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Explorations of Plant's Chemodiversity: Role of Nitrogen-Containing Secondary Metabolites in Plant Defense

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Abstract

In nature, plants are surrounded by a number of biotic and abiotic environmental stresses. Biotic ecosystems contain a wide variety of bacteria, viruses, fungi, nematodes, mites, insects, mammals, and other herbivorous animals, greatly responsible for heavy reduction in crop productivity. Henceforth, to cope up from these biotic stresses, the plant defense mechanism increasingly requires the availability of large numbers of phytochemicals. Chemodiversity in plants offers a valuable source; for example, nitrogen-containing secondary metabolites, previously regarded as waste products, are now recognized for their resistant activity against herbivores, pests, pathogens, and diseases. In this chapter, I have described the increasing role of nitrogen-containing secondary metabolites during plant defense. These metabolites impose their effects by acting as deterrence/antifeedant, toxicity, or precursors to physical defense systems. Many specialized herbivores and pathogens do not merely circumvent the deterrent or toxic effects of secondary metabolites but actually utilize these compounds as host recognition signals and/or nutrients. This is true for both cyanogenic glucosides and glucosinolates which are discussed in detail. Their biochemical and molecular mechanism of action is compared and contrasted.

Keywords

Secondary metabolites · Plant defense · Pathogen · Herbivores

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14.1 Introduction

The term chemodiversity, generally, leaves aside larger molecules, which involve in vital primary metabolic functions and form the majority of the organic body mass of living beings. Thus, small molecules that often have a defensive or offensive signaling function mainly contribute to the chemodiversity. Since the beginning, humans have utilized the plants, one of the most prolific sources of biochemical diversity, for its own benefits. Since ancient times, plants have provided mankind with cures for health problems and continue to be the most capable pool of bioactive chemicals for the development of modern drugs (Dias et al. 2012; Cragg and Newman 2013; Harvey et al. 2015). More than 20,000 natural molecules have been studied so far, and numerous have been used as novel anticancer, antibiotic, anti-inflammatory or anti-pain agents, etc. In the previous few decades, plants have turned into a critical source for the discovery of novel and unique pharmaceutical compounds (Cordell 2000; Farnsworth 1988; Newman et al. 2000). Plants are reported to have high chemodiversity including more than 21,000 alkaloids, 700 nonprotein amino acids (NPAAs), 200 cyanogenic glycosides (CGs) and glucosinolates, >20,000 terpenoids, >10,000 polyphenols, >1500 polyacetylenes and fatty acids, 750 polyketides, and 200 carbohydrates (Wink 2008, 2013; Theis and Lerdau 2003).

Approximately 450 million (M) years ago, plants began to inhabit the terrestrial earth during the mid-Ordovician period and over the subsequent 40 M years spread across the earth surface. The evolution of species-specific metabolic systems from core metabolic pathways of aquatic ancestors was one of the reasons behind the success of early land plants, as they were able to synthesize the structurally and functionally diverse chemicals to cope with frequent biotic and abiotic ecological pressures (Weng et al. 2012). Several of these chemicals, such as cuticular components and phenolic compounds, are universal in all land plants and, therefore, provide indispensable physical and chemical protection against desiccation and UV radiation (Fig. 14.1). Other classes of specialized metabolites, including those that contribute to plant-specific flavors, colors, and scents, frequently occur in a lineage-specific manner and play specialized roles for the host species in their natural habitat (Weng et al. 2012). Present knowledge of secondary metabolism and its evolution in the plant has been primarily driven by studying of angiosperms or flowering plants, ranging from well-studied model species, such as rice and *Arabidopsis* (Romeo 2004; D'Auria and Gershenzon 2005), to the reference species including medicinal plants with remarkable pharmaceutical properties, e.g., *Vinca minor*, *Catharanthus roseus*, and *Rauvolfia serpentina* (Facchini and De Luca 2008; De Luca et al. 2012; Patra et al. 2013). These studies revealed massive chemical diversity in flowering plants and provide deep insight on their widespread speciation and global domination over the last 170 M years following the Permian-Triassic extinction event (Wikström et al. 2001). The vast expansion of plant chemodiversity associated with secondary metabolites reflects the tremendous adaptability of land-dwelling plants. For example, plant hormones regulate various aspects of plant growth and development in response to environmental cues, whereas phenolic and waxy cuticles act as UV protectant and prevent excessive water loss. Plant polymers

