour alkaloids, terpenes and antimalarial compounds.

The strategic benefit is maximised by scaling up to industrial scale using bioreactors specifically designed for plant cells Figure 1. These reactors allow the production process to be scaled up with precise control of the biological, chemical and physical conditions to maximise the production of the target metabolites[17]. This integrated system thus forms the basis for an industrial biomanufacturing platform that directly contributes to enhancing drug and food security by providing a sustainable and reliable source of high-value plant materials.

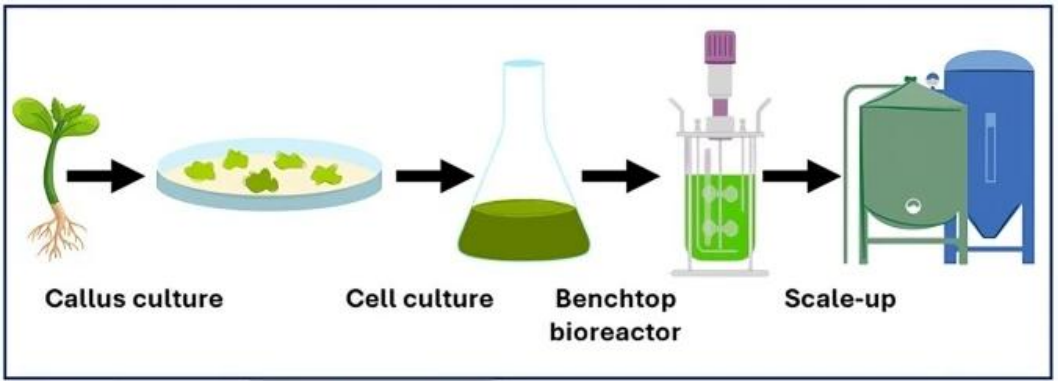

Fig. 1: shows the method of producing active compounds using a bioreactor.

III. Fundamental Challenges in Plant Cell Culture Optimization

Transforming plant cells into efficient production platforms requires addressing several interconnected challenges:

A. Low basal productivity: Secondary metabolite biosynthesis in plants is typically developmentally regulated, tissue-specific, and triggered by environmental stresses or differentiation signals [1**8**]. Undifferentiated cell suspension cultures lack these developmental cues, resulting in minimal constitutive production. Many valuable compounds accumulate in specialized structures (glandular trichomes, laticifers, idioblasts) absent in cell cultures.

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B. Pathway complexity and incomplete knowledge: Plant natural product biosynthesis often involves 15-25 enzymatic steps catalyzed by enzymes from multiple gene families, with pathway organization across different cellular compartments[19]. Complete pathway elucidation remains challenging for many compounds, limiting rational engineering efforts.

C. Genetic and phenotypic instability: Plant cell cultures exhibit genomic plasticity, including chromosomal rearrangements, ploidy changes, and epigenetic modifications during prolonged cultivation. This instability can compromise engineered phenotypes and productivity over time[20].

D. Metabolic burden and growth-production trade-offs: Channeling significant carbon flux toward secondary metabolite production diverts resources from primary metabolism and growth, creating inherent tensions between biomass accumulation and product synthesis[21].

E. Scale-up challenges: Plant cells' sensitivity to shear stress, tendency to form aggregates, slow growth rates, and complex nutritional requirements complicate bioreactor design and large-scale cultivation compared to microbial fermentation [22].

IV. The Biotechnology Solution Framework

Modern Biotechnology strategies address these challenges through systematic, multi-layered interventions:

A. Genetic layer: Precision genome editing and synthetic biology tools enable targeted pathway optimization, transcriptional regulation engineering, and introduction of heterologous biosynthetic capabilities [23].

B. Metabolic layer: Systems metabolic engineering balances precursor supply, cofactor availability, competing pathways, and product compartmentalization to maximize biosynthetic flux.

C. Process layer: Advanced bioprocess engineering optimizes culture conditions, feeding strategies, elicitation protocols, and bioreactor design for each specific cell line-product combination.

D. Control layer: Implementation of Quality by Design principles, process analytical technology, and advanced process control ensures reproducible, high-quality pharmaceutical production meeting regulatory requirements.

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V. Metabolic Engineering

Metabolic engineering is defined as an integrated methodology that relies on molecular and systems biology tools, aiming to reprogram metabolic pathways in living organisms to increase the production of valuable target compounds[24]. In the context of plant secondary metabolites, this technology provides an advanced scientific framework for understanding the gene expression responsible for the biosynthesis of these compounds. Studies involving gene overexpression enable the modification of their biosynthetic pathways and the redirection of metabolic flux towards the desired product [25]. This approach is based on a comprehensive study of metabolic networks across multiple levels, including the genome, transcriptome, proteome, and metabolome. It is followed by precise manipulation of the genes encoding critical and rate-limiting enzymes in the pathway [23]. Although the theoretical principle suggests the potential to enhance the productivity of plant cell cultures by upregulating the expression of these regulatory genes , practical outcomes may not always translate into increased production due to the complexity of metabolic networks and the presence of compensatory regulatory mechanisms or other unforeseen bottlenecks [26].

