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Secondary Metabolites in Plants

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Abstract:

Plants are one of the potential sources for the discovery of valuable compound for human health and drug development, commercial importance of plant secondary metabolites boost scientific research in a great interest in its production. In case of plant, secondary metabolites are one of the crucial components for plant survival and its health, these metabolites play very crucial roles for plant growth and development including defense against herbivores, pathogens and pests. Over and above, it also helps plant for organismal interactions as well as against environmental stresses. In this chapter, We described about the plant secondary metabolites, classification, synthesis pathway of secondary metabolites and its applications. In addition to that chapter also described about recent advances in plant secondary metabolites.

Keywords: Secondary metabolites, Alkaloids, Terpenes, MEP Pathway, Stress

Introduction

Plants produce several metabolites that are necessary for their survival and functioning. Broadly, there are two classes of metabolites that are produced by plants – primary and secondary. The primary metabolites are vital for the plants to grow and develop properly. However, unlike the primary metabolites, the secondary metabolites produced by plants are a group of specialized small compounds that do not directly contribute to their growth but instead have a role to play in defence, stress response and in ecological communication of the plant with its surrounding environment.

German biochemist, Albrecht Kossel, first coined the term “secondary metabolites” in 1891 to recognize them as a class of metabolites that are functionally distinct from the primary metabolites (Kossel A,1891).Several years later, a Polish botanist Friedrich Czapek first adopted the term in his work *Biochemistry of Plants*in around 1921, describing these as the end product of metabolism of nitrogen, and the term has been in use even since (Czapek, 1922–1925)

As the plant cells grow and differentiate morphologically, the production of secondary metabolites begins. Most secondary metabolites are usually produced in response to stress-biotic and abiotic to adapt the plants to physiological and ecological challenges or as response molecules for plant defence. Increased production of plant secondary metabolites in response to stress, a process called elicitation, safeguards the plant’s endurance and fecundity in a competitive environment. Given the increased industrial application of plant secondary metabolites, artificial elicitors such as hormones, heavy metals, temperature, salt etc. can be used to enhance their production.

More than 50,000 secondary metabolites that are produced by different plants have already been discovered and the number is gradually rising on the account of the importance of these metabolites in pharmaceutical industry and cosmetics. Secondary metabolites, due to their varied distribution, were once widely used for taxonomic classification of plant species before the era of modern taxonomy aided by Next Generation Sequencing began (Teoh, 2016).

Classification of Secondary Metabolite

The classification of secondary metabolites can be done based on many attributes viz. chemical structure (e.g. Having rings, containing a sugar), solubility in different solvents,

pathways of biosynthesis etc. Since the biosynthesis pathways, properties and the mode of action often overlaps, it is quite difficult to classify plant secondary metabolites (Bodas et al. 2012). The classification is usually made on the basis of their biosynthetic pathways and can be broadly divided into three categories:

