Chapter 15
Plant Secondary Metabolites and Their Impact on Human Health

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15.1 Introduction

The plant kingdom creates a huge number of low-molecular-weight organic molecules (Matthias & Daniel, 2020). According to their function in fundamental metabolic processes, the phytochemical components of plants are typically divided into two groups called primary and secondary metabolites. Based on the ascribed roles for these substances, the scientific community has functionally categorized them

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into three: (1) primary metabolites, (2) secondary metabolites, and (3) hormones (Hussein & EL-Anssary, 2018). Primary metabolites are very important for plant growth (Fernie & Pichersky, 2015); secondary metabolites facilitate plant interactions with abiotic and biotic factors (Hartmann, 2007) and phytohormones, which control processes in the organism and the synthesis of other metabolites by interacting with receptor proteins (Davies, 2004; Upadhyay et al., 2022a, b).

Primary plant metabolites are more or less similar in all living cells because they are involved in basic life processes (Hussein & EL-Anssary, 2018). However, secondary plant metabolites are subsidiary processes of the shikimic acid pathway. The plant kingdom has more than 50,000 secondary metabolites. Secondary metabolites have been found to be multifunctional in the course of the investigation; they can serve as medicinal impact of herbals, which is focused on secondary plant metabolites, relieving different ailments in traditional medicine and folk applications. In modern medicine, they contributed lead molecules for the creation of drugs to treat a range of illnesses, from cancer to migraine. The primary categories of secondary plant metabolites are phenolics, alkaloids, saponins, terpenes, and lipids.

The physiology of plants and developmental stage of the plant's mineral nutrients affects production of secondary metabolites modulated by growth condition and environmental factors (Li et al., 2018; Clemensen et al., 2020). In many recent literature, the most popular method for assessing how nutrition affects plant secondary metabolites involves physiological changes brought on by plant growth conditions through analysis of metabolite profiles in response to supra- or sub-optimal nutrient concentrations and analysis of their impact on the development, growth, and biosynthesis of the plant secondary metabolites. For instance, stress caused by nitrogen, phosphate, potassium, and sulfur induced the biosynthesis of phenylpropanoids and phenolics in a number of plant species. There are lots of secondary metabolites that we can eat to improve our health, for example, carotenoids that are found in plants, algae, and photosynthetic microorganisms in their natural forms. In general, most of the carotenoids come from fruits and vegetables. The vibrant colors of pumpkins, sweet potatoes, cantaloupes, papayas, and tomatoes are derived from carotenoids, which are red, orange, and yellow (Khoo et al., 2011). The body obtains the majority of its carotenoids from leafy greens like spinach. Lycopene and zeaxanthin are two important carotenoids, which contain antioxidants that clean the human body of reactive oxygen and nitrogen species; zeaxanthin and lycopene consumption has implications for the prevention of cancer (Rao & Rao, 2007). Flavonoids are found naturally in plants and mainly found in tomatoes, mango, and litchi. Similar to carotenoids, flavonoids have antioxidant effects (Jideani et al., 2021). Free radicals damage the circulatory system's endothelial walls and may be a factor in atherosclerotic alterations. Flavonoids protect the circulatory system's walls and lower the risk of heart disease by scavenging free radicals (Lobo et al., 2010). Additionally, flavonoids inhibit the development of tumors, osteoporosis, and viral infections (Nijveldt et al., 2001). Glucosinolate is produced from amino acids which are present in cruciferous vegetables like broccoli, collard greens, cabbage, and mustard as the dietary source of humans. It acts in controlling the amount of replicating cells in a region of uncontrollable cell development by triggering apoptosis for the prevention of cancer. They also possess antioxidant capabilities, which help to defend the body against oxidative stress (Traka & Mitchen, 2008). Allium species, including onions and garlic, contain a category of terpenoids called saponins, and they are also rich in spinach, tea, and legumes. By attaching to and eliminating cholesterol from cell membranes, saponins help to maintain heart health. The danger of injury to the heart is increased by a stiff vascular system. By attaching to that cholesterol and removing it from artery membranes, saponins can stop that from happening (Böttger & Melzig, 2013). Hence, consuming saponins is thus one way to support and help in improving heart health (Marangos et al., 1984). However, a variety of conditions have an impact on their production, altering plant mechanisms. The adverse environmental stress and climatic factors are the primary stressors that influence plant physiology and have a stimulating effect on secondary metabolites in crops and medicinal plants (Wink, 2015; El-Hendawy et al., 2019). In several plant species, productions of secondary metabolites are very low which can be improved by altering biotic and abiotic elicitors and application of biotechnological tools.

15.2 Plant Secondary Metabolites

Plant synthesizes numerous low-molecular-weight organic compounds using simple inorganic compounds, and based on their potential functions, these compounds are basically divided into three classes, namely, primary metabolites, secondary metabolites, and hormones (Fig. 15.1). Primary metabolites include amino acids, common sugars, protein, and nucleic acids such as pyrimidines and purines, chlorophyll, etc. (David, 1995). Unlike primary metabolites, plant secondary metabolites (PSMs) are not essential for normal growth, development, and multiplication of living cells (Fraenkel, 1959). The word secondary often implies that this group of metabolites may not be very significant for plants but this however is not true considering the benefits and impacts of this group of metabolites. Most of the PSMs provide protection to plant from any possible damage or harm in the ecological environment (Stamp, 2003) andother possible interspecies protection (Samuni-Blank et al., 2012). PSMs may not be universal to all plants, but extraction of these metabolites from all known sources is said to be engaged in large number of biological activities. The PSMs have gained importance particularly in the fields of medicines, drugs, cosmetics, pharmaceuticals, and chemicals or recently in the field of nutraceutics (Tiwari & Rana, 2015). In fact about 25% of the total molecules used in pharmaceutical industries are of plant origin (Payne et al., 1991). For example, the active molecule in aspirin, that is, acetylsalicylate, is isolated in huge amount from plants like *Betula lenta* and *Spiraea ulmaria* (Payne et al., 1991). In the last few decades, these metabolites have been an important topic of research owing to their immense potential in human health care.