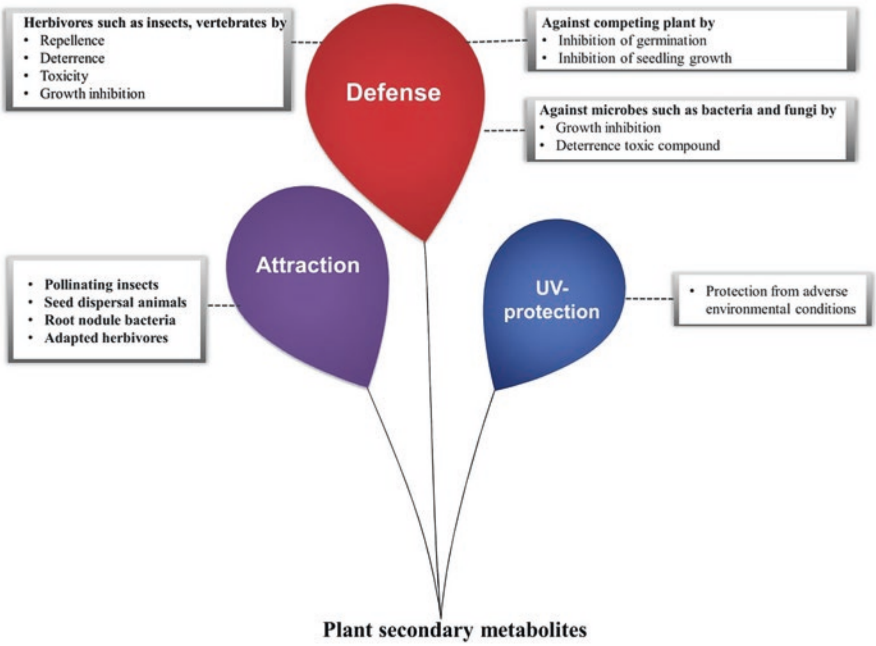

Fig. 14.1 Functional diversity of plant secondary metabolites

including lignin and sporopollenin provide mechanical support, gamete protection, and wound healing. New metabolic pathways continuously arose throughout terrestrial plant evolution, resulting in a contemporary collection of secondary metabolites. Therefore, some of these specialized metabolites are common across various taxonomic groups, while others were found in some limited species.

14.2 Secondary Metabolites Are Divided into Three Major Groups

On the basis of their chemical nature, plant secondary metabolites can be divided into three chemically distinct groups: terpenes, phenolics, and nitrogen-containing compounds.

14.2.1 Terpenes

Terpenes (also known as terpenoids) constitute the largest class of secondary metabolites. Plants and other natural sources are reported to produce more than 30,000 terpenoids (Bohlmann et al. 1998).

In plants, terpenes are biosynthesized in at least two different pathways. The main and well-studied biosynthetic route is known as the mevalonic acid (MA) pathway.

Table 14.1 Important molecules of terpenoids

Number of carbon	Name	Example
C5	Hemiterpene	Isoprene, prenol, isovaleric acid
C10	Monoterpene	Limonene, eucalyptol, pinene
C15	Sesquiterpene	ABA (abscisic acid)
C20	Diterpene	Gibberellin
C25	Sesterterpenes	Ophiobolin A, ceroplastol
C30	Triterpene	Brassinosteroids, squalene, lanosterol
C40	Tetraterpene	Carotenoids, lycopene
C>40	Polyterpenes	Ubiquinones, rubber, cytokonines, vitamin E

In the MA pathway, three molecules of acetyl-CoA are joined together in a stepwise manner to form MA. This key six-carbon intermediate then undergoes different chemical modifications like pyrophosphorylation and decarboxylation to produce isopentenyl diphosphate (IPP). Finally, IPP acts as a building block of terpenes. The second route of terpene biosynthesis is known as methylerythritol-4-phosphate (MEP) pathway, which operates in plastids (Tholl and Lee 2011; Lichtenthaler 1999). Glyceraldehyde-3-phosphate and two carbon atoms derived from pyruvate condense to form the five-carbon intermediate, 1-deoxy-d-xylulose 5-phosphate. The 1-deoxy-d-xylulose 5-phosphate further rearranged and reduced to MEP, which eventually converted into IPP.

Terpenes are the structurally diverse class of secondary metabolites from hemi- to polyterpenes (Table 14.1). All terpenes are originated from the union of five-carbon elements (also referred to as C5 units) that have the branched carbon skeleton of isopentane. The basic structural elements of terpenes are also known as isoprene, and, thus, terpenes are sometimes also called as isoprenoids. The terpenes can be classified in different groups on the basis of a number of C5 units they comprised of (Table 14.1). For instance, 10-carbon terpenes, which contain two C5 units, are called monoterpenes, while 15-carbon terpenes (three C5 units) are sesquiterpenes. In spite of structural similarities, terpenes can be synthesized in different compartments in the cell. For instance, nowadays it is believed that sesquiterpenes and triterpenes are synthesized through the cytosolic MA pathway, whereas mono-, di-, and tetraterpenes are derived from the chloroplastic MEP pathway (Thimmappa et al. 2014).

Terpenes have roles in both primary and secondary metabolism. Certain terpenes have been well studied for their functions in plant growth or development and therefore can be considered as primary rather than secondary metabolites. For instance, the gibberellins, an important group of phytohormones which are essential for numerous growth and developmental processes in plants including seed germination, leaf expansion, stem elongation, pollen maturation, trichome development, and the induction of flowering (Achard and Genschik 2009), are diterpenes. Brassinosteroids, also a class of plant hormones with growth-regulating functions such as activation of the cell cycle during seed germination (Zadvornova et al. 2005), control of cell cycle progression (González-García et al. 2011), and induction of exaggerated growth of hydroponically grown plants (Arteca and Arteca

2001), are derived from triterpenes. Terpenes are toxins and also act as a feeding deterrent to many herbivorous insects and mammals (Gershenzon and Croteau 1992). For instance, pyrethroids, a monoterpene ester reported from *Chrysanthemum* species, show remarkable insecticidal activity (Mori 2012). Monoterpenes accumulate in resin ducts found in the needles, twigs, and trunk of conifers, such as Douglas-fir, lodgepole pine, *Pinus contorta*, *Picea engelmannii*×*glauca*, and *Abies lasiocarpa*×*bifolia*, and are toxic to numerous insects, including bark beetles, a serious pest of conifer species throughout the planet (Trapp and Croteau 2001).

Essential oils, which lend a characteristic odor to their foliage, are mixtures of volatile monoterpenes and sesquiterpenes. Essential oils have been broadly used for bactericidal, virucidal, fungicidal, insecticidal, medicinal, and cosmetic applications (Isman 2000). Recently they are also used in pharmaceutical, sanitary, cosmetic, agricultural, and food industries (Holley and Patel 2005). *Mentha piperita*, *Citrus limon*, *Ocimum basilicum*, and *Salvia officinalis* are some well-known plants that contain essential oils. Essential oils are frequently found in glandular hairs and serve to repel the potential herbivores even before they take a trial bite. Caryophyllene, a sesquiterpene, is a common constituent of the essential oil of numerous plants including *Piper nigrum* and *Syzygium aromaticum*. Caryophyllene is known to possess anti-inflammatory, antimicrobial, anticarcinogenic, antibiotic, antioxidant, and local anesthetic properties (Legault et al. 2013; Kuwahata et al. 2012; Lee et al. 2005).