To maximize effectiveness, metabolic engineering employs multifaceted strategies that go beyond simply enhancing the target pathway. These include inhibiting competitive or branching pathways to divert metabolic flux, or even deliberately inhibiting downstream enzymes to allow the accumulation of valuable precursor intermediates. The notable success in applying these methodologies to the phenylpropanoid biosynthetic pathway responsible for synthesizing a wide range of secondary compounds serves as practical evidence of the power of this integrated approach[27]. However, the widespread application of this strategy still faces a fundamental challenge: the lack of detailed and dynamic understanding of many biosynthetic pathways, their regulatory mechanisms, and their interactions with primary metabolism[28]. To meet industrial demand for these metabolites, there is an urgent need for interdisciplinary research aimed at fully mapping these pathways, accurately identifying all regulatory points and bottlenecks, and integrating various omics technologies with computational modeling. Furthermore, promising techniques such as precise gene editing (e.g., CRISPR) and the design of expert strains are emerging as pivotal tools to overcome these challenges, enabling the transformation of cells into efficient, programmable "bio-factories" for sustainable production.

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VI. Genetic Engineering Strategies

A. CRISPR-Based Genome Editing for Pathway Optimization

CRISPR/Cas systems have revolutionized plant metabolic engineering by enabling precise, predictable genome modifications without the positional effects and instability issues associated with random transgene integration[29]. The technology's impact on pharmaceutical production derives from several key capabilities:

1) Gene Knockout for Pathway Streamlining

Eliminating competing metabolic pathways represents one of the most effective strategies for enhancing product titers(table2). CRISPR-mediated gene knockout redirects carbon flux from competing routes toward target compound biosynthesis [30]. For example, in terpenoid production systems, knockout of genes encoding enzymes in competing isoprenoid pathways (such as sterol or carotenoid biosynthesis) increases precursor availability for pharmaceutical terpenoid synthesis. Similarly, eliminating oxidative catabolism enzymes prevents product degradation, enhancing accumulation.

Advanced CRISPR applications include multiplexed editing, where simultaneous targeting of multiple genes achieves comprehensive pathway restructuring in single transformation events. This dramatically accelerates strain development compared to sequential genetic modifications. Cas12a (Cpf1) systems offering different PAM requirements and cleavage patterns expand targeting flexibility, particularly valuable when Cas9 target sites are unavailable at optimal positions.

2) Transcriptional Regulation Engineering

Rather than complete gene knockout, fine-tuned modulation of gene expression often proves more beneficial. CRISPRa (activation) and CRISPRi (interference) systems using catalytically dead Cas9 (dCas9) fused to transcriptional activators or repressors enable reversible, tunable expression control without permanent genome modification [31]. This approach proves particularly valuable for:

1- Essential gene modulation: When complete knockout proves lethal, CRISPRi-mediated downregulation achieves partial suppression compatible with cell viability while still redirecting metabolic flux[32].

2- Temporal control: Inducible CRISPRa/i systems enable stage-specific pathway activation, separating growth and production phases to optimize both biomass accumulation and product synthesis [33].

3-High-throughput screening: Libraries of guide RNAs targeting different genes or regulatory elements enable systematic screening to identify optimal engineering targets before committing to permanent genome modifications [40].

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3) Base Editing and Prime Editing for Precision Tuning

Base editors and prime editors represent the cutting edge of precision genome engineering, enabling single-nucleotide changes without inducing double-strand breaks or requiring DNA templates[33]. These technologies facilitate subtle metabolic optimizations:

1-Enzyme engineering: Introducing beneficial mutations identified through directed evolution or computational design improves enzyme kinetics, substrate specificity, or product selectivity. Base editing enables rapid testing of multiple point mutations to optimize enzyme performance within native genomic context[41].

2-Promoter optimization: Fine-tuning promoter strength through targeted nucleotide changes achieves optimal expression levels for pathway enzymes. This approach avoids the binary on/off nature of gene knockout while providing more precise control than CRISPRa/i systems[42].

3-Regulatory element modification: Altering transcription factor binding sites or epigenetic regulatory elements modulates pathway expression patterns without introducing foreign genetic material, potentially simplifying regulatory approval [42].