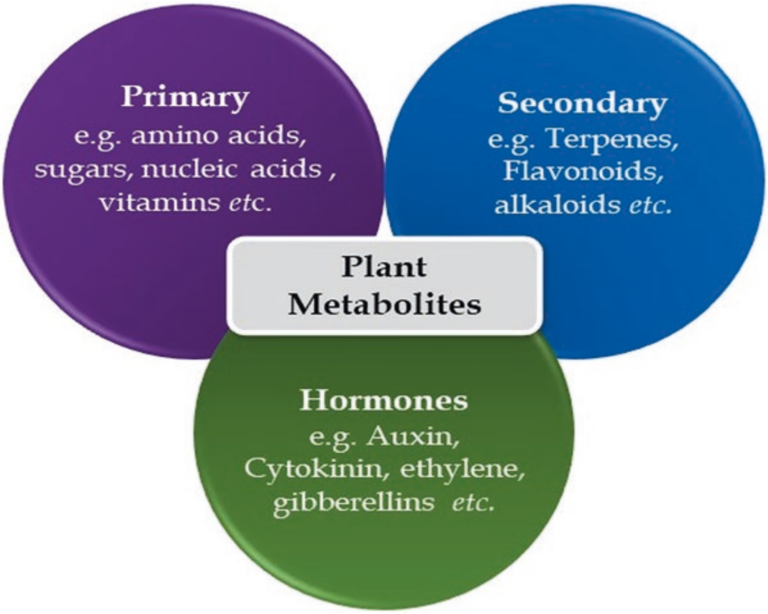

Fig. 15.1 Types of plant metabolites

15.3 Sources of Plant Secondary Metabolites

Plant secondary metabolites (PSMs) are generally considered products with high economic value and act as active ingredients in certain chemical products like medicines, flavoring agents, perfumes and fragrances, insecticides, pesticides, dyes, etc. (Thirumurugan et al., 2018). As the name suggests, these PSMs are mainly produced inside plants through various biosynthesis pathways. In common, plants are the source of 80% of secondary metabolites, and the rest is contributed by microorganisms (bacteria, fungi) and different marine species such as sponges, snails, tunicates, and corals. Table 15.1 enlists the different sources of secondary metabolites and their probable numbers (Berdy, 2005), and similarly, Table 15.2 enlists some important secondary metabolites and their source. Many more secondary products from these sources are continuously being researched upon.

15.4 Biosynthesis Pathways

Metabolites are synthesized through biochemical pathways, and their production process requires energy source which is obtained from adenosine triphosphate (ATP) (Herbert, 1989). These pathways mainly operate utilizing the energy produced during tricarboxylic acid cycle (TCA) cycle and glycolysis of carbohydrates

Table 15.1 Secondary metabolites and their abundance in nature

Sources	Identified compounds	Bioactive compounds	Antibiotic compounds
Natural products	More than a million	0.2–0.25 million	25,000–30,000
Plant kingdom	600,000–700,000	150,000–200,000	~ 25,000
Microorganisms	More than 50,000	22,000–23,000	~17,000
Algae and lichens	3000–5000	1500–2000	~1000
Higher plants	500,000–600,000	~100,000	10,000–12,000
Animal kingdom	300,000–400,000	50,000–100,000	~5000
Protozoa	Several hundreds	100–200	~50
Invertebrates	100,000	NA	~500
Marine organisms	20,000–25,000	7000–8000	3000–4000
Insects, worms, etc.	8000–10,000	800–1000	150–200
Vertebrates (mammals, fishes, amphibians, etc.)	200,000–250,000	50,000–70,000	~1000

Source: Berdy (2005)

NA – data not available

Table 15.2 Important secondary metabolites and their sources

Source	Secondary metabolites	References
Plants		
Papaver somniferum	Morphine and codeine	Siah and Doran (1991)
Sapium sebiferum	Tannin	Neera and Ishimaru (1992)
Torreya nucifera var. radicans	Diterpenoid	Orihara and Furuya (1990)
Capsicum annuum	Capsaicin	Johnson et al. (1990)
Allium sativum	Alliin	Malpathak and David (1986)
Azadirachta indica	Azadirachtin	Sujanya et al. (2008)
Cassia acutifolia	Anthraquinones	Nazif et al. (2000)
Cornus kousa	Polyphenols	Ishimaru et al. (1993)
Eriobotrya japonica	Triterpenes	Taniguchi et al. (2002)
Polygala amarella	Saponins	Desbène et al. (1999)
Camellia chinensis	Flavones	Nikolaeva et al. (2009)
Arachis hypogaea	Resveratol	Kim et al. (2008)
Gentiana macrophylla	Glucoside	Tiwari et al. (2007)
Microorganisms		
Streptomyces sp. BD21–2	Bonactin	Schumacher et al. (2003)
Streptomyces chibaensis	Resistoflavine	Gorajana et al. (2007)
Streptomyces sp. M491	Chalcomycin A and terpenes	Wu et al. (2007)
Bacillus coagulans	Coagulin	Le Marrec et al. (2000)
Bacillus amyloliquefaciens FZB42	Bacillomycin	Ramarathnam et al. (2007)
B. subtilis	Bacilysocin	Tamehiro et al. (2002)
P. stutzeri KC	Pseudomonine	Lewis et al. (2000)
Penicillium raistrickii	Oxaline	Sumarah et al. (2011)
Monascus ruber, *Aspergillus terreus*	Lovastatin	Dewick (2009)

(Kabera et al., 2014). The production of ATP takes place from the catabolism that involves oxidation of primary metabolites like amino acids, fats, and glucose. Adenosine triphosphate utilized here is reutilized in anabolic processes involving intermediate molecules of the pathways. Catabolism occurs through oxidation whereas anabolism process requires reduction, and hence, there is a need for reducing agent which is usually the NADP (nicotinamide adenine dinucleotide phosphate). The catalyst for the reaction is coenzyme, and the most dominant coenzyme A (CoA) is made up of ADP (adenosine diphosphate) and pantetheine phosphate which is chiefly responsible for donating or accepting hydrogen in anabolic and catabolic reactions, respectively (Michal & Schomburg, 2013). Biosynthesis of glycosides and polysaccharides occurs through pentose phosphate pathway whereas biosynthesis of phenols occurs through shikimic acid pathway (Kabera et al., 2014). Acetate malonate pathway leads to biosynthesis of alkaloids, and mevalonic acid pathways steer the biosynthesis of steroids and terpenes (Dewick, 2002). Fig. 15.2 briefly outlines the process of biosynthesis of PSMs through the