1. Phenolic

2. Terpenes and steroids

3. Alkaloids

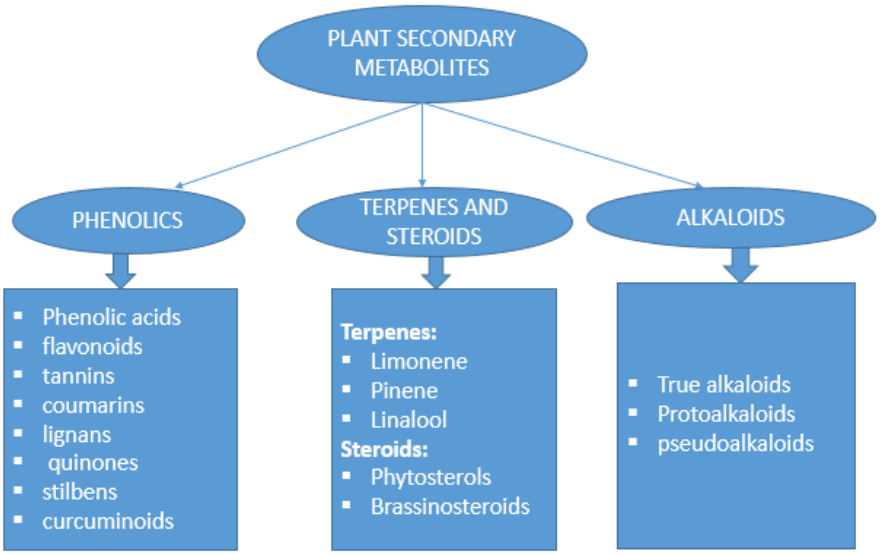


Fig1. Classification of Plant Secondary metabolites

1. Phenolics

Phenolic compounds are those compounds having a hydroxyl group (-OH) which is bonded to an aromatic hydrocarbon group. These are one of the most common and important plant allelochemicals in the ecosystem. They are chemical compounds consisting of a hydroxyl group (-OH) bonded directly to an aromatic hydrocarbon group. Within the perspective of allelopathy, the term "phenolic compounds" has a wobbly meaning, but it is commonly considered of as containing a collection of compounds that include structures such as simple aromatic phenols, hydroxy and substituted benzoic acids and aldehydes, hydroxy and substituted cinnamic acids, coumarins, tannins, and perhaps a few of the flavonoids.

2. Terpenes and Steroids

A group of cholesterol derivatives having low molecular weight, lipophilic compounds are called as steroids. All classes of steroids play an important role in various physiological and biochemical aspects in both plants and animals. A wide variety of steroids are used extensively as anti-hormones, as anticancer, antibiotics, contraceptives etc.in medical fields (Balandrin and Klocke, 1998).

Steroids which are derived from plants can be broadly divided into two categories:

1. Phytosterols: These are also called as plant sterols and are a group of steroid containing alcohol which occurs naturally in plants. They are usually white in color with a mild odor,

soluble in alcohols but insoluble in water. Some of the applications of phytosterols include food additives, medicine and cosmetics. They are also sometimes devised as cholesterol lowering substances in human (Banthrope 1994; Viera *et al*., 2005; Delvin 2002).

2. Brassinosteroids: Brassinosteroids (BRs) are an assembly of steroid hormones, very important for plant development and growth. BR is universally distributed in all growing tissues of higher plants, although the concentrations are reported much higher in fruit, seeds and pollen. Brassinolide (BL) is the most active form of BR for which the precursor is campestrol (CR). The signaling of BR promotes cell expansion and cell division. It also plays an important role in etiolation and reproduction (Ngoguchi *et al*., 2000; Li and he, 2020).

3. Alkaloids

Alkaloids are an assembly of naturally occurring compounds containing one or more nitrogen atoms arranged in a heterocyclic ring and are usually plant derived compounds. Some alkaloids may also contain some neutral or weakly acidic compounds (Manske and Holmes, 2014; McNaught and McNaught, 1997). Alike proteins, alkaloids are also derivatives of amino acid but they differ from protein by being alkanine in nature. Alkaloids are reportedly present in around 20 % of higher plants although some are also reported in animals. Many organic compounds like amino acids, proteins, carbohydrates, fats and alkaloids are produced by plants which are usually considered as secondary metabolites. They are usually stored in different amounts in different parts of the plant such as leaves, stem, roots and fruits. Once considered a waste product, but now evidences supports that these compounds play some important roles in plants in various ways.

Some of the prominent plant family rich in alkaloids are Papaveraceae**,** Ranunculaceae, Solanaceae and Amaryllidaceae. The first alkaloid isolated was morphine in the year 1804 from opium poppy in crystalline form. Alkaloids are suggested to have diverse physiological effects such as antibacterial, anti-inflammatory, analgesic, psychotropic and antitumor activity (Kurek 2019).

Alkaloids can be classified based on many aspects but are divided into three major categories:

1) True Alkaloids

2) Protoalkaloids

3) Pseudoalkaloids

Table 1. Different types of alkaloids with its derivatives and importance

Types of alkaloids	**True alkaloids**	**Protoalkaloids**	**Pseudoalkaloids**
Derivatives	Derived from amino acid containing nitrogen heterocyclic ring	Derived from amino acid but not part of heterocyclic ring	Not derived directly from amino acids but are connected with an amino acid pathways
Examples	Cocaine, morphine, quinine	Yohimbine, mescaline, and hordenine	Capsaicin, caffeine, ephedrine
Importance	Sedatives, drugs, etc.	health disorders, including mental illness, pain, and neuralgia	Drugs, stimulants, etc.

