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Biotechnological approaches for enhancing active compounds in medicinal plants

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ABSTRACT

Medicinal plants have always depended on their rich reserves of bioactive compounds in the traditional and modern healthcare environments. Nevertheless, environmental conditions, developmental stages, and species restrict the production of these compounds. Fortunately, what is being attempted with the biotechnology breakthrough is to increase the number and quality of bioactives. This review takes us through a series of biotechnology techniques, including in vitro culture and cell suspension cultures, hairy root cultures, and root trichome culture, which help scientists control and upscale the production of secondary products. Meanwhile, genetic engineering, particularly using the CRISPR/Cas9, combined with metabolic engineering and synthetic biology, has proven promising in large-scale re-engineering of biosynthetic pathways to increase productivity. Phytochemicals are identified and enhanced using omics and nanotechnology-based elicitors. These combining approaches have provided a leading pattern in plant improvement not only medically but also economically to enable future plant-based drugs discovery and production.

Keywords: Medicinal plants, Bioactive compounds, In-vitro culture, CRISPR/Cas9, Metabolic engineering, Nanotechnology-based elicitors

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Introduction

Various forms of medicine are available in the market, including Ayurvedic, Unani, Homeopathic, and Allopathic modalities. Numerous pharmaceutical companies utilize diverse raw materials in the formulation of these distinct types of medicines [1]. For thousands of years, plants have served as a fundamental source of medicinal remedies for humans. Throughout the history of civilization, medicinal plants have provided essential resources for humans in combating diseases. Current literature indicates that a wide variety of phytochemicals, including significant herbal constituents, are utilized in the treatment of serious health conditions, such as irregular heart rhythms and congestive heart failure [2]. The use of medicinal plants in traditional and modern therapeutics, with the WHO estimating that over 20,000 plant species have documented medicinal uses. Ethnomedical records suggest that approximately 14-28% of higher plant species have been used in various cultures for medicinal purposes, with estimates indicating that 35,000-70,000 species may possess bioactive compounds [3]. Bioactive compounds serve a prominent position in pharmaceuticals, particularly in the discovery and development of antibiotics, enzyme inhibitors, and vaccines, thereby illustrating their effectiveness in treating and preventing various diseases. Additionally, they hold considerable economic value in various applications, including flavors and fragrances, dyes and pigments, as well as food preservatives [4]. But environmental factors such as development stages and pathogen attacks, as well as species specialization, frequently limit the generation of bioactive chemicals in medicinal plants. Increasing the production of bioactive compounds via biotechnological methods guarantees a sustainable supply for medical use [5]. Recent advancements in biotechnology have transformed the production of bioactive molecules with medical benefits. Plant biotechnology is being studied in detail to produce bioactive compounds. Furthermore, this process makes use of a variety of approaches, including elicitation, tissue culture, and genetic mutation. Biotechnological methods may be able to find and create new bioactive substances, which would enhance healthcare and human well-being in the long run [6].

Biotechnology techniques for enhancing medicinal compounds:

Plants are "green chemical factories" with diverse chemical properties that can assist various businesses, including food, feed, medicine, and biomaterials.

In Vitro Culture Strategies

In vitro propagation techniques are employed to obtain healthy plants, multiply unusual plant genotypes, transform germplasm, and produce plant-derived bioactive compounds with significant commercial value. Aseptic culture is a significant method for the continual synthesis of active chemicals like secondary metabolites and synthetic molecules. The in vitro culture of *Agave salmiana* has been used to enhance the production of saponins, which are valuable for their medicinal properties [7].

Cell suspension culture

Plant secondary metabolites, such as flavonoids and phenolics, have extremely high medicinal benefits, including antioxidant, anti-inflammatory, anticancer, antihypertensive, antihyperglycemic, neuroprotective, and hypolipidemic actions [8]. Phenolic compound production in *Sageretia thea* can be improved by cell suspension cultures utilizing optimum conditions, including methyl jasmonate as an elicitor, which resulted in a considerable increase in phenolic and flavonoid content, as well as antioxidant activity. Cell suspension cultures in bioreactors produced significant fresh and dry biomass, with HPLC analysis indicating greater levels of bioactive chemicals such as catechin hydrate and chlorogenic acid. This indicates the efficacy of cell suspension cultures in increasing secondary metabolite production for herbal medicine [9].

Root trichome culture

Growing in vitro organs like roots or buds is a method to get beyond the restrictions placed by the undifferentiated nature of cell suspensions and calli. Specifically, over the last 30 to 40 years, isolated roots of a number of medicinal plants have been cultivated in vitro to create a few medicines, such as hyoscyamine and tropane alkaloids [10]. Furthermore, trichomes, many of which have glandular functions, are of great interest.

Hairy root Culture

Hairy root culture is a plant biotechnology technique that utilizes *Agrobacterium rhizogenes* to induce the formation of genetically stable, fast-growing adventitious roots (hairy roots) in plants. This is achieved through the transfer of Ri plasmid genes (*tms1* and *tms2*), which stimulate auxin synthesis and root proliferation. Hairy roots are widely used for the production of phytochemicals due to their rapid growth and genetic stability, though they are limited to compounds synthesized in root tissues and not in aerial plant parts [11].