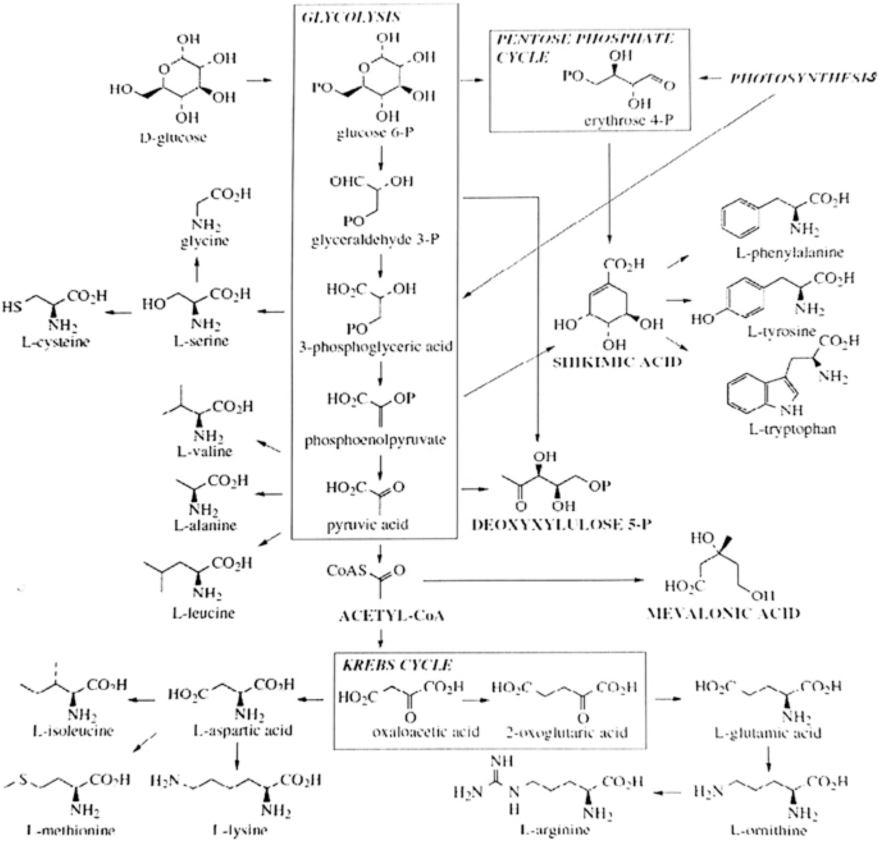

Fig. 15.2 Schematic representation of biosynthesis of plant secondary metabolites. (Adapted from Kabera et al., 2014)

process of photosynthesis, glycolysis, TCA, or Krebs cycle. Generally, the important building block involved in the biosynthesis of secondary metabolites is derived from acetyl-CoA (acetyl coenzyme A), shikimic acid, mevalonic acid, and 1-deoxylulose 5-phosphate ((Kabera et al., 2014). Commercial production of these secondary metabolites may be done through modified synthetic pathways either from primary metabolites or from substrates having primary metabolite origin. Apart from chemical synthesis, PSM production was earlier achieved through cultivation of medicinal plants; however, it is a very time-consuming method. Plants originating from particular biotopes were not easy to cultivate outside their existing local environmental conditions; also there were problems of pathogen sensitiveness. Also the amount of PSM produced in nature is very meagre and thus requires immense harvesting to obtain sufficient quantities of these molecules for preparation of botanical drugs, etc. As a result, plant cell, tissue, and organ culture approach was considered by scientists and biotechnologists as an alternative way for PSM production (Thirumurugan et al., 2018). These culture techniques can be used in a routine manner under aseptic conditions from explants such as roots, shoots, leaves, meristems, etc. for both extraction and multiplication purposes. The process of in vitro production of PSM has been used and reported from commercial medicinal plants. Zenk (1991) were able to observe that differentiated cell culture from commercial medicinal plants could produce anthraquinones @2.5 g/l of medium. This was the beginning of an era of use plant tissue cultures for the production of PSM of pharmaceutical and industrial interests (Bourgaud et al., 2001). This method showcased some real life practical advantages over conventional method which are listed as follows:

1. There was no dependency on climate and soil conditions for production of PSMs, and useful molecules can be produced under controlled conditions.
2. Since cultured cells would be prepared under aseptic conditions, it would be devoid of microbial contamination.
3. Metabolites produced under harsh climates can also be easily produced and multiplied in laboratory conditions.
4. Automatic system of regulation of cell growth would reduce the labor cost to a great extent and improve productivity.
5. Substances with organic origin could also be extracted from callus cultures.

Due to these benefits, research in the area of tissue culture technology for production of PSM has become quite popular in recent years.

15.5 Classification of Plant Secondary Metabolites (PSMs)

More than 2.14 million secondary metabolites have already been identified, and their vast diversity in structure, function, and biosynthesis serves as the basis of classification of PSMs. Basically, PSMs are classified into three broad groups, that

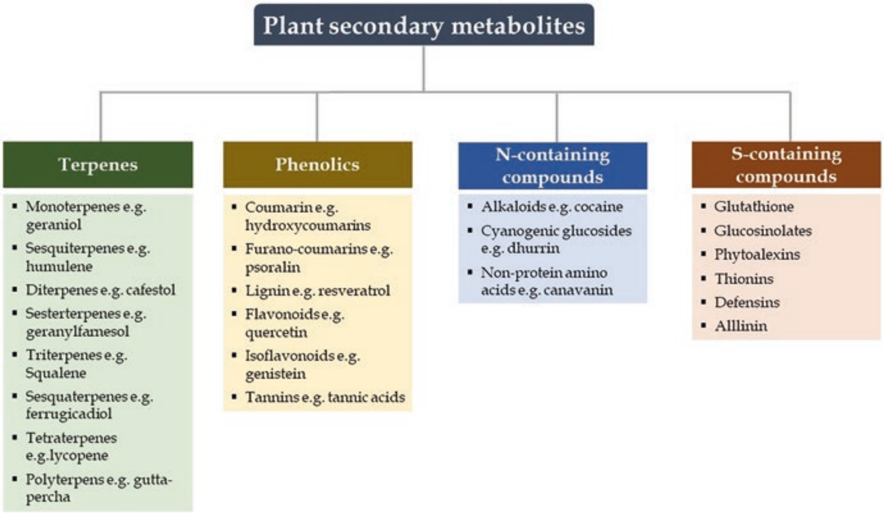

Fig. 15.3 Types of plant secondary metabolites. (Source: Twaij & Hasan, 2022)

is, terpenes, phenolics, and nitrogen- and sulfur-containing compounds. The types of secondary metabolites under each broad category have been outlined in Fig. 15.3.