Secondary metabolites produced by plants are not only physiologically important to the plants, but they have greatindustrial applications as well. The secondary metabolites regulate how plants interact with the biotic and abiotic components around. These interactions can be utilized in improving agricultural practices.

Some key roles that the secondary metabolites play in plants are summarized as follows:

1. Plant defence against biotic stress: Plants face the risk of being damaged by biotic stress such as pathogens, herbivores etc. To counter these risks several secondary metabolites are produced by the plants. Lignin gives structural integrity to the plants by accumulating around the cell wall, thus giving the first line barrier against any kind of mechanical damage. This hinders the attachment and penetration of several kind of pathogens in the cell wall, thus offering first resistance to diseases due to pathogenic attack (Vance, 1980).

Many plants produce cyanogenic glycosides which break down via endogenous metabolic process when tissue damage occurs due to chewing of the plant by the herbivores. This leads to production of hydrogen cyanide, by a process called cyanogenesis, which is either toxic or very distasteful to the herbivores. Thus herbivores tend to avoid those plants that produce cyanogenic glycosides as a metabolic product (Gleadow, 2002). Sterols produced from terpenes are aromatic compounds that act as repellent to some insects or herbivores (Abe I., 2007)

2. Resistance to environmental stress: With diversification of Kingdom Plantae in variable habitats, need for adaptation to these new habitats was imperative. Many new secondary metabolites produced through novel metabolic pathways helped in countering the environmental threats upon the plants due to new habitat. A diverse range of secondary metabolite produced by plant, phenylpropanoid, produced from amino acids phenylalanine and tyrosine, are known to shield the plants from the harmful effects of UV radiation in light and waterproofing the cell wall of the plants (Lowry et al., 1980). Phenylpropanoids are also precursor to compounds such as lignin, which were absent in bryophytes, now began to be developed in vascular plants. Lignin provides structural support to the plants to adapt them in the terrestrial environment, thus also protecting them from strong winds or from getting trampled by mechanical forces (Bateman et al., 1998). Draught stress signals in plants trigger synthesis of various volatile compounds such as cyanogenic glycosides, terpenes etc. that safeguard the plants from the low water conditions (Griesser et al., 2015). Besides this, different hormones in plants, such as cytokinin, auxin, gibberellin, abscisic acid, etc. are also known to provide protection to the plants from stress due to environmental vagaries.

3. Ecological interactions: Secondary metabolites do not just serve the plants that produce them, but they are known to influence the plant interaction with the biotic environment around it. One of the ecological roles of these compounds are in plant- pollinator interaction. Plant – pollinators derive mutualistic benefits from each other. Nectar produced by plants, which entices the pollinator insects, contains many metabolites that serves not just the plants but are important to the pollinators as well. For example, significant level of phenolics present in nectar act as attractant to the pollinators and prevent microbial growth in nectar, thus in turn benefitting the health of the pollinator insects (Afik et al., 2006; Bhattacharya et al., 2010). Some volatile metabolites like purine alkaloids in nectar act as signals to attract the pollinators towards the food source (Wright et al., 2013; Couvillon et al., 2015; Singaravelan et al., 2005). However, some secondary metabolites if present in nectar in more than the required concentration can be toxic to the pollinators and hence, they repel the pollinators or any other insects (Kessler and Baldwin 2008).

Metabolites produced by plants are also known to regulate their interaction with the microbiome around them. Secondary metabolites such as benzoxazinoid, coumarin terpenes, etc that are released by plant roots mediate the association of beneficial or harmful microbes with the plants. This in turn influences the plant productivity. Such plant- microbiome interactions are often studied to understand the mechanism of increasing the crop yield in agricultural practices (Pang et al., 2021). The secondary metabolites are thus crucial in modulating how the plants interact with their pollinators or other biotic factors.

4. Growth and development: Although not directly related, secondary metabolites are known to modulate various growth and developmental functions in plants. Various physiological functions such as scavenging of reactive oxygen species, production of antioxidants, coenzymes, photoprotection that are necessary for plant growth and development are associated with biosynthesis of secondary metabolites (Zhao *et al.*, 2005).