14.2.2 Phenolic Compounds

Plants produce a large variety of secondary metabolites that contain a phenol group: one or more hydroxyl functional groups on benzene rings (Randhir et al. 2004). These substances are classified as phenolic compounds or phenolics. The structures of these phenolics may range from simple phenolic molecule to complex high-molecular-weight polymer (Velderrain-Rodriguez et al. 2014). Phenolic compounds are found in nearly all the plant kingdom and located in nearly all plant parts. Main classes of phenolic compounds reported in higher plants are given in Table 14.2.

Shikimic acid and malonic acid are two basic pathways involve in the biosynthesis of phenolic compounds in plants. The shikimic acid pathway is involved in biosynthesis of most plant phenolics. Shikimic acid pathway converts simple carbohydrate precursors derived from glycolysis and the pentose phosphate pathway (PPP) into the three aromatic amino acids: phenylalanine, tyrosine, and tryptophan. Phenylalanine acts as a precursor of biosynthesis of most abundant classes of secondary phenolic compound in the plant.

Phenolic compounds play a vital role in growth and reproduction of plants, providing protection against pathogens and herbivores (Bravo 1998). Phenolic compounds are also involve in providing the color and sensory characteristics of fruits and vegetables (Alasalvar et al. 2001), in absorbing harmful ultraviolet (UV) radiation, and in reducing the growth of nearby competing plants. Phenolic compounds also have a wide range of physiological properties, such as antiallergenic, antiatherogenic, anti-inflammatory, antimicrobial, cardioprotective, and vasodilatory

Table 14.2 Main classes of phenolic compounds in higher plants

Classes and subclasses	Examples of specific compounds	Natural sources
Non-flavonoid compounds		
Phenolic acids	Hydroxybenzoic acids; hydroxycinnamic acids	*Macrotyloma uniflorum*
Benzoic acids	Gallic acid; protocatechuic acid	Quercus infectoria, *Hibiscus sabdariffa*, *Vitex agnus-castus*
	4-hydroxybenzoic acid	
Hydroxycinnamic acid	Coumaric acid; caffeic acid; ferulic acid; sinapic acid	*Arachis hypogaea*, *Eucalyptus globulus*, *Citrus limon*
Hydrolyzable tannins	Pentagalloylglucose	*Rhus chinensis*
Stilbenes	Resveratrol	*Fallopia japonica*
Lignans	Secoisolariciresinol; matairesinol; lariciresinol; pinoresinol	*Linum usitatissimum*, *Sesamum indicum*
Flavonoid compounds		
Condensed tannins or proanthocyanidins	Procyanidin, prodelphinidins	*Vitis vinifera*
Anthocyanidins	Pelargonidin; cyanidin; malvidin	*Geranium dissectum*, *Philodendron bipinnatifidum*
Flavanols	Catechins; gallocatechins	*Uncaria rhynchophylla*, *Camellia sinensis*
Flavanones	Naringenin; hesperetin	Citrus × paradisi, *Mentha aquatica*
Flavones	Apigenin; luteolin	*Petroselinum crispum*, *Apium graveolens*, *Ambrosia psilostachya*
Flavonols	Kaempferol; quercetin; myricetin	*Aloe vera*, *Coccinia grandis*
Isoflavones	Daidzein; genistein; glycitein	*Pueraria mirifica*

effects (Benavente-Garcia et al. 2000; Manach et al. 2005; Middleton et al. 2000; Puupponen-Pimiä et al. 2001; Samman et al. 2001).

Lignin is formed from three different phenylpropanoid alcohols, namely, coniferyl, coumaryl, and sinapyl. The physical toughness of lignin acts as a herbivore deterrent, while its chemical durability makes it relatively indigestible to herbivore and insect pathogens (Lattanzio et al. 2006; Rosenthal and Berenbaum 2012). The flavonoids, one of the largest classes of plant phenolics, are involved in pigmentation and defense (Treutter 2005). Tannins, a mainly constituent of woody plants, are general toxins that significantly reduce the growth and survivorship of many herbivores and also act as feeding repellents (Barbehenn and Peter Constabel 2011). Protocatechuic acid prevents smudge in onions, a disease caused by the fungus *Colletotrichum circinans*, and prevents spore germination and growth of other fungi as well (Kakkar and Bais 2014).

14.2.3 Nitrogen-Containing Compounds

A large number of plant secondary metabolites have nitrogen as part of their structure. They are synthesized from common amino acids. Nitrogen-containing secondary metabolites can be categorized into four categories: alkaloids, cyanogenic glycosides, glucosinolates, and nonprotein amino acids.