	CRISPR technology/Modification type	Targeted medicinal plant	Targeted gene/pathway	The goal of modification	Improved medical compound	
1	Gene knockout	Nicotiana tabacum	XYLT and FacT genes	Production of non-immunological glycoproteins	Xylase- and fucose-free glycoproteins (biological drugs)	[34]
2	Gene activation (CRISPRa)	Stevia rebaudiana	` Activation of the UGT76G1 gene	Increased expression of key genes in the pathway	Increased production of steviol glycosides (sweeteners)	[35]
3	gene activation	Salvia miltiorrhiza	Gene SmCYP76AH 1	Optimizing the biosynthetic pathway	Increased production of tanchinones (for cardiovascular disease)	[36]
4	Disabling pathways	Papaver somniferum	STORR and CYP82Y1 genes	Disabling unwanted precursor paths or rerouting the path	Improved production of opioid alkaloids	[37]
5	Gene editing/activation	Camptotheca acuminata	Ca7g14120 and CaTDC1 genes	Enhancing the biosynthesis of the target compound	Increased production of camptothenic acid (anticancer agent)	[38]
6	Traction modification (via UGT genes)	Glycyrrhiza glabra	UDP glucuronyl transporter (UGT) genes	Controlling the sugar encapsulation step of the compound	Regulation of glycyrrhizin production (anti-inflammatory and antiviral agent)	[39]

Table 1. The role of CRISPR-Cas9 gene editing technologies in enhancing the production of biologically active compounds.

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B. The modification approach to rebuilding metabolic pathways

Despite advances in gene editing technologies, traditional genetic modification methodologies remain an essential tool for introducing foreign genes, enlarging metabolic pathways, and recreating complex biological systems. This approach aims to improve cellular performance by engineering enzymatic, transporter, and regulatory functions using recombinant DNA technology [42].

The process typically involves identifying specific rate-limiting steps in a known metabolic pathway and then improving these bottlenecks through genetic modification [43]. Most strategies focus on introducing highly efficient genes from other organisms, using strong promoters to enhance gene expression, or applying gene silencing techniques to achieve the desired phenotype. A common example is genetic transformation mediated by Rhizobium rhizogenes, which allows the transfer of specific target genes into the plant genome. Alternative transformation methods such as precision particle bombardment and direct protoplast transformation are also available [44].

Genetic modification techniques enable the redirection of secondary metabolic pathways in plants to produce compounds of high medicinal value, through the introduction of genes encoding enzymes that catalyse specific biological reactions such as hydroxylation, methylation and glycosylation[45], [46].

Table 2. Examples of increasing the production of selected secondary metabolites by interfering with metabolic pathways in transgenic cultures grown in bioreactors.

	Plant used	Tissue culture system	The gene that modifies	Type of Metabolites	Pharmaceutical/Biological Application	
1	Scopolia parviflora	Roots (modified by R. rhizogenes)	the 6-β hydroxylase gene	Scopolamine	anticholinergic class of drugs is used to relieve post-operative nausea, vomiting, and motion sickness	**[47] [48]**
2	Senna obtusifolia	Roots modified	the PgSS1 gene from Panax ginseng	betulinic acid, a triterpenoid saponin	antioxidant, anti-inflammatory, and anti-cancer.	**[49] [50]**
3	Panax ginseng	Roots	gene PgSQS1(the ginsenoside's biosynthetic pathway key)	Ginsenosides and phytosterols	antioxidation and anti-inflammatory factors and have beneficial effects on cardiac and vascular diseases	**[51] [52]**
4	Leonurus sibiricus	Roots modified	the AtPAP1 transcriptional factor	the production of phenolic acids	Natural antioxidants	**[53] [54]**
5	Catharanthus roseus	Roots	ORCA3 and strictosidine glucosidase	the production of terpenoid indole alkaloids	anticancer, antimalarial, and antiarrhythmic functions	**[55]**
6	Taxus baccata	Roots modified	The TXS gene	The taxanes, paclitaxel and docetaxel,	anticancer agents	**[56] [57]**

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V. Bioprocess Engineering and Optimization

A. Advanced Bioreactor Design

Bioreactor design profoundly influences productivity, reproducibility, and economics. Modern systems address plant cells' unique requirements while enabling industrial scale-up:

1) Shear-Sensitive Culture Systems

Plant cells' large size and rigid cell walls make them susceptible to shear damage from agitation. Specialized bioreactor designs minimize shear while maintaining adequate mixing and oxygen transfer: modified stirred-tank reactors with low-shear impellers,airlift bioreactors using bubble-driven circulation; wave bioreactors with gentle rocking motion; and rotating drum bioreactors providing mixing without mechanical agitation**[58]**.

Computational fluid dynamics (CFD) simulations optimize impeller geometry and operating parameters for specific cell lines, balancing shear stress minimization with mass transfer requirements. Real-time monitoring of cell viability markers enables adaptive control adjusting agitation intensity to prevent damage while maintaining productivity**[59]**.

2) Perfusion and Continuous Culture

Continuous perfusion systems offer advantages over traditional batch culture: higher cell densities through continuous nutrient supply and waste removal; extended production periods maintaining cells in productive state; continuous product harvest simplifying downstream processing; and reduced batch-to-batch variability improving product consistency**[60]**.

