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Pharmacologically Active Compound Synthesis in Plant Cell Cultures

(*Himani Sharma, Arti Ghabru, Shivani Chauhan, Abhishek Thakur and Aruna Mehta)
Dr YS Parmar University of Horticulture & Forestry, COH &F Neri, Hamirpur (HP)
*Corresponding Author's email: sharmahimani8@gmail.com

Metabolites are small molecules that are produced during metabolism as products or intermediates. They perform a wide range of functions, including energy, support for structural integrity, signal transmission, regulation of enzyme activity, involvement in defense systems, and interactions with other living organisms that exist. Secondary metabolites are organic compounds derived from primary metabolites, but are more selectively distributed within the plant kingdom, often confined to specific taxonomic groups such as species, genera, families, or closely related groups of families. Within the kingdom of plants, the distribution of these secondary metabolites is not uniform. While secondary compounds do not typically serve direct functions in a plant's primary metabolism, they often play important ecological roles. These roles may include attracting pollinators, adapting to environmental stresses, or acting as chemical defenses against microorganisms, insects, higher predators and even other plants (known as allelochemics). Plants tend to accumulate secondary metabolites in smaller quantities compared to primary metabolites. Moreover, their extraction and purification can be challenging due to their complex structures and limited presence. Consequently, secondary metabolites used commercially, such as pharmaceuticals, flavors, fragrances, and pesticides, are often considered higher value but lower volume products compared to primary metabolites.

Synthesis of secondary metabolites typically occurs in specialized cell types and at specific developmental stages within plants, further complicating their extraction and purification processes. Due to their specialized nature and intricate biosynthesis pathways, many secondary metabolites are regarded as specialty materials or fine chemicals rather than bulk chemicals like primary metabolites. These secondary metabolites are often large organic molecules that necessitate numerous specific enzymatic steps for their production, like tetracycline synthesis requires 72 different enzymatic steps.

Plant Secondary Metabolites

Plant secondary metabolites serve as defense mechanisms against pathogens and are known as phytoalexins. Some of these compounds also exhibit anti-germinative properties or toxicity towards other plants, categorized as allelopaths. These secondary metabolites can be grouped into five major categories based on their biosynthetic pathways: polyketides, isoprenoids, alkaloids, phenylpropanoids, and flavonoids.

Under stressful conditions, secondary metabolite biosynthesis in plant cells can be induced by elicitors or precursors, or a combination of both. Precursors are substrates, intermediate products, or enzymes involved in secondary metabolite biosynthesis pathways. However, improper use of precursors can have toxic or inhibitory effects on plant cells. Elicitors, whether biotic or abiotic, induce enzymatic activity against stress, leading to the accumulation of secondary metabolites. Examples of elicitors include heavy metals, pesticides, detergents, cold shock, UV radiation, and high pressure. Methyl jasmonate and chitin are two general elicitors of secondary metabolite synthesis in plants. Chitin, containing reactive functional groups, can form covalent bonds with proteins, inducing stress in plant cells.

Methyl jasmonate plays a regulatory role in plant immune systems. Low concentrations of methyl jasmonate induce gene expression, while higher concentrations induce chemical stress, leading to secondary metabolite biosynthesis. UV irradiation triggers the accumulation of secondary metabolites to protect against DNA damage. These mechanisms highlight the complex interplay between environmental stressors, elicitors, precursors and plant responses in secondary metabolite production, which ultimately contribute to the plant's defense and survival strategies.

Classification

Secondary metabolites can be categorized based on various criteria such as chemical structure, composition, solubility or biosynthetic pathways. Three main families of large molecules are commonly recognized: Phenolics, Terpenes and Steroids and Alkaloids, Flavonoids.