15.5.1 Terpenes

This class of PSM is considered as one of the most dominating groups among all secondary metabolites. It is a group of most active compounds having more than 23,000 known structures. Structurally, terpenes are hydrocarbon-based natural product with isoprene (5-carbon units) as the basic unit. These polymers of isoprene derivatives are synthesized from acetate via the mevalonic acid pathway. Their classification is based on number of units incorporated into a particular terpene.

They have a general formula of C_5H_8 where depending upon value of n, it is classified as monoterpenoids, diterpenoids, triterpenoids, and so on. These terpenes have pharmacological importance and are used for treatment of ailments in both humans and animals. Recently, the potential of this group of metabolites to showcase antihypertensive activity has been discovered which can represent a new era of medicine (Kabera et al., 2014). Besides, they also have antibacterial and insecticidal properties which make them important for manufacturing of insecticides and pesticides for agricultural and horticultural use to counter the biotic stress (Kabera et al., 2014). The monoterpenoids include menthol, eugenol, and camphor which are reported to be possessing high antioxidant property. Certain groups of diterpenoids like resins and taxol have been identified to have anticancer properties. The triterpenoids like cardiac glycosides, ursolic acid, and steroids possess significant cytotoxic, sedative, and anti-inflammatory properties (Velu et al., 2018).

15.5.2 Phenolics

Phenolic groups of secondary metabolite are characterized by the presence of a hydroxyl functional group (phenol group) on aromatic ring. Phenolics act as a major defense system against pest, diseases, and pathogens including root-infesting nematodes. They have anti-inflammatory, anti-oxidative, anticarcinogenic, antibacterial, and anti-helminthic properties and also provide protection from oxidative stress (Park et al., 2001). These are produced by plants which are recognized to have health benefits like vegetable, fruits, tea, cocoa, etc. These groups of secondary metabolites occur in almost all plants and are subjected to a number of biological, agricultural, chemical, and medical researches (Dai & Mumper, 2010). Phenolics are classified on the basis of (i) number of hydroxylic groups; (ii) chemical composition, namely, mono-, di-, oligo-, and polyphenols; and (iii) number of aromatic rings and carbon atoms in the side chain, for example, phenolic with one, two aromatic rings, quinones, and polymers. Polyphenols are further subdivided into flavonoids and non-flavonoids like tannins. Flavonoids are found in vacuole of plant cell as water-soluble pigments which are further subdivided into anthocyanin, flavones, and flavonols. Tannins are also water-soluble compound, and they can form the complex with proteins, cellulose, starch, and different minerals. Their synthesis is mainly governed by shikimic acid pathway, also known as the phenylpropanoid pathway as it also leads to the formation of other phenolics such as isoflavones, coumarins, lignins and aromatic amino acids, etc. (Kabera et al., 2014).

15.5.3 Nitrogen- and Sulfur-Containing Compounds

This group is inclusive of phytoalexins, defensins, thionins, and alliin which have been associated directly or indirectly with the defense of plants against various microbes having pathogenic activity (Grubb & Abel, 2006). Glucosinolate (GSL) is a group of low-molecular-mass N (nitrogen) and S (sulfur) containing plant glucosides that is produced by higher plants. This GSL imparts resistance against the unfavorable effects of predators, competitors, and parasites because when it breaks down, certain volatile-defensive substances are released exhibiting toxic or repellent effects (Jamwal et al., 2018). Nitrogen-containing PSM includes alkaloids, cyanogenic glucosides, and nonproteins amino acids, and most of N-containing PSMs is biosynthesized from amino acids (Jamwal et al., 2018). Alkaloids are compounds composed of nitrogen, carbon, oxygen, and hydrogen, but in some cases, elements like phosphorus, chlorine, sulfur, and bromine may also be present in the alkaloid structures (Nicolaou et al., 2011). They are found in approximately 20% of the species of vascular plant and primarily responsible for defense against microbial infection. The primary, secondary, and tertiary amines responsible for the basic nature present in the alkaloid groups are classified on the basis of the number of nitrogen atom existing in the alkaloid group (Velu et al., 2018). The extent of basicity of alkaloids depends upon the variation in the chemical configuration of the molecular structure and the occurrence of various functional groups at different locations in the alkaloid molecule (Sarker & Nahar, 2007). Some important alkaloids are morphine (used as analgesics), berberine (used as antibiotics), vinblastine (with anticancer properties), etc. Apart from these, other important alkaloids include codeine, nicotine, coniine, cytisine, solanine, quinine, strychnine, tomatine, etc.

15.6 Functions of Secondary Metabolites in Plants

Secondary substances have signaling functions, influence the activities of other cells, regulate their metabolic activities, and coordinate the development of the whole plant. Other substances, such as flower color, help communicate with pollinators and protect plants from animal damage and infection by producing specific phytoalexins after fungal infection and fungal hyphae within plants, and inhibits body diffusion (Mansfield, 2000). Plants also use phytochemicals (such as volatile essential oils and colored flavonoids or tetraterpenes) to attract insects for pollination and other animals for seed dispersal. Compounds belonging to terpenoids, alkaloids, and flavonoids are currently used as pharmaceuticals or dietary supplements to treat or prevent various diseases (Raskin et al., 2002) and cancer (Reddy et al., 2003; Watson et al., 2001). It is estimated that 14–28% of higher plant species are used for medicinal purposes, and 74% of pharmacologically active plant constituents were discovered after ethnomedical use of plants (Ncube et al., 2008). Secondary metabolites are metabolic intermediates or products that occur as a product of differentiation in restricted taxa, are not essential for the growth and life of the producing organism, and are derived from one or more common metabolites. They are biosynthesized via more diverse metabolic pathways (Mansfield, 2000). The presence of volatile monoterpenes or essential oils in plants provides plants with an important defense strategy, especially against herbivorous pests and pathogens. Volatile terpenoids also play important roles in plant interactions and act as pollinator attractants (Tholl, 2006). They function as signaling molecules and show evolutionary relationships with their functional roles. Soluble secondary compounds such as cyanogenic glycosides, flavonoids, and alkaloids can also be toxic to animals.