14.2.3.1 Alkaloids

Alkaloids are typically defined as plant-derived pharmacologically active basic compounds, which synthesized from amino acids and may contain one or more heterocyclic nitrogen atoms. The alkaloids are an extremely heterogeneous group of more than 15,000 nitrogen-containing secondary metabolites. The alkaloids include more than 150 families and found in around 20% of the vascular plant species. Alkaloids in plants are common in families of seed-bearing vascular plants or angiosperms, e.g., Magnoliaceae, Solanaceae, Papaveraceae, Leguminosae, Ranunculaceae, Rubiaceae, and Apocynaceae. The alkaloidal plant species may contain single or multiple alkaloids. For example, *Catharanthus roseus* contains 130 terpenoid indole alkaloids, including anticancerous vinblastine, and their synthesis can be regulated by multiple pathways (van Der Heijden et al. 2004; Patra et al. 2013). The alkaloids can accumulate in a different part of the plants including leaf, epidermal and hypodermal cells, bundle sheaths, and latex vessels. Alkaloids are usually synthesized from one of a few common amino acids, such as lysine, tyrosine, or tryptophan. However, the basic carbon skeleton of some alkaloids may contain a component derived from the terpene pathway also. Table 14.3 lists the major alkaloid types, their amino acid precursors, and natural plant sources. Alkaloids usually occur as salts of organic acids, such as acetic, malic, lactic, citric, and oxalic, in plants, while some basic alkaloids, like nicotine, also occur freely in nature (Ramawat et al. 2009). Very often, the alkaloids are biosynthesized in a particular plant organ but accumulate in another. For example, in tobacco, nicotine is synthesized in roots but is translocated to and stored in leaves (Shoji et al. 2000; Yazaki 2005; Morita et al. 2009). The alkaloids may be divided into three subclasses: proto-alkaloids, true alkaloids, and atypical alkaloids. Proto-alkaloids and true alkaloids are directly derived from amino acids, while atypical alkaloids are derived from sources other than amino acids, e.g., terpenoid-containing alkaloids.

14.2.3.1.1 Proto-alkaloids

These are nitrogen-containing alkaloids which originated from amino acids. Proto-alkaloids include mescaline, adrenaline, and ephedrine.

14.2.3.1.2 True Alkaloids

These alkaloids, generally, contain a heterocyclic ring with nitrogen, derived from amino acids and always basic in nature. These alkaloids are toxic and normally present in plants as salts of organic acids, e.g., nicotine, morphine, and codeine.

Table 14.3 Example of some true alkaloids and their natural sources

Alkaloid class	Example	Natural occurrence	Biosynthetic precursor
Pyrrolidine	Stachydrine, hygrine	*Erythroxylum coca*, *Leonurus japonicus*	Aspartate
Piperidine	Coniine, piperine, solenopsin	*Piper nigrum* *Psilocaulon absimile* *Petrosimonia monandra* *Conium maculatum*	Lysine
Tropane	Atropine, racemic, hyoscyamine	*Atropa belladonna* *Hyoscyamus niger* *Mandragora officinarum*	Aspartate
Isoquinoline	Papaverine, narcotine, berberine	*Papaver somniferum* *Argemone mexicana*	Tyrosine
Quinolizidine	Lupinine	*Lupinus albus*	Lysine
Indole	Reserpine, ergatomine	*Ipomoea violacea* *Turbina corymbosa*	Tryptophan
Pyrrolizidine	Heliotridine	*Adenostyles alliariae* *Cordia myxa*	Aspartate

14.2.3.1.3 Atypical Alkaloids

These are alkaloid-like compounds that do not derive from amino acids. The atypical alkaloids include terpene-like alkaloids, steroid-like alkaloids, and purine-like alkaloids such as caffeine, theobromine, ephedrine, colchicine, erythromycin, and taxol. These are less commonly found in nature.

14.2.3.2 Cyanogenic Glycosides (CGs)

CGs are a group of nitrile-containing plant secondary metabolites that produce cyanide following their enzymatic breakdown. There are approximately 25 known CGs which occur in at least 2600 plant species, such as members of Fabaceae, Rosaceae, Leguminosae, Linaceae, and Compositae family, of which a number of species are used as food including apples, apricots, cherries, peaches, plums, quinces, cassava, peas, beans, barley, and sorghum (Eisler 1991; Haque and Bradbury 2002; Ganjewala et al. 2010; Vetter 2000). Chemically, CGs are glycosides of α-hydroxynitriles which are stored in cell vacuoles (Vetter 2000; Fleming 1999). The CG content in plant discourages feeding by insects and other herbivores. Most of the CGs are believed to be derived from L-valine, L-isoleucine, L-leucine, L-phenylalanine, L-tyrosine, and cyclopentenyl-glycine, a nonprotein amino acid. In plants, CG biosynthesis occurs in three steps (Vetter 2000). In the first step, two successive N-hydroxylations of amino group of parent amino acid are catalyzed by an enzyme of cytochrome P450 family which, finally, converted into aldoxime. The second step includes conversion of aldoxime into cyanohydrin by another cytochrome P450 enzyme. In the final step, cyanohydrins get glycosylated by a soluble enzyme

UDP-glucosyltransferase. CGs play pivotal roles in organization of chemical defense system in plants and in plant-insect interactions (Zagrobelny et al. 2004).

14.2.3.3 Glucosinolates

Glucosinolates (also known as mustard oil glycosides) are the second class of glycoside after CGs. Glucosinolates are sulfur- and nitrogen-containing plant secondary metabolites common in the agriculturally important Brassicaceae family. Glucosinolates degrade to produce the compounds responsible for the smell and taste of vegetables such as cabbage, broccoli, and radishes, which act as toxin and herbivore repellents. More than 130 glucosinolates have been identified in plants (Radojčić Redovniković et al. 2008). The glucosinolate biosynthesis comprises three steps: amino acid chain elongation, conversion of the amino acid moiety to the glucosinolate core structure, and subsequent side chain modifications. The structural diversity of glucosinolates arises from side chain elongation of the amino acid precursors and from various secondary modifications including oxidation, desaturation, hydroxylation, methoxylation, sulfation, and glucosylation. Most glucosinolates in the member of the Brassicaceae are synthesized from methionine that is modified by the sequential addition of one to nine additional methylene groups to its side chain (Graser et al. 2000). Glucosinolates are stored in the intact plant discretely from the enzymes (myrosinase) that hydrolyze them, and they are brought into contact with the hydrolyzing enzymes only when the plant is crushed because of wounding and insect or pathogen attack. Loss of cellular integrity triggers the binary glucosinolate-myrosinase system and causes the generation of thioglucose, sulfate, and an unstable intermediate which spontaneously rearranges into several degradation products which can include nitriles, epithionitriles, isothiocyanates, oxazolidine-2-thiones, and thiocyanates (Radojčić Redovniković et al. 2008).