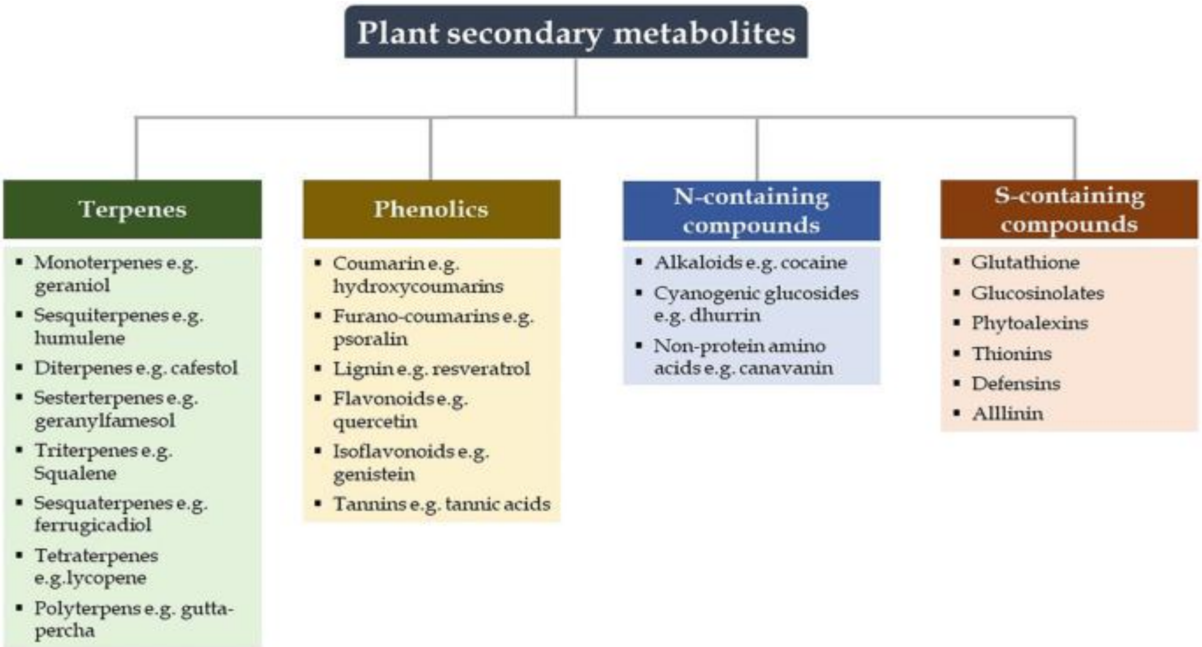
Alkaloids: are nitrogen-containing compounds derived from plants with pharmacological activity. They can interfere with ion channels, enzymes, or neurotransmission, leading to severe consequences such as hallucinations, loss of coordination, convulsions, vomiting, and even death.

Phenolics: can disrupt digestion, inhibit growth, block enzyme activity or simply taste unpleasant.

Terpenes: a diverse group of hydrocarbon-based natural products derived from isoprene, have ecological and physiological functions in plants such as allelopathy, insecticidal properties, attracting insect pollinators and serving as plant hormones.

Flavonoids: comprising a vast class of phenolic compounds, are found in various plant tissues and play diverse roles. They can protect plants from UV radiation and occur as monomers, dimers, or higher oligomers.

Coumarins and Stilbenes: other classes of plant metabolites, have roles in defense mechanisms and heartwood protection. Coumarins have antimicrobial, UV-screening and germination inhibitor properties, while stilbenes are present in various plant groups and have significance in pharmacology and human health.