15.7 Benefit of Plant Metabolites in Human Health

1. Anti-inflammatory and Antioxidant Compounds.

Diseases like diabetes, cancer, and photoaging can be attributed to inflammation as their causative agent or triggering factor. Inflammatory responses modify the transcriptome by upregulating several transcription factors and pro-inflammatory cytokines of our tissues. A solution to unresolved inflammation could be plant bioactive compounds that exhibit natural anti-inflammatory activities, often in conjugation with antioxidant properties (Teodoro, 2019).

2. Neuroprotective Compounds.

The neurological disorders such as Alzheimer's disease, multiple sclerosis, Parkinson's disease, neuropathic pain, etc. can be traced back to neuro-inflammation. Both age-related conditions and age-independent pathologies could lead to neuro-inflammation via similar cascade. About two million people worldwide die of cerebral ischemic diseases every year. Some remedies for this condition come from herbal sources (Teodoro, 2019). The effect of total flavonoids was studied from *Abelmoschus esculentus* L. against transient cerebral ischemia reperfusion injury (Lau et al., 2008). It was suggested that the protective effects were due to direct or indirect antioxidant actions via free radical scavenging or activation of Nrf2-ARE pathway, respectively. Oxidative damage plays an important role in neuronal damage, which may proceed to cause neurodegenerative diseases such as Alzheimer's disease. Pequi, a phytomedicine derived from *Caryocar brasiliense* of Caryocaraceae family, is known to be a potential neuroprotective medicine. de Oliveira et al. (2018) reported the mechanism of this neuroprotective effect to be due to anticholinesterase or antioxidant properties. Some procyanidins, extracted from lotus seedpod, exhibited anti-Aβ effects in rat models.

3. Anticancer Compounds.

Nowadays, several plant bioactive compounds are gaining importance as anticancer agents. Several studies also show that these natural components increase the efficacy of chemotherapy and sometimes even reduce the side effects of chemotherapeutic drugs (Ramakrishna et al., 2021). Four such plant-based bioactive compounds, namely, curcumin, myricetin, geraniin, and tocotrienols, are well known for their anticancer properties (Subramaniam et al., 2019). A major class of vitamin E, tocotrienol, is also known for its anticancer properties. It is present in plant products like rice bran oil, palm kernel oil, etc. (Aggarwal et al., 2010). Both in vitro cell-based studies and in vivo animal model experiments proved that tocotrienol exhibits antitumor properties and prevents proliferation of cancer cell lines such as pancreatic, liver, stomach, lung, and breast cancers (Ramakrishna et al., 2021).

4. Antiviral Effects of Plant Bioactive Compounds.

Bioactive herbal extracts have long been used to treat ailments such as viral infections. In the current situation of the COVID-19 pandemic, we can rely on some of these plant bioactive secondary metabolites as antiviral agents. Human coronaviruses, such as the COVID-19 severe acute respiratory syndrome (SARS) coronavirus (Geller et al., 2012) and the Middle East respiratory syndrome coronavirus (MERS-CoV), can cause the common cold, which primarily affects the respiratory tract, but there is no vaccine. Sometimes it turns out to be fatal. Naturally occurring terpene iodine glycosides such as saikosaponins (A, B2, C, and D) found in *Bupleurum* spp., *Heteromorpha* spp., and *Scrophularia scorodonia* are known for their antiviral activity against one of the human coronaviruses HCoV229E (Cheng et al., 2006).

15.8 Effect of External Factors on Plant Secondary Metabolites

Plant secondary metabolites (PSMs) are generally unique sources of medications, food additives, flavors, and biochemicals of industrial significance. In plants exposed to various elicitors or signal molecules, the buildup of such metabolites frequently occurs. Secondary metabolites are crucial for a plant's environmental adaptability and stress tolerance. The effects of temperature, humidity, light intensity, water availability, minerals, and CO_2 on plant growth and the synthesis of secondary metabolites are many (Akula & Gokare, 2011). Examples of environmental conditions that have a detrimental effect on plant development and agricultural productivity include drought, high salt, and cold temperatures. The various outside variables that affect plant secondary metabolites are as follows:

Influence of Salt Stress The presence of salt in the environment encourages cellular dehydration, which results in osmotic stress and water loss from the cytoplasm and a decrease in the volumes of the cytosol and vacuoles. Ionic and osmotic stresses are brought on by salt stress in plants, and this leads to the accumulation or loss of certain secondary metabolites. In contrast to salt-sensitive plants, salt-tolerant alfalfa plants quickly quadrupled their proline concentration in roots (Petrusa & Winicov's, 1997). Proline accumulation and salt tolerance, however, were found to be correlated in *Lycopersicon esculentum* and *Aegiceras corniculatum*, respectively (Aziz et al., 1998). It was discovered that endogenous JA accumulated in tomato cultivars during salt stress. In general, biotic or abiotic stressors enhance the synthesis and accumulation of polyphenols. Numerous plants have also been shown to contain more polyphenols in various tissues when exposed to increased salt. According to Navarro et al. (2006), red peppers had an elevated total phenolic content and a fairly high salt content. It has been demonstrated that plant polyamines have a role in the way plants react to salt. It was discovered that the levels of free and bound polyamines in the roots of sunflower (*Helianthus annuus* L.) changed as a result of salinity. The examples of salt stress on various secondary metabolites in plant are summarized in Table 15.3.