Genetic Engineering for enhanced phytochemical production

Artemisinin, a critical malaria treatment that is particularly needed in disadvantaged areas. Artemisinin is derived from the herb Artemisia annua, although it is not produced in sufficient quantities for widespread use. To address this issue, scientists applied advanced genetic engineering to improve the plant's ability to manufacture artemisinin. They accomplished this by introducing more copies of six critical genes involved in the artemisinin manufacturing pathway. The findings were impressive, and genetically engineered plants produced up to 200% more artemisinin in the first generation (T1) and up to 232% more in the second generation (T2) than conventional plants [12].

Metabolic Engineering and Synthetic Biology

Metabolic engineering improves crop nutrition and economic value by adding novel biotransformation pathways. ZFNs, TALENs, and CRISPR/Cas9 are examples of genetic modification tactics and genome editing tools designed to advance metabolic engineering research [13].

CRISPR-CASS9

CRISPR/Cas gene editing technique provides benefits and convenience of use in genome engineering. It has been employed in plant species to edit genes, but its usage in medicinal plants is still in its early stages, to improve plant medicinal characteristics and agricultural value [14].

EXAMPLES

- The knockout approach of the SmCPS1 gene in *Salvia miltiorrhiza* through the CRISPR/Cas9 technique was successfully employed as an essential enzyme in the pathway of synthesis of tanshinone. The current study reveals the prospect of the gene editing process that uses the CRISPR-Cas9 new tool/system as a potential method of enhancing the quality and productivity of pharmacologically relevant secondary metabolites in medicinal plants [15].
- CRISPR/Cas9-mediated genetic modification has been used to boost GABA levels in crops such as rice and tomatoes, which may have health benefits by lowering blood pressure. To boost GABA accumulation, researchers added a premature stop codon near the autoinhibitory domain that interacts with calcium-bound calmodulin of GAD genes [16].

Omic Technologies

Multi-omics analysis, combined with bioinformatics and statistical analysis, is a comprehensive technique to discover the chemical variety, regulatory mechanisms, and pharmacological qualities of medicinal plants. Once the genes, metabolites, peptides, or proteins involved in the biosynthetic pathways of active medicinal plant bio-compounds have been identified, genome engineering or synthetic biology can be used to efficiently and sustainably generate them [17]. Omics technologies, coupled with modern analytical tools such as mass spectrometry, play an important role in improving bioactive molecule discovery in plants by allowing for structural identification, mode-of-action study, and molecular validation via transcriptomics, proteomics, and metabolomics. Integration with bioinformatics, molecular docking, and network pharmacology speeds up natural product research and herbal medication creation [18].

Nanotechnology assisted Enhancement

Many researchers have examined the role of nanoparticles (NPs) as a novel elicitor for the manufacture of bioactive substances in recent years, and it has been demonstrated that NPs can impact the plant's secondary metabolism in plant and cultural systems. Recent research has emphasized the potential implications of nanotechnology in crop production by enhancing the nutraceutical and nutritional quality of plants [19].

Table 1.1: Biotechnological approaches to enhance bioactive compounds in eight commonly used medicinal plants, highlighting key compounds and techniques.

Sr. No.	Plant name (Scientific name + Common name)	Bioactive Compound	Biotechnological approaches	References
1.	*Ocimum tenuifolum* L. (Holy basil)	Eugenol	EGS1 (Eugenol Synthase 1) gene identification and editing.	[20]
2.	*Curcuma longa* (Turmeric)	Curcumin	Enhance the expression of Curcuminoid synthase (CUS) by In-vivo directed evolution, Cell membrane engineering.	[21]
3.	*Allium sativum* L. (Garlic)	Allicin	Enhanced callus and shoot development, Tissue culture	[22]
4.	Mentha arvensis (Mint)	Menthol, Menthone	Hairy root culture, Enhanced phenolic acid biosynthesis by Phytohormone application.	[23]
5.	*Withania somnifera* (Ashwaghandha)	Withanaloides	Metabolic engineering, Funtional characterization of key enzymes as cytochrome P450 monooxygenase and dehydrogenase.	[24]
6.	*Panax ginseng* (Ginseng)	Gensenosides	Identification of differentially expressed genes, post translational modifications, Multiomic approaches.	[25]

Future Prospects and Applications

The integration of modern biotechnological technologies has enormous potential for the long-term and large-scale production of bioactive chemicals in medicinal plants. Future research is planned to concentrate on the use of gene editing, metabolic engineering, and synthetic biology to fine-tune biosynthesis pathways for increased yield and specificity. Furthermore, the use of omics technologies and artificial intelligence will improve our understanding of complicated plant metabolism, allowing for more precise interventions. These advancements not only promise to lessen reliance on wild plant resources, but they also pave the path for the creation of innovative plant-based therapies with improved efficacy and consistency.

Conclusion

Biotechnological interventions have revolutionized the production of secondary metabolites in medicinal plants, especially with the advancements made over the years on these products. Utilization of in vitro culture systems, genetic engineering, omics and nanotechnology-based elicitation will provide specific, efficient, and scalable science to further increase the yield, quality, and stability of pharmaceutically important bioactive compounds. Such methods are efficient in overcoming the invincible differences presented by environmental change, biosynthetic restrictions that impose on species, and the inherent weaknesses of low metabolite accumulation. In the long term, the sustainable and targeted cultivation of high-value phytochemicals can substantially leverage combinatorial strategies involving the strategic integration of synthetic biology, metabolic pathway engineering, and nano-enabled tools. An aggregate of these innovations will not only have an advancement in plant-based drug discovery and development but will also lead to other milestones in pharmaceutical biotechnology and world health.

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