14.2.3.4 Nonprotein Amino Acids (NPAAs)

There are common 20 amino acids, also referred to as protein amino acids, which are incorporated into proteins by plants and animals. Nonetheless, several plants also contain unusual amino acids, called NPAA, that are not incorporated into proteins. Instead, these NPAAs are present in the free form and act as defensive molecules. Many NPAAs are very similar in structure to protein amino acids and, therefore, have similar properties. NPAAs can mimic the behavior of standard amino acids and, thus, can act as metabolic antagonists or inhibitors. For instance, canavanine and azetidine-2-carboxylic acid have structure much like that of arginine and proline, respectively. About 900 NPAAs have been isolated from plants. Of these, some 250 are found, particularly, within a small subset of plant families including the Hippocastanaceae, Leguminosae, Sapindaceae, Aceraceae, and Cucurbitaceae (Wink 2011).

14.2.4 Role of Nitrogen-Containing Secondary Metabolites in Plant Defense

Plants have a range of defense mechanisms, which occur soon after the pathogen attack that leads to the formation of a wide range of phytochemicals and by-products including nitrogen-containing secondary metabolites. These chemicals help the plant to respond to the incompatible interaction and finally help them to cope up with adverse conditions (Dixon 2001).

14.2.4.1 Alkaloids

Alkaloids are a diverse group of secondary metabolites with a variety of targets and biological activities including interference with neurotransmitters, disruption of DNA replication, and inhibition of protein synthesis (Mithöfer and Boland 2012). Alkaloids are produced by a large number of higher plant species and mostly involved in defense-related functions such as inhibition of competitors and herbivore deterrents (Roberts 2013). The inhibitory effects of alkaloids on glycosidase and trehalose metabolism deter herbivores, and the capability to quench singlet reactive oxygen confers protection against this toxic photosynthetic by-product (Mithöfer and Boland 2012; González-Lamothe et al. 2009). Alkaloids also act as phytoanticipins and phytoalexins and, naturally protect the plants from disease (González-Lamothe et al. 2009). The α-tomatine, for example, is a spirosolane-type alkaloid that occurs in tomato plants and possesses antimicrobial, antifungal, and anti-inflammatory activities (Friedman 2002; Chiu and Lin 2008; Ito et al. 2007; Morrow et al. 2004; Simons et al. 2006; Thorne et al. 1985). Several potently antibacterial alkaloids have been identified in the different classes of alkaloid including indole, indolizidine, isoquinoline, aaptamine, piperazine, quinoline, quinolone, aaptamine-indole, bisindole, and indole-quinoline in plants like *Zanthoxylum tetraspermum*, *Prosopis glandulosa*, *Clausena heptaphylla*, and *Teclea afzelii* (Maneerat et al. 2012; Chakraborty et al. 1995a, b; Samoylenko et al. 2009; Nissanka et al. 2001; Iwasa et al. 2001; Kuete et al. 2008; Wang et al. 2013).

Alkaloids have toxic and repellent effects on a wide range of generalist herbivores in order to reduce or prevent damage to plants (van Dam et al. 1995; Hartmann 1999; Hartmann and Ober 2000; Ober 2003). Sugar-mimic alkaloids act as inhibitors of several sugars and glycosidase-metabolizing enzymes leading to toxic effects on the insect. Morus species are a good example of plants that contain sugar-mimic alkaloids. Leaves exude of *Morus* species rich in sugar-mimic alkaloids, 1,4-dideoxy-1,4-imino-d-arabinitol and 1-deoxynojirimycin, which are toxic to the *Samia ricini* (also known as eri silkworm), a generalist herbivore, but not to the domesticated silkworm, *Bombyx mori*, a mulberry specialist (Hirayama et al. 2007). Yasuda et al. (2002) reported 13 sugar-mimic alkaloids from the pods of *Angylocalyx pynaertii*, a member of Leguminosae (Yasuda et al. 2002). The nature of toxicity and target of plant alkaloid can be diversified but frequently involves in cell signaling disruption (Mithöfer and Boland 2012). Sanguinarine ((13-methyl[1,3]benzodioxolo[5,6-c]-1,3-dioxolo[4,5]phenanthridinium), a benzophenanthridine alkaloid, mainly found in the Papaveraceae family, which includes *Sanguinaria* *canadensis*, *Argemone mexicana*, and *Chelidonium majus*, is shown to have antioxidant, antitumor, antibacterial, and anti-inflammatory properties (Chaturvedi et al. 1997). Sanguinarine is also reported to suppress cyclooxygenase, lipoxygenase, cholinesterase, Na^+/K^+-ATPase, cAMP- and Ca^{2+}-dependent protein kinase, NF-κB activation, nitric oxide synthase, and mitogen-activated protein kinase phosphatase-1 activities (Jeng et al. 2007; Vavrečková et al. 1996; Ulrichová et al. 1983; Seifen et al. 1979; Wang et al. 1997; Chaturvedi et al. 1997; Huh et al. 2006; Vogt et al. 2005). Sanguinarine inhibits choline acetyltransferase, an enzyme that catalyzes the biosynthesis of the neurotransmitter acetylcholine, and, finally affect neurotransmission. Nicotine, mostly found in leaves of *Nicotiana* species, binds to nicotinic acetylcholine receptors and blocks or displaces the endogenous neurotransmitters. Nicotine acts as either an agonist or antagonist targeting nicotinic acetylcholine receptors in insects, causing continual stimulation of the parasympathetic nervous system which finally leads to paralysis and death of insect (Dewey and Xie 2013).