Influence of Drought Stress Among the most critical environmental stresses affecting plant growth and development are oxidative stress and flavonoids and phenolic acids in willow leaves. Willows grown under drought stress were reported to have increased flavonoid and phenolic acid amounts. Chlorophyll "a" and "b" and carotenoids are affected by drought stress. A reduction in chlorophyll was noticed in cotton under drought stress. Saponins were reported to have lower amounts in *Chenopodium quinoa* plants growing in high water-deficit conditions compared to those growing in low water-deficit conditions. Anthocyanins accumulate in plants under drought stress and at cold temperatures. Plant tissues containing anthocyanins are usually resistant to drought. Anthocyanins are flavonoids that are primarily responsible for shielding plants against drought. For example, chili plants with purple colors withstand drought better than green ones.

Table 15.3 Salt stress on various secondary metabolites in plant

Plant species used	Secondary metabolites	Source
Tomato (*Lycopersicon esculentum* L.)	Sorbitol	Tari et al. (2010)
Sesame (*Sesamum indicum* L.)	GABA	Bor et al. (2009)
Barley (*Hordeum vulgare* L.)	Flavonoids	Ali and Abbas (2003)
Tomato (*Lycopersicon esculentum* L.)	Jasmonic acid	Pedrazani et al. (2003)
Sea rocket (*Cakile maritime*)	Polyphenol	Ksouri et al. (2007)
Prickly burr (*Datura innoxia*)	Tropane alkaloids	Brachet and Cosson (1986)
Silky oak (*Grevillea spec.*)	Anthocyanins	Parida and Das (2005)
Soybean (*Glycine max* L.)	Trigonelline	Cho et al. (1999)
White clover (*Trifolium repens*)	Glycinebetaine	Varshney and Gangwar (1988)
Rice (*Oryza sativa* L.)	Polyamines	Krishnamurthy and Bhagwat (1989)
Wheat (*Triticum aestivum* L.)	Glycine betaine	Krishnamurthy and Bhagwat (1990)
Cenchrus pennisetiformis	Sucrose and starch	Ashraf (1997)

Influence of Heavy Metal Stress Secondary metabolites are also controlled by metal ions (lanthanum, europium, silver, and cadmium) and oxalate (Marschner, 1995). The urease enzyme, which contains nickel (Ni), is crucial to plant growth and requires Ni. Increased Ni concentrations, on the other hand, inhibit plant growth. The anthocyanin levels decrease significantly. Ni has also been established to inhibit anthocyanin accumulation (Hawrylak et al., 2007). Ni has been shown to inhibit accumulation of anthocyanins (Krupa et al., 1996). The concentration of metals (Cr, Fe, Zn, and Mn) produced an oil content of 35% in *Brassica juncea*, which was effective at accumulating metals (Singh & Sinha, 2005). Cu^{2+} and Cd^{2+} have been shown to increase the production of secondary metabolites like shikonin (Mizukami et al., 1977) and digitalin (Ohlsson & Berglund, 1989). Cu^{2+} enhances betalain production in *Beta vulgaris* (Trejo-Tapia et al., 2001). Co^{2+} and Cu^{2+} stimulate the production of betalains in *Beta vulgaris* (Trejo-Tapia et al., 2001).

Influence of Cold Stress The most harmful abiotic stress affecting temperate plants is low temperature. Cold stress boosts phenolic production and subsequent incorporation into the cell wall as suberin or lignin. Cold stress recently has been shown to influence polyamine accumulation. When wheat (*Triticum aestivum* L.) leaves are exposed to a chilly temperature, putrescine (6–9 times) accumulates instead of spermidine, and spermine declines moderately. In addition, alfalfa (*Medicago sativa* L.) produces putrescine under low temperature stress. Cold tolerance is associated with higher amounts of polyamines (agmatine and putrescine), and their amount can be an important indicator of chilling tolerance in seedlings of *P. antiscorbutica*, according to Hummel et al. (2004).

Influence of Light It is known that light is an abiotic factor that affects metabolite production in *Z. officinalis*. It stimulates such secondary metabolites as gingerol and zingiberene in *Z. officinalis* culture when it is combined with UV light. The effect of UV light on anthocyanin accumulation in light-colored sweet cherries was studied by Arakawa et al. (1985). Anthocyanins are synthesized synergistically when UV light with a wavelength of 280–320 nm is combined with red light in apples (Arakawa et al., 1985). The effects of environmental factors such as light intensity, irradiance (continuous irradiance or continuous darkness), and cell biomass yield and anthocyanin production in *Melastoma malabathricum* cultures were investigated by Chan et al. (2010). Moderate light intensity (301–600 lx) resulted in higher anthocyanin levels, while cultures that were exposed to a 10-day period of continuous darkness showed the lowest pigment concentration. Conversely, cultures that were continuously irradiated showed the highest pigment concentration.

Influence of Polyamines In addition to bacteria, plants, and animals, putrescine, spermine, and spermidine are present in a wide variety of organisms (Gill & Tuteja, 2010). Polyamines play an important role in plant development, senescence, and stress responses. Polyamines are present in plants in high quantities and are involved in a variety of physiological processes. Polyamines are present in a wide range of plants and are involved in various physiological processes, including development, senescence, and response to stress. Plants that are tolerant to environmental stresses have higher levels of polyamines than susceptible plants. Polyamine biosynthesis is enhanced in response to environmental stresses in stress-tolerant plants as compared with susceptible plants.

Influence of Plant Growth Regulators Plant organ and tissue cultures have been reported to generate secondary metabolites. Many researchers have tried to increase the productivity of plant tissue cultures by studying hormone-dependent media composition, media composition, and light exposure (Karuppusamy, 2009; Ravishankar & Venkataraman, 1993; Tuteja & Sopory, 2008). Anthocyanin production in plant cell cultures is more productive, with a dry weight yield of up to 20% (Ravishankar & Venkataraman, 1993). 2,4-D, IAA, and NAA, among other cytokinins, promoted growth and anthocyanin synthesis when supplemented at varying concentrations (Narayan et al., 2005; Nozue et al., 1995). Kinetin, which was supplied at 0.1 and 0.2 mg l-1, was the most productive cytokinin. Anthocyanin production and methylation were enhanced when IAA was supplemented at 2.5 mg l-1 and kinetin at 0.2 mg l-1, which was superior to other combinations. Lower concentrations of 2,4-D in the medium limited cell growth and increased both anthocyanin production and methylation (Narayan et al., 2005; Nozue et al., 1995).