Besides proving to be beneficial to the plants that synthesize them, the following are some of the industrial applications of plant secondary metabolites:

1. Medical Application: There is an array of therapeutic benefits that plant derived secondary metabolites offer. Due to increasing demand more and more metabolites are being explored to test their properties as medicines. Metabolites used individually or in concoction with others have proven to have many therapeutic benefits. If not directly, they are also used to elicit the effect of synthetic medicines. The following chart describes the source plant and the therapeutic applications of a few plant derived secondary metabolites (Seca et al, 2019).

SOURCE PLANT *Scientific name* (Common Name)	**CONSTITUENT SECONDARY METABOLITE**	**MEDICINAL PROPERTIES**
Ocimum sanctum(Tulsi)	Terpenes , phenols, flavonoids, sterols	Used in treatment of cough, upper respiratory tract disorders, poisoning, and arthritis
Sargassumincisi folium(Brown algae)	Sarganaphthoquinoic acid, sargaquinoic acid	Shows Anti-plasmodial activity, used to treat Malaria. Also used in treatment of inflammatory bowel diseases
Boswellia sp. (a genus of resiniferous trees)	Triterpenoids, diterpenes	Used for treatment of diabetes, inflammatory diseases, Alzheimer's Disease
Eriobotrya japonica (Japanese plum)	Terpenoid glycosides	Shows anti-microbial and cytotoxic properties, can be used as a source of antioxidants
Cannabis sp.(Marijuana)	Cannabinoids	Treatment of Glaucoma, Alzheimer's Disease, nausea; used as chronic pain

		reliever
Juniperus sp.(Junipers)	Diterpenes, Lignan, flavonoids	Shows antitumor, antiviral, antibacterial properties
Scabiosa sp. (genus of Pincushion flowering plants**)**	Flavonoids, saponins, iridoids	Shows Anti-tumoral, anti-inflammatory properties

2. Flavour enhancers in food: Many plant products are utilized as spices in food. The secondary metabolites content of these spices do not just enhance the flavour and colour of food, but they have a host of medicinal properties as well. A few condiments used in food and some of their constituent secondary metabolites are described in the table below (Zachariah et al., 2018) :