Toxic effects of plant alkaloids on bacterial and fungal activities have been shown in a number of studies. Quinolizidine alkaloids (QAs) which frequently occur in members of Fabaceae family, like *Lupinus*, *Baptisia*, *Thermopsis*, *Genista*, *Cytisus*, *Echinosophora*, and *Sophora*, are involved in plant protection against insect pests (Philippi et al. 2015; Wang et al. 2000; Zhao et al. 1998). QAs extracted from *Lupinus angustifolius* and *Genista vuralii* have shown to have antibacterial properties (Erdemoglu et al. 2007, 2009). The antifungal properties of alkaloids also have been proved for several plant-associated fungi by bioassay experiments (Wippich and Wink 1985; Ma et al. 1999; Zhao et al. 1998; Zhou et al. 2003). The antifungal alkaloids are reported from different plants, such as *Corydalis incisa*, *Corydalis ambigua*, *Dictamnus dasycarpus*, and *Veratrum taliense*, which are reported to be effective against a wide range of phytopathogenic fungi including *Cladosporium cucumerinum*, *Erysiphe graminis*, *Cladosporium herbarum*, *Phytophthora capsici*, and *Rhizoctonia cerealis*.

14.2.4.1.1 Cyanogenic Glycosides

CGs can act as a defense molecule both against herbivory and phytopathogens. In general, an inverse correlation is frequently reported between the degree of herbivore pressure and the CG content in plant (Schappert and Shore 1999; Gleadow and Woodrow 2000; Ballhorn 2011). Dhurrin (4-hydroxymandelonitrile-β-d-glucoside) is a well-studied CG, reported to be present in several plant species including *Sorghum bicolor.* Dhurrin acts as an oviposition activator for the pests such as *Atherigona soccata* and *Chilo partellus* (Alborn et al. 1992). Efficient hydrolysis of dhurrin and, subsequent, release of cyanide are essential to deter insect herbivory in *Sorghum bicolor* (Krothapalli et al. 2013). Larvae of *Phyllotreta nemorum* eat 80% less tissue of the dhurrin-overproducing transgenic *Arabidopsis* plant compared to wild-type (Tattersall et al. 2001). The CG content, the rate of HCN release, and the susceptibility of the attacker to HCN are three main factors which determine the effectiveness of CGs against attackers (Ballhorn et al. 2005; Kadow et al. 2012). Many organisms, including humans, have mechanisms to detoxify and excrete HCN; therefore, HCN poisoning occurs only when the rate of detoxification is lesser than the rate of intake. Depending on the insect species, CGs can act both as feeding deterrents or phagostimulants. For instance, CG acts as a feeding stimulant for *Spodoptera eridania* larvae as it prefers to graze on CG-containing plants, such as *Phaseolus lunatus*, and grows better when cyanide is present in their diet (Brattsten et al. 1983). In contrast, *Prunus dulcis* plants with a high concentration of CGs are resistant to larvae of *Capnodis tenebrionis* (Malagon and Garrido 1990). Ellsbury et al. (1992) studied the variation in feeding damage to *Trifolium repens* (white clover) by larvae of *Hypera postica* (alfalfa weevils) (Ellsbury et al. 1992). They found that larvae of *Hypera postica* preferred leaflets of *Trifolium repens* with less or no CG content. Although all CGs have a potential danger through the production of HCN, there are differences in the sensitivity of different animal species. CG content of *Prunus padus*, also known as bird cherry, triggers the anorexia, weakness, depression, stupor, circling, bruxism, excessive salivation, and tenesmus in herbivores which, finally, leads to death (Sargison et al. 1996). CGs are also reported to have the antifungal properties. For instance, CGs can inhibit the growth of some fungi, such as *Magnaporthe oryzae* (also known as blast fungus), in dose-dependent manner (Seo et al. 2011).

CGs can be harmful to human also. Different types of CGs may be found in various cyanogenic food plants, for example, taxiphyllin in bamboo shoots and linamarin and lotaustralin in cassava (Organization 2013). The tubers of cassava which is used as staple food in many tropical countries, such as the Pacific Island countries, Latin America, Africa, and regions of Asia, contain high levels of CGs. Although traditional tuber processing methods, such as grating, grinding, soaking, and drying, caused the removal or degradation of a major fraction of the CGs present in cassava tubers. However, partial paralysis of the limbs caused by chronic cyanide poisoning is still widespread in cassava-eating regions. Tropical ataxic neuropathy and konzo are some health-related issues that can be caused by continuous dietary exposure to CGs (Tylleskär et al. 1992; Ernesto et al. 2002; Oluwole et al. 2000).

14.2.4.1.2 Glucosinolates

Most of the glucosinolates in plants are involved in responses to external or environmental stimuli. Glucosinolates are also involved in communicating and activating a variety of information relating to plant defense against insects, bacteria, and fungi. Depending on developmental stage and environmental condition, glucosinolate pattern varies between species and ecotypes as well as between and within individual plants. Environmental conditions such as temperature and light (Hasegawa et al. 2000; Engelen-Eigles et al. 2006), changes in nutritional status (Kaur et al. 1990; Underhill et al. 1980), biotic (e.g., fungal infection and insect damage), and abiotic (e.g., wounding) (Halkier and Gershenzon 2006; del Carmen et al. 2013) stress can alter the glucosinolate profile significantly. A change of the glucosinolate profile by several environmental factors has supported the idea regarding possible roles of glucosinolates in the plant defense against insects, herbivores, and microbial pathogens.