Influence of Nutrient Stress When plants are deprived of nutrients, secondary metabolite production may increase because photosynthesis is usually less inhibited than growth, and carbon is allocated predominantly to secondary metabolites. In addition, nutrient deprivation has a significant effect on phenolic levels in plant tissues. Because of the accumulation of phenylpropanoids and lignifications caused by deficiencies in nitrogen and phosphate, osmotic stress resulting from sucrose and other osmatic agents controls anthocyanin production in *Vitis vinifera* cultures.

Influence of Climate Change The level of biodiversity and crop productivity, human and animal health, and well-being in the coming decades will depend on climate change (IPCC, 2007). In the next 50 years, the productivity of cold weather crops such as rye, oats, wheat, and apples is estimated to decrease by 15% (Pimm, 2009). Climate change will cause a decrease in productivity of strawberries by as much as 32% in the next 50 years (Pimm, 2009). In particular, plants are very sensitive to climate change and do not adapt quickly to abnormal conditions. Ozone exposure has been shown to increase conifer phenolic concentrations, whereas low ozone exposure has no effect on monoterpene and resin acid concentrations (Kainulainen et al., 1998). When grown in high CO_2 levels, plants exhibit substantial chemical adjustments. N concentration is lowered in vegetative plant parts, seeds, and grains as a result of lowered protein levels, resulting in decreased protein amounts. In a previous study, elevated CO_2 caused a decline in N concentration in vegetative plant parts, as well as those in seeds and grains, resulting in a decline in the protein level.

15.9 Improving the Production of Secondary Plant Metabolites

The plant secondary metabolite (PSM) synthesized in the plants is very important because of the various health benefits of it in the human body. The major PSMs are phenolic compounds, flavonoids, and anthocyanins. The significant benefits of using phenolics are due to its antioxidant activity, as well as its anti-inflammatory, anticancer, and antitumor properties. These compounds are synthesized with the shikimate pathway in the plant. The accumulation of secondary metabolites usually occurs in plants where they are subject to several stressors and elicitors. Various chemical, physiological, and microbial features act as abiotic or biotic triggers, ultimately leading to increased secondary metabolites (Radman et al., 2003). Drought, salinity, and cold/hot weather are natural conditions that adversely affect crop growth and production (Ramakrishna & Ravishankar, 2011). Elicitors are compounds from abiotic and biotic sources that stimulate plant stress responses, leading to enhanced secondary metabolites or introduction of secondary metabolites (Naik & Al-Khayri, 2016). Various abiotic (salt, light, heavy metals, temperature, drought, etc.) and biotic (proteins, carbohydrates, fungi, arbuscular mycorrhizal fungi) promote the production of the following metabolites (Table 15.4). Several horticultural products such as pears, peaches, mangoes, lychees, onions, apples, hibiscus flowers, green tea, pineapples, and sweet potatoes contain large amounts of antioxidants. Flavonoids are naturally produced in plants. They are phenolic compounds that contribute to their antioxidant capacity. There are some crops with low natural production of flavonoids. In this case, genetic engineering could help improve flavonoid production in crops (Hichri et al., 2011). Anthocyanins are a class of naturally occurring flavonoids found in plants that produce red, purple, and blue colors in

Table 15.4 Biotic and abiotic stresses on the production of various secondary metabolites in plants

Common name	Plant species	Elicitor	Compounds	References
California poppy	*Eschscholzia californica*	Yeast cell	Benzophenanthridine	Farber et al. (2003)
London plane	*Plantanus acerifolia*	Glycoprotein	Coumarin	Alami et al. (1998)
Ashwagandha	*Withania somnifera*	Chitosan	Withaferin A	Gorelick et al. (2015)
Turmeric	*Curcuma longa* L.	Chitosan	Curcumin	Sathiyabama et al. (2016)
Capsicum	*Capsicum annuum*	Cellulase	Capsidol	Patrica et al. (1996)
Opium poppy	*Papaver somniferum*	Chitin	Sanguinarine	Radman et al., 2003
Grape	*Vitis vinifera*	Oligogalacturonic acid	Trans-resveratrol, Viniferin	Taurino et al. (2015)
Plumbago indica	*Plumbago rosea*	Oligogalacturonic acid	Plumbagin	Komaraiah et al. (2003)
Common rue	*Ruta graveolens*	Oligogalacturonic acid	Fluoroquinolone alkaloids	Orlita et al. (2008)
Chinchilla	*Tagetes minuta*	*Pseudomonas fluorescens* and *Azospirillum brasilense*	Monoterpenes, phenolic compounds	Cappellari et al. (2013)
Candy leaf	*Stevia rebaudiana*	*Bacillus polymyxa*, *Pseudomonas putida*, *Azotobacter chroococcum* and *Glomus intraradices*	Stevioside	Vafadar et al. (2014)
Tulsi	*Ocimum basilicum*	*Bacillus subtilis*	α-Terpineol and eugenol	Banchio et al. (2009)
Sweet marjoram	*Origanum majorana* L.	*Pseudomonas fluorescens* and *Bradyrhizobium* sp.	Terpinene-4-o1, cis-sabinene hydrate, trans-sabinene hydrate, and α-terpineol	Banchio et al. (2008)
Pea	*Pisum sativum*	*Pseudomonas aeruginosa* and *Pseudomonas fluorescens*	Phenolic compounds (gallic, cinnamic, ferulic acid)	Bahadur et al. (2007)
Malabar begonia	*Begonia malabarica*	*Glomus mosseae*, *Bacillus coagulans*, and *Trichoderma viride*	Total phenols, orthodihydroxy phenols, tannins, flavonoids, saponins, and alkaloids	Selvaraj et al. (2008)
Cape periwinkle	*Catharanthus roseus*	*Trichoderma viride*	Ajmalicine	Namdeo et al. (2002)

(continued)

Table 15.4 (continued)