Cell retention technologies (spin filters, acoustic separators, tangential flow filtration) enable perfusion while preventing cell washout. Perfusion rates and bleeding strategies maintain optimal cell density and viability. For products secreted into medium, perfusion dramatically simplifies purification by continuously diluting product away from cells, preventing feedback inhibition.

B. Medium Engineering and Feeding Strategies

Culture medium composition critically influences both growth and secondary metabolism. Modern medium development employs systematic optimization:

1) Rational Medium Design

Design of experiments (DoE) approaches systematically explore medium composition space: Plackett-Burman screening identifies significant components; response surface methodology optimizes concentrations; and mixture designs determine optimal ratios of carbon sources, nitrogen sources, and mineral nutrients.

Stoichiometric modeling predicts nutrient requirements based on biomass composition and product formation. Elemental balancing ensures sufficient supplies of limiting elements (nitrogen, phosphorus, sulfur). Multi-objective optimization balances competing goals: maximizing both growth rate and product titer, minimizing medium cost while maintaining productivity**[61].**

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2) Advanced Feeding Strategies

Fed-batch and continuous feeding maintain optimal nutrient concentrations throughout cultivation:

1- Constant feeding: Pre-determined feeding rates based on stoichiometric models maintain nutrient levels within optimal ranges. Simple to implement but doesn't adapt to culture variability.

2-Sensor-based feedback feeding: Online sensors monitoring glucose, nitrate, or other nutrients trigger feeding when concentrations fall below setpoints. More responsive than constant feeding but requires reliable sensors**[62]**.

3-Model-predictive feeding: Mathematical models predicting culture trajectory guide feeding to achieve specific objectives (maximum biomass, maximum product, minimum cost). Machine learning models trained on historical data optimize feeding strategies autonomously**[62]** (Bolmanis, et al,2023).

C. Elicitation Strategies

Elicitors triggering plant defense responses activate secondary metabolite biosynthesis**[63].** Strategic elicitation enhances productivity:

1) Biotic elicitors: Compounds mimicking pathogen attack (methyl jasmonate, salicylic acid, chitosan, yeast extract) activate defense pathways producing pharmaceutically relevant metabolites. Elicitor type, concentration, and timing require optimization for each system**[64]**.

2) Abiotic stress: Controlled exposure to osmotic stress, temperature shifts, UV light, or nutrient limitation triggers stress responses activating secondary metabolism. However, severe stress compromises viability, requiring careful balance**[63]**.

3) Temporal elicitation: Two-stage cultivation separates growth and production: rapid biomass accumulation under optimal growth conditions, then elicitation triggering product synthesis. This maximizes overall productivity by optimizing each phase independently.

D Process Analytical Technology and Control

Real-time process monitoring and adaptive control ensure consistency and quality:

1) Multi-modal sensing: Integration of online sensors (pH, dissolved oxygen, optical density), offline measurements (viability, metabolite concentrations), and spectroscopic monitoring (NIR, Raman) provides comprehensive process understanding. Sensor fusion algorithms combine multiple data streams for robust state estimation**[65]**.

2) Soft sensors and digital twins: Mechanistic or machine learning models estimate difficult-to-measure variables from easily measured parameters. Digital twins simulate culture behavior, predicting future states and enabling proactive control interventions**[66]**.

3) Advanced process control: Model-predictive control (MPC) optimizes multi-variable processes considering constraints and future trajectories. Adaptive control adjusts parameters responding to process drift. Artificial intelligence systems learn optimal control strategies from data, autonomously improving performance over successive batches **[66].**

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III. VI. CONCLUSION

The conversion of plant cell cultures into drug production platforms is an attractive development of modern biotechnology. In this review, we discuss a number of approaches that in combination overcome the major hurdles which have previously hindered large-scale industrial exploitation of plant cell culture systems. The coming together of critical technologies such as CRISPR-mediated genome editing, system biology analytics and synthetic biology regulatory circuits as well as sophisticated bioprocess control modi has substantially changed productivity. The earliest cell culture production concentrations were prohibitively low and biotechnologically more advanced systems are capable of titers that match or exceed the value of the parent plant for certain compounds. The commercial success of the industrial manufacture of paclitaxel, in particular, has illustrated the technical and economic feasibility of this strategy when systems engineering philosophies are consistently applied. However, the fact that these plant cells are converted to competitive biofactories still relies on specific substances and investments are considerable. Success entails the combined optimization of several bioengineering layers: precise genetic alteration to optimize biosynthesis pathways; metabolic engineering toward precursor supply, cofactor availability and nutrient distribution; synthetic biology for dynamic regulation and re-wiring of metabolic processes; and bioprocess optimization for scalable, robust production with consistent quality.

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