Glucosinolates and their hydrolysis products evidently act as mediators in plant-insect interactions. Glucosinolates can function as general poison and deterrent for generalist insects. Glucosinolates in *Brassica* show growth inhibition or feeding deterrence to a wide range of general herbivores such as birds, land slugs, and generalist insects (Giamoustaris and Mithen 1995, 1996). Martin and Müller (2007) found that *Sinapis alba* (white mustard) respond to *Athalia rosae* (turnip sawfly) damage by systematically accumulating higher levels of glucosinolates and, thus, apparently increasing their resistance (Martin and Müller 2007). An increase in short-chain aliphatic methylsulfinyl glucosinolates in *Arabidopsis thaliana* in response to both specialist and generalist phloem-feeding aphids is also known (Mewis et al. 2005). *Brassica napus* lines with higher glucosinolate content are also reported to have less damage in response to generalists such as pigeons and slugs (Giamoustaris and Mithen 1995). *Brassica juncea* with high glucosinolate concentrations is less prone to damage caused by both crucifer specialist, *Plutella xylostella*, and the generalist, *Spodoptera eridania* (Li et al. 2000). Moreover, insect herbivore feeding may substantially increase the levels of glucosinolates in plants. In *Arabidopsis*, comparison of glucosinolate accumulation and expression of glucosinolate biosynthetic genes in wild-type and mutant lines affected in defense signaling indicated that feeding of the aphid generalist *Myzus persicae (Sulzer)*, the aphid specialist *Brevicoryne brassicae* (L.), and the *Spodoptera exigua Hübner*, a lepidopteran generalist, can increase the accumulation of aliphatic glucosinolate content (Mewis et al. 2006). The plant also alters the nature of glucosinolates in affected area to deter the herbivores. For instance, *Myzus persicae* feeds on *Arabidopsis* and causes an overall decrease in glucosinolate content, but the production of 4-methox yindol-3-ylmethylglucosinolate is induced. This altered composition of glucosinolate, finally, acts as a deterrent for herbivores (Kim and Jander 2007).

The role of glucosinolates in defense against pathogens is not well studied like for herbivores. However, there are several reports indicating glucosinolate and its hydrolysis products can be toxic to bacteria and fungi (Smolinska et al. 2003; Mari et al. 2002; Li et al. 1999). *Brassica* crops are used as a break crop. The glucosinolates and their hydrolysis products secreted from *Brassica* canola and Indian mustard show inhibitory effects on soilborne fungal pathogen, *Gaeumannomyces graminis* var. *tritici*, which causes take-all of wheat (Angus et al. 1994). The 4-methylsulphinylbutyl isothiocyanate, a glucosinolate-derived isothiocyanates, is reported to have broad spectrum of antimicrobial activity. Growth of wide range of the fungi, such as *Alternaria brassicicola*, *Plectosphaerella cucumerina*, *Botrytis cinerea*, *Fusarium oxysporum*, and *Peronospora parasitica*, and bacteria, like *Erwinia carotovora* and *Pseudomonas syringae*, is inhibited by the presence of 4-methylsulphinylbutyl isothiocyanate (Tierens et al. 2001). Also, tryptophan-derived indole glucosinolates are reported to enhance the resistance of *Arabidopsis thaliana* against fungi like *Plectosphaerella cucumerina* and *Phytophthora brassicae* (Sanchez-Vallet et al. 2010*;* Schlaeppi et al. 2010).

Additionally, exogenous treatment of phytohormones like jasmonic acid (JA) and salicylic acid (SA), key signal regulators of plant defenses, to the plant also alters the glucosinolate profile which, again, proves the role of glucosinolates in plant defense. Previous studies showed that exogenous JA application can induce the accumulation of indole glucosinolate content in white mustard and oilseed rape (Bodnaryk 1994; Doughty et al. 1995). In addition, SA application is also reported to alter glucosinolate accumulation in oilseed rape (Kiddle et al. 1994). The hydrolysis products of glucosinolate have negative effects on vertebrates too. A diet highly rich in glucosinolates can cause the growth depression, poor palatability, decreased food efficiency, hypertrophy and hyperplasia of the thyroid, and liver lesions and necrosis in vertebrates (Anilakumar et al. 2006).

14.2.4.1.3 Nonprotein Amino Acids

NPAAs are commonly found in plants. NPAAs are present in widely consumed animal foods also. For instance, *Medicago sativa* is rich in canavanine, while *Lens culinaris*, a widely used edible pulse, contains homoarginine. In plants, NPAAs possess different roles including antiherbivory, antimicrobial, and allelochemical activity. The NPAA can protect the producer plants against stress, microorganisms, plants, insects, or higher animals including human (Bell 2003; McSweeney et al. 2008). NPAAs exert their toxicity in several ways. Some block the synthesis or uptake of protein amino acids, while others can be misincorporated into proteins and, finally, lead to production of nonfunctional proteins.

The protein-synthesizing machinery of plants that produce NPAAs can discriminate between protein and NPAAs, and, therefore, they are not susceptible to the toxicity of NPAAs. For instance, *Convallaria majalis* produces an analog of the protein amino acid L-proline known as L-azetidine-2-carboxylic acid. Although *Convallaria majalis* can differentiate the L-proline and L-azetidine-2-carboxylic acid, it can be easily misincorporated in proteins of *Vigna aureus*, which does not synthesize azetidine-2-carboxylic acid, and strongly inhibit the growth of germinating seedlings (Fowden 1963).