Common name	Plant species	Elicitor	Compounds	References
Red sage	*Salvia miltiorrhiza*	*Bacillus cereus*	Tanshinone	Zhao et al. (2010)
Tropical soda apple	*Solanum viarum*	*Glomus aggregatum*, *Bacillus coagulans*, and *Trichoderma harzianum*	Total phenols, orthodihydroxy phenols, tannins, flavonoids, saponins, and alkaloids	Hemashenpagam and Selvaraj (2011)
Common basil	*Ocimum basilicum*	*Aspergillus niger*	Rosmarinic acid	Bais et al. (2002)
Nepal yam	*Dioscorea deltoidea*	*Rhizopus arrhizus*	Steroid (diosgenin)	Rokem et al. (1984)
Common bean	*Phaseolus vulgaris*	*Colletotrichum lindemuthianum*	Krevitone	Dixon et al. (1981)
Turmeric	*Curcuma longa*	*Azotobacter* and *Azospirillum*	Curcumin	Sena and Dass (1998)
Tamarind	*Azadirachta indica*	*Claviceps purpurea*	Azadirachtin	Satdive et al. (2007)
Coleus	*Coleus forskohlii*	*Glomus mosseae* and *Trichoderma viride*	Forskolin	Body and Bagyaraj (2003)
Grape	*Vitis vinifera*	Ethylene, IAA + GA3, and BAP + NAA	Stilbene, resveratrol, anthocyanins	Kin and Kunter (2009) and Qu et al. (2006)
Indian snakeroot	*Rauvolfia serpentina*	BAP + IAA	Serpentine	Salma et al. (2008)
Neem	*Azadirachta indica*	2,4-D	Azadirachtin	Sujanya et al. (2008)
Capsicum	*Capsicum annuum*	2,4-D + GA3, 2,4-D + Kin, and 2,4-D + Kn	Capsaicin	Umamaheswai and Lalitha (2007)
Alexandrian senna	*Cassia acutifolia*	2,4-D + kinetin	Anthraquinones	Nazif et al. (2000)
Beet	*Beta vulgaris*	IAA	Betalain	Taya et al. (1992)
Ashwagandha	*Withania somnifera*	Methyl salicylate	Withaferin A	Gorelick et al. (2015)
Grape	*Vitis vinifera*	Salicylic acid	Stilbene	Xu et al. (2015)
Carrot	*Daucus carota*	Salicylic acid	Chitinase	Muller et al. (1994)
Foxglove	*Digitalis purpurea*	Salicylic acid	Digitoxin	Patil et al. (2013)
Red sage	*Salvia miltiorrhiza*	Salicylic acid	Tanshinones	Xiaolong et al. (2015)
Indian madder	*Rubia cordifolia*	Salicylic acid	Anthraquinone	Bulgakov et al. (2002)
Peppermint	*Mentha piperita*	Jasmonic acid and methyl salicylate	Rosmarinic acid	Krzyzanowska et al. (2012)

Table 15.4 (continued)

Common name	Plant species	Elicitor	Compounds	References
Grape	*Vitis vinifera*	Methyl salicylate and jasmonic acid	Anthocyanin, stilbene, and trans-resveratrol	Xu et al. (2015) and Taurino et al. (2015)
Red raspberry	*Rubus idaeus*	Methyl salicylate	Rubusidaeus ketone benzal acetone	Pedapudi et al. (2000)
Ashwagandha	*Withania somnifera*	Methyl salicylate	Withanolide A, withanone, and withaferin A	Sivanandhan et al. (2013)
Mexican cedar	*Cupressus lusitanica*	Methyl salicylate	β- hujaplicin	Zhao et al. (2001)
Opium poppy	*Papaver somniferum*	Drought stress	Morphine alkaloids	Szabo et al. (2003)
Red sage	*Salvia miltiorrhiza*	Water stress	Salvianolic acid	Liu et al. (2011)
Candy leaf	*Stevia rebaudiana*	Polyethylene glycol	Steviol glycosides	Pratibha et al. (2015)
Salix	*Salix* sp.	Drought	Flavonoids and phenolics	Larson (1988)

flowers, fruits, and leaves and also have antibacterial properties. Health benefits of anthocyanins include protecting coronary arteries, improving vision, and preventing diabetes and obesity. The mechanism of action of anthocyanins is cell signaling-mediated antioxidant activity in mammals. Genetic engineering is used in various crops such as papaya and tomato. Although the anthocyanin content in tomato is very low, a large number of transcription factors and enzymes are involved in anthocyanin biosynthesis. In this regard, anthocyanin-rich transgenic tomatoes are enhanced by highlighting the endogenous ANT1 gene, which helps regulate the binding properties of anthocyanins and extracts, resulting in anthocyanin-rich purple tomatoes. Purple tomatoes were discovered in 2008 by two snapdragon gene compounds, Delilah (Del) and Rosea1 (Ros1), that cause anthocyanin accumulation (Mooney et al., 1995). These genes triple the antioxidant capacity of the tomato fruit, giving the fruit a purple exocarp and mesocarp. Furthermore, feeding tomato-sensitive mice with tomato anthocyanin content was found to extend the life span of the mice, suggesting that these compounds may reduce cancer growth (Giampieri et al., 2018). The transcription factors MYB75 and PAP1, identified in *Arabidopsis*, are involved in anthocyanin regulation (Zuluaga et al., 2008). These genes are introduced into the tomato genome. They have also been shown to independently induce anthocyanin production into tomato plant tissues (Bassolino et al., 2013). Carnation- and rose-transgenic plants probe a dark purple anthocyanin known as delphinidin to synthesize DRF-A and F5’30H from petunia (including the anthocyanin pathway). Transgenic cotton plants producing the Lc gene (a leaf color gene involved in anthocyanin regulation) resulted in purple leaves and reddish anthers and anthers through the accumulation of anthocyanins. Naturally, through the use of genetic engineering and the use of newly developed generic drugs, it is possible to enhance one’s health with the help of professional consumption of fruits and vegetables that have increased levels of metabolites produced in the future. Furthermore, excess phytoene desaturase (ctrI) enzyme in tomatoes showed a 50% decrease in carotenoid content and an almost threefold increase in β-carotene. Furthermore, transgenic tomato plants producing the β-cyclase gene produced up to 60 μg/g new weight μ-carotene in tomato fruit. Plant biotechnology, such as genome editing techniques and second-generation transgenic plants, can play an important role in combating hunger, malnutrition, and certain diseases through the development of nutritionally improved crops. However, more information and policy changes are needed to bring genetically liberated transgenic plants to market and solve the human health problems of our world.

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