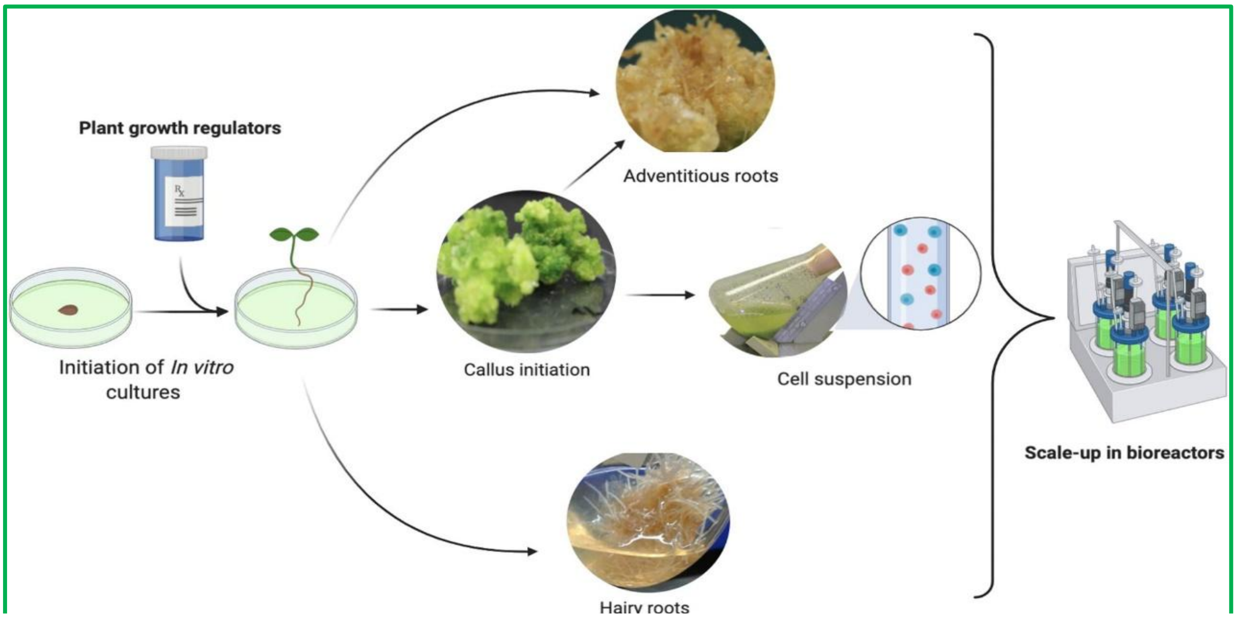
Production of Secondary Metabolites

Plant secondary metabolites have been utilized for centuries in traditional medicine and are now valued in modern applications such as pharmaceuticals, cosmetics, fine chemicals, and nutraceuticals. Despite their significant biological activities, it's important to ensure their appropriate and safe use. Production of plant secondary metabolites is crucial for various industrial applications such as pharmaceuticals, food additives, and fine chemicals. While direct extraction from plants and chemical synthesis are common methods, plant cell culture technology offers a promising alternative, especially for compounds that are difficult to obtain through traditional methods. Despite decades of research, the yield of plant secondary metabolites in plant cell cultures remains a challenge. Strategies have been developed to enhance production, including the use of elicitors, signal compounds, and various stresses to mimic natural conditions that induce metabolite synthesis. However, productivity often falls short for industrial applications. Recent advancements aim to improve secondary metabolite production through several approaches: Manipulation of plant cell cultures to enhance productivity through improved chemical processing, bioreactor performance, or the use of elicitors and stresses. Study of signal transduction pathways involved in metabolite biosynthesis to identify effective strategies. Investigation of transcription factors and genetic manipulation to regulate metabolite production. Cloning and genetic modification of key biosynthetic genes to enhance metabolic flux towards target compounds. Profiling metabolic intermediates to understand pathway regulation and optimize production. Analysis of global gene expression to comprehensively understand the regulation of plant secondary metabolism.

Plant cell culture systems have shown potential for secondary metabolite production, challenging the previous notion that only differentiated cells or specialized organs could produce these compounds. The advantages of cell culture over traditional cultivation include controlled conditions, freedom from contaminants, scalability and the ability to produce metabolites from various plant species.

Transgenic hairy root cultures have emerged as a stable and efficient platform for secondary metabolite production, offering genetic stability, rapid growth and ease of maintenance. Advances in tissue culture and genetic engineering, particularly transformation technology, have paved the way for high-volume production of valuable compounds. Once promising compounds are identified from plant extracts, the initial step involves collecting a diverse genetic pool of plant individuals known to produce these substances. This allows for the screening of hyper-producing plants that yield the most valuable secondary metabolites. However, secondary compound synthesis is highly inducible, so the next phase involves *in-vitro* cultures with callus initiation. This process primarily focuses on determining the optimal growth medium for cultivation.

During callus initiation, it's common for somaclonal variation to occur, especially over several subculture cycles. This variability can impact secondary metabolite production. Therefore, achieving genetic stability is crucial. Once stability is attained, callus lines are screened to identify those with the highest potential for efficient metabolite production. Each callus line undergoes evaluation for growth rate and both intracellular and extracellular metabolite concentrations to assess productivity. As growth slows down, carbon becomes less needed for primary metabolism, leading to increased synthesis of secondary compounds. Bioreactor studies represent the final phase toward potential commercial production of secondary metabolites from plant cell cultures. This phase is critical, as scaling up from Erlenmeyer flasks poses numerous challenges. After optimizing biomass production in a bioreactor, the focus shifts to adapting processes to ensure efficient secondary metabolite production.



Production of plant secondary metabolites

Conclusion

Advancements in techniques for culturing plant cell cultures are highlighted as particularly promising, potentially enabling the commercialization of even rare plants and the chemicals they produce. Emphasizing a holistic perspective is deemed crucial for evaluating strategies to improve productivity in this domain. The significant progress is made in recent years in enhancing secondary metabolite production from plant cell cultures. It anticipates that ongoing efforts in this field will lead to the effective biotechnological synthesis of specific, valuable and presently unknown plant compounds. Overall, the future integration of metabolic engineering, biotechnological methods and plant cell culture techniques holds promise for extending the utility of higher plants as renewable sources of chemicals, particularly medicinal compounds. Continued and increased focus on these approaches is expected to yield further advancements in the biotechnological synthesis of valuable plant compounds.