14.2.4.1.4 Aliphatic NPAAs

β-methylamino-L-alanine (BMAA) is a derivative of the alanine with a methylamino group on the side chain. BMAA is produced by the cyanobacteria in root nodules of cycads and has potent neurotoxic properties. BMAA is also accumulated in the seeds of cycads and causes amyotrophic lateral sclerosis/parkinsonism-dementia (ALS/P-D) (Steele and Guzman 1987; Ince and Codd 2005). ALS is a rare group of progressive neurological disorders that mainly involve the neurons responsible for controlling voluntary muscle movements such as chewing, walking, and breathing. Dencichine (β-N-oxalyl-l-α,β-diaminopropionic acid) is a hemostatic agent present in widely used traditional Chinese medicinal herbs, such as Panax species and *Lathyrus sativus*. Dencichine is a neuro-excitatory NPAA which causes the motor neuron disease, neurolathyrism, a condition with acute neurotoxic symptoms such as the inability to stand, neck stiffening, and head retraction (Campbell et al. 1993). Canavanine, an arginine analog, is synthesized in some leguminous plants (Bell et al. 1978) and plays a pivotal role in plant chemical defense against insects (Rosenthal 2001). Canavanine functions as an allelopathic chemical and inhibits plant growth (Nakajima et al. 2001). Incorporation of canavanine in place of arginine produces structurally aberrant proteins which exhibit altered protein conformation and impaired function in insects, such as *Manduca sexta* and *Heliothis virescens* (Rosenthal and Dahlman 1986; Berge et al. 1986). Animals fed on seeds of canavanine-containing plants developed hematological and serological abnormalities and induce antibody-mediated autoimmune phenomena (Bell 2003). Indospicine is a hepatotoxic NPAA found in *Indigofera* plant species. It accumulates as the free amino acid in the tissues (like muscle) of grazing animals including the horse and acts as a competitive inhibitor of arginase and causes reproductive losses and severe to mild liver disease (Fletcher et al. 2015). Djenkolic acid commonly found in *Archidendron pauciflorum* causes djenkolism, an acute kidney malfunction (Bunawan et al. 2014; Bell 2003). L-methionine sulfoximine, seleno-cystathionine, selenomethionine, and dl-phosphinothricin are examples of other NPAAs of plant origin that are involved in plant defense (Bell 2003; Shaw et al. 1999; Schrauzer 2000; Kitajima and Chiba 2013; Tardito et al. 2012).

14.2.4.1.5 NPAAs with Aromatic Skeletons

Plants produce several NPAAs with aromatic skeletons, such as L-3,4-dihydroxyphenylalanine (L-DOPA) and m-tyrosine, that are involved in plant defense. L-DOPA is a compound with strong allelopathic activity. It is found in leaves and seeds of *Mucuna pruriens* (velvet bean) that has a nutritional quality similar to the soybean (Nishihara et al. 2005). L-DOPA acts as a precursor of many alkaloids, such as catecholamines and melanin, which are released into soils and inhibit the growth of nearby plants. L-DOPA is an important secondary metabolite for chemical defense against herbivores in plants (Huang et al. 2011; Van Alstyne et al. 2006). Plants with high L-DOPA content are less prone to attack of small mammals or insects (Rehr et al. 1973). It is also a key chemical involving in sclerotization and melanization of insects which finally affects the development and immunity of insects (Gallot et al. 2010; Andersen 2010). The L-DOPA acts as a herbicide and suppresses the growth of several weed species such as *Sinapis arvensis*, *Cirsium arvense*, *Papaver rhoeas*, and *Lamium amplexicaule* (Topal and Kocaçalişkan 2006). *m*-Tyrosine is an example of another NPAA with aromatic skeletons with phytotoxic properties. It is exuded from the roots of fine fescue grasses and inhibits the growth of a wide range of neighboring plant and, therefore, grants a competitive advantage to fescue grasses (Bertin et al. 2007; Huang et al. 2012). The toxicity of *m*-tyrosine is due to its misincorporation into cellular protein in place of protein amino acid phenylalanine (Gurer-Orhan et al. 2006; Klipcan et al. 2009). The *m*-tyrosine can also prevent the growth of bacteria including *Escherichia coli* and *Bacillus* species (Smith et al. 1964; Aronson and Wermus 1965).

14.2.4.1.6 NPAAs with Cyclic and Heterocyclic Skeletons

The 5-hydroxytryptophan (5-HTP) is found in the seeds of *Griffonia simplicifolia* and has been associated with the insecticidal properties (Janzen et al. 1977). Homoproline, a lysine-derived NPAA, is a critical regulator of systemic acquired resistance (SAR) and basal immunity to bacterial infection in plants including *Arabidopsis thaliana* and *Nicotiana tabacum* (Navarova et al. 2012*;* Vogel-Adghough et al. 2013). Homoproline signals the plants for effective biosynthesis of defense signal SA, accumulation of the phytoalexin camalexin, and expression of defense-related genes. Mimosine and its derivatives (α-amino-β-(3-hydroxy-4-oxo-1,4-dihydropyridin-1-yl)-propanoic acid), found in a leguminous *Leucaena leucocephala* (Xuan et al. 2006), have a strong herbicidal impact on several plants namely *Brassica rapa* and *Phaseolus vulgaris* (Xuan et al. 2006, 2016). Mimosine has insecticidal (Ishaaya et al. 1991) properties also and can inhibit the growth of first-instar larvae of *Tribolium castaneum*. β-(Isoxazolin-5-on-2-yl)-alanine (BIA), found in *Pisum*, *Lens*, *Lathyrus*, and *Vicia* plant species (Lambein et al. 1990), is a potent growth inhibitor of several eukaryotic organisms, such as yeasts; unicellular green algae; phytopathogenic fungi, such as *Botrytis cinerea*, *Pythium ultimum*, and *Rhizoctonia solani*; and higher plants (Schenk et al. 1991).

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