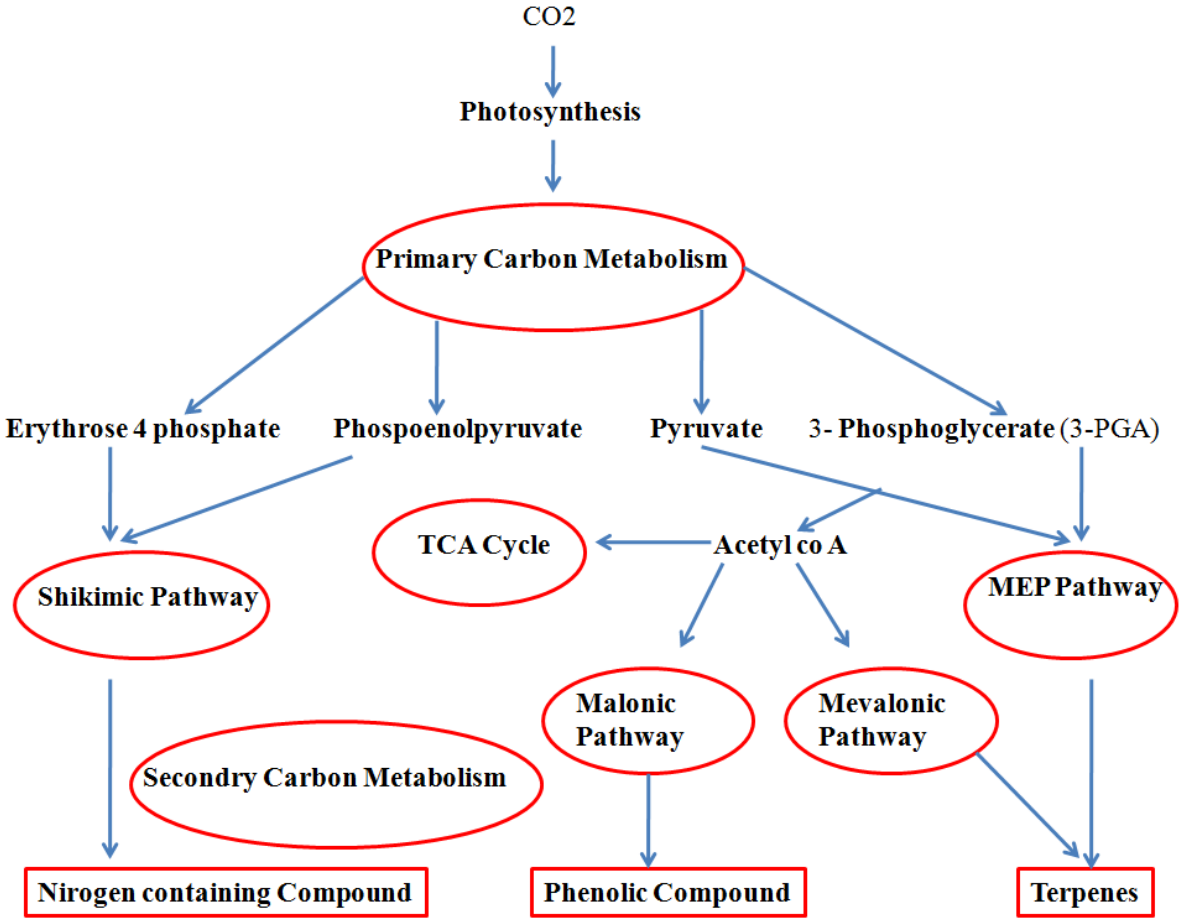
SPICES COMMONLY USED IN FOOD	SOME CONSTITUENT SECONDARY METABOLITES
Black Pepper	Alkaloid Piperine, Terpenes
Cardamom	1,8-cineole, α-terpinyl acetate
Ginger	Monoterpene, sesquiterpene hydrocarbons (eg:zingiberene)
Turmeric	Curcumin, Turmerones, oleoresin
Cinnamon	Monoterpenes, Sesquiterpenes, phenyl propenes,Cinnamaldehyde
Clove	Phenols (eg : Eugenol), methyl amyl ketone, methylsalicylate
Nutmeg	Myristic, petroselinic and palmitic acids, sabinene,α-pinene

3. Ingredients in cosmetics: The different active ingredients in secondary metabolites produced by plants have widely been used as cosmetics over the years. Because of the skin firming and whitening properties of Polyphenol, flavonoid, pelargonidin, ferulic acids, etc. and the scar repairing properties of papain these are widely used in face creams. Sunscreen formulations have flavonoids, phenolics and Chologenic acids that act as UV filters and have antioxidant properties. Several volatile compounds like Methyl jasmonate, Pinenes, etc have been used as the aromatic components of perfumes (Faccio, 2020).

4. Metabolites biosynthesis by plant system

The metabolism is explained as the sum of all the biochemical reactions occurred in a living organism. Compounds produced by plants system during biochemical reactions are categorized as a primary and secondary metabolites, Primary metabolic pathways synthesize limited numbers of end products, while secondary metabolic pathways diverge too many products (Hartmann, 2007) . Primary metabolites of plants such as carbohydrates, proteins and lipids are very much involved in the regulation of plant growth and development. In contrast, Secondary metabolites are versatile and multifunctional compounds, it plays crucial roles in plant survival and it also involved in ecological connections creation with the other

species. During metabolic reactions, plants synthesize a huge number of diverse secondary metabolites with complex chemical composition, which are produced in response to several abiotic and biotic environmental factors, as well as to fulfil some essential physiological tasks, for example attracting pollinators, establishing symbiosis and providing structural components to plant cell and tissues (Pott et al., 2019) .The type and concentration of secondary molecules biosynthesis by a plant is controlled by several componets such as plant species, genotype, developmental stage, physiology and environmental factors during growth and development. The fundamental metabolite biosynthetic pathways are conserved in the majority of plant species, in most of case, there are three important biosynthesis pathway for primary metabolites: theEmbden Meyerhof-Parnas Pathway (EMP), the Entner-Dourdorof pathway, and the hexose monophosphate (HMP) pathway. While Secondary metabolites are produced by the plant cell through metabolic pathways derived from the primary metabolic pathways. The TCA cycle, Malonic acid pathway, Mevalonic acid pathway and the shikimate pathway often serve as precursors for the synthesis of large number of secondary metabolites inside plant (Kroymann, 2011). On the basis metabolites study in plants, concerned researchers suggested that in comparison to primary metabolic pathway, secondary metabolism pathways has greater diversity at the level of cell, tissues, organs , species and even at various developmental stages (Wink et al., 2010). Some of the recent studies data on plant metabolites also strongly supported the evolution of secondary metabolism pathway by the recruitment of metabolites and enzymes from the primary metabolites synthesis pathway (de Kraker and Gershenzon, 2011; Kroymann, 2011; Carrington et al., 2018). Origin of secondary metabolic pathways from the different crucial nodes of the primary metabolic pathway, indicating that emergent specific enzymatic activity against primary metabolites yielded new molecules or compounds that were enhanced plant adaptation capacity to the particular environments and theses newly synthesize compounds were slowly modified into the specialized metabolites for plants (Weng, 2013).



Schematic Diagram of crucial metabolic pathway for secondary metabolites synthesis: This is a self explanatory sketch of some important pathway which are involve in secondary metabolites synthesis by plants.

Recent advances in plant secondary metabolites

India covering two important biodiversity hotspots out of the total 25 hotspots, is rich in all three levels of diversity namely, genetic, habitat and species diversity. Out of the total 3,00,000 species of higher plants in India, only a small percent has been studied so far (Rath, 2005). Due to increase demand in drugs and medical assistance, India is considered as a solution to many of these problems which may lead to the discovery of many novel drugs. Since time immemorial, India has been considered an origin of ayurvedic therapies which has a history of curing many diseases through herbal medicines like malaria, jaundice, cough, snake bite, hypertension, diabetes etc. (Senthilkumar and Vijayakumari, 2016).

Apart from India, many other indigenous cultures around the world have used traditional herbal medicine to treat innumerable maladies. Plants constitute a collective alternative for treatment of cancer in many countries. More than 3000 plants in the whole world have been described to have anticancer properties (Alves-Silva *et al.*, 2017; Tariq *et al.*, 2017). Plant secondary metabolites used for cancer treatment includes Vincristine, Paclitaxel, Homoharringtonine etc. Vincristine (1) was first approved for its clinical use as an anticancer in 1963 and it was one of the first plant-derived anticancer agents (Newman and Cragg, 2016). It is a naturally occurring alkaloid found abundantly in the leaves of Catharanthusroseus (L.) G.Don (formerly Vincarosea L.). it has been used extensively in chemotherapy mainly in pediatric oncology practice against acute lymphoblastic leukemia.

The most common methods to obtain these compounds can be by extraction from plant raw materials, by chemical synthesis and by using plant in vitro cultures. Many a times chemical synthesis of these plant metabolites is not feasible economically. In the recent decades, plant biotechnology has given a new horizon to provide not only a better tool to produce these compounds effectively but also has enhanced the quantity of production too. Till date many attempts has been made to further enhance the production using various methodologies which would aim in enhancing the metabolite biosynthesis and accumulation.

Plant cell and tissue cultures embrace great potential for controlled production of uncountable number of useful secondary metabolites. The discovery of cell cultures proficient of producing precise metabolite at a rate similar or superior to that of plants have also accelerated the advance in this field in the last few years (Varma, 2010). In order to achieve high yields for commercial exploitation, efforts have been made on isolating the cultured cell which could achieve optimum cultural conditions and further selecting high-producing strains and employing precursor feeding, transformation methods, and immobilization techniques (Dicosmo and Misawa, 1998). Transgenic hairy root cultures have transformed the role of plant tissue culture in secondary metabolite production. They are found unique due to its genetic and biosynthetic stability. They also grow faster and can be maintained easily. A wide variety of metabolites has been synthesized using this method (Giri and Narasu, 2000). These systems will become a sustainable source of important secondary metabolites as the recent advances in the field of molecular biology, enzymology and fermentation tecgnology suggests. Genome manipulation is another advance made in the production of compounds by engineered virus infected plants. These new technologies will assist to spread and enhance the constant usefulness of higher plants as renewable sources of chemicals, especially medicinal compounds.

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