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Review

Plant secondary metabolites and its dynamical systems of induction in response to environmental factors: A review

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Under natural conditions, the plants are, usually, surrounded by a series of potential enemies. They had created strategies of defense against pathogens and herbivores' attacks, allowing its perpetuation throughout evolution. These defense mechanisms are closely associated with the synthesis of secondary metabolites, which are also worldwide used in several areas of industry. This bibliographic review was conducted aiming to better understand how plants synthesize these substances in response to biotic or abiotic stimuli. The results discussed here revealed that synthesis of plant secondary metabolites is dependent on changes in several metabolic pathways, being often directly associated with the primary metabolism. Injury by herbivores or pathogens, temperature, CO_2 levels, solar radiation and drought, are the factors related to the environment that express the most significant signs of inhibition or synthesis of plant secondary metabolites. Global climatic changes recently observed can affect the metabolic pathways network and, consequently, secondary metabolites synthesis. Nowadays, genomic tools have been useful alternatives that are leading to a new revolution of plant breeding, allowing the overexpression or inhibition of these substances. Some limitations and challenges to be achieved upon the dynamics of secondary metabolite synthesis in plants are presented.

Key words: Jasmonic acid, transcription factors, inhibition, synthesis.

INTRODUCTION

Plants produce a range of organic compounds which, a priori, have no direct relation to its growth and development. Originating of primary metabolism, these compounds are known as secondary metabolites. These metabolites show no functions hitherto recognized in vital processes of plants, such as photosynthesis, cellular respiration, protein synthesis, solute transport and nutrient assimilation, unlike the primary metabolites. The synthesis of a specific secondary metabolite is not observed in all species of the plant kingdom, being restricted to one or a few species (Taiz and Zeiger, 2010).

For a long time, the importance of secondary metabolites was not fully understood. Nowadays, with advances in research, technology, and especially with the genome sequencing of some species such barley (Mayer et al., 2012), tomato (Consortium, 2012), *Pinus taeda* (Kovach et al., 2010), pear (Wu et al., 2013) and rice (Project, 2005), and with the recently gene-editing technique (Gaj et al., 2013; Woo et al., 2015; Bortesi and Fischer, 2015) many doubts about the role of these compounds in the evolution of the main grown species were clarified.

It is known that biotic factors such as pathogen and herbivores attack, and abiotic such as radiation, temperature, hydric and nutritional stress, have the potential to induce physiological changes in plants by altering metabolic pathways. In this context, the aim of this bibliographic review was to discuss the biosynthetic pathways responsible for the synthesis of the main secondary metabolites, its main functions in plants, and how the environment can influence, positively or negatively, the synthesis of these compounds.

SECONDARY METABOLITES

We now know that much of the secondary metabolites has important functions but not vital in plants, such as its protection to parasites (fungi, insects, bacteria), attractive features (color, odor, taste) for pollinators and seed dispersers, as well as in acting as subjects in plant-plant competition and plant-microorganism symbioses. However, the same metabolites responsible for increasing plant production performance can also make them undesirable for human consumption. As an example, we can consider the production of capsaicin, a capsaicinoid responsible for the pungency in peppers (*Capsicum* spp.). Its synthesis is controlled by a dominant allele locus *Pun1*. In its homozygous recessive state, *pun1 / pun1*, capsaicin's synthesis does not occur (Blum et al., 2002). Different degrees of poignancy observed among genotypes occur so, both due to the environmental effects where the genotype is subjected, as due genotype x environment interaction, being found variations in pungency level among and within genotypes (Zewdie and Bosland, 2000).

This can be explained due to high outcrossing rates (7 to 90%), which may occur among cultivars, although this species be considered autogamous (Bozokalfa et al., 2009). It is known that the genotype x environment interaction is characterized by the differential response of each genotype in each environment; and that this interaction is caused mainly by the variation of meteorological elements of each site. Studies have shown that temperatures above 30°C (Ohta, 1960) and water restriction (Gurung et al., 2011; Sung et al., 2005), increment the capsaicin level in *Capsicum* spp.

Secondary metabolites can be divided into three chemically distinct main groups: terpenes, phenolic compounds and nitrogen compounds.

Terpenes

Terpenes, also known as isoprenoids are the largest class of known secondary metabolites, containing about 50,000 identified substances (Vranová et al., 2012). These substances are formed by the fusion of five carbon units which have a branched backbone. These can be divided into monoterpenes (10 carbons), sesquiterpenes (15 carbons), and diterpenes (20 carbons). The largest terpenes include triterpenes, tetraterpenes and poly-terpenoids, with 30, 40 and > 40 carbons, respectively (Taiz and Zeiger, 2010). Terpenes are synthesized from primary metabolites by at least two different pathways: the mevalonate pathway (joining three molecules of Acetyl-CoA) and the non-mevalonate pathway, which both produce Isopentenyl diphosphate (IPP) and Dimethylallyl diphosphate (DMAPP), respectively, being the basic units in the synthesis of terpenes (Figure 1). As can be noted, the basic source of terpenes and other secondary metabolites is directly related to the primary metabolism of plants. In this case, the presence of Acetyl-CoA at the pathway of IPP and Pyruvate plus Glyceraldehyde 3-Phosphate, at the pathway of DMAPP, is essential for the synthesis of terpenoids in plants.

Several plants show a mix of terpenes with volatile compounds, which confer to they a specific odor. Among some species, it can be highlighted the lemon, mint, basil and sage. These compounds, known as essential oils, can be extracted from plants, being commercially important in pharmaceutical, cosmetic and food industries.

Some terpenes show important functions on growth and development of plants, such as gibberellins (diterpenes) and brassinosteroids (triterpenes). Though some terpenes show metabolic importance, a great part of them, are basically associated with the defense of several plants against herbivores as insects (Trapp and Croteau, 2001; Veitch et al., 2008) and nematodes (Soriano et al., 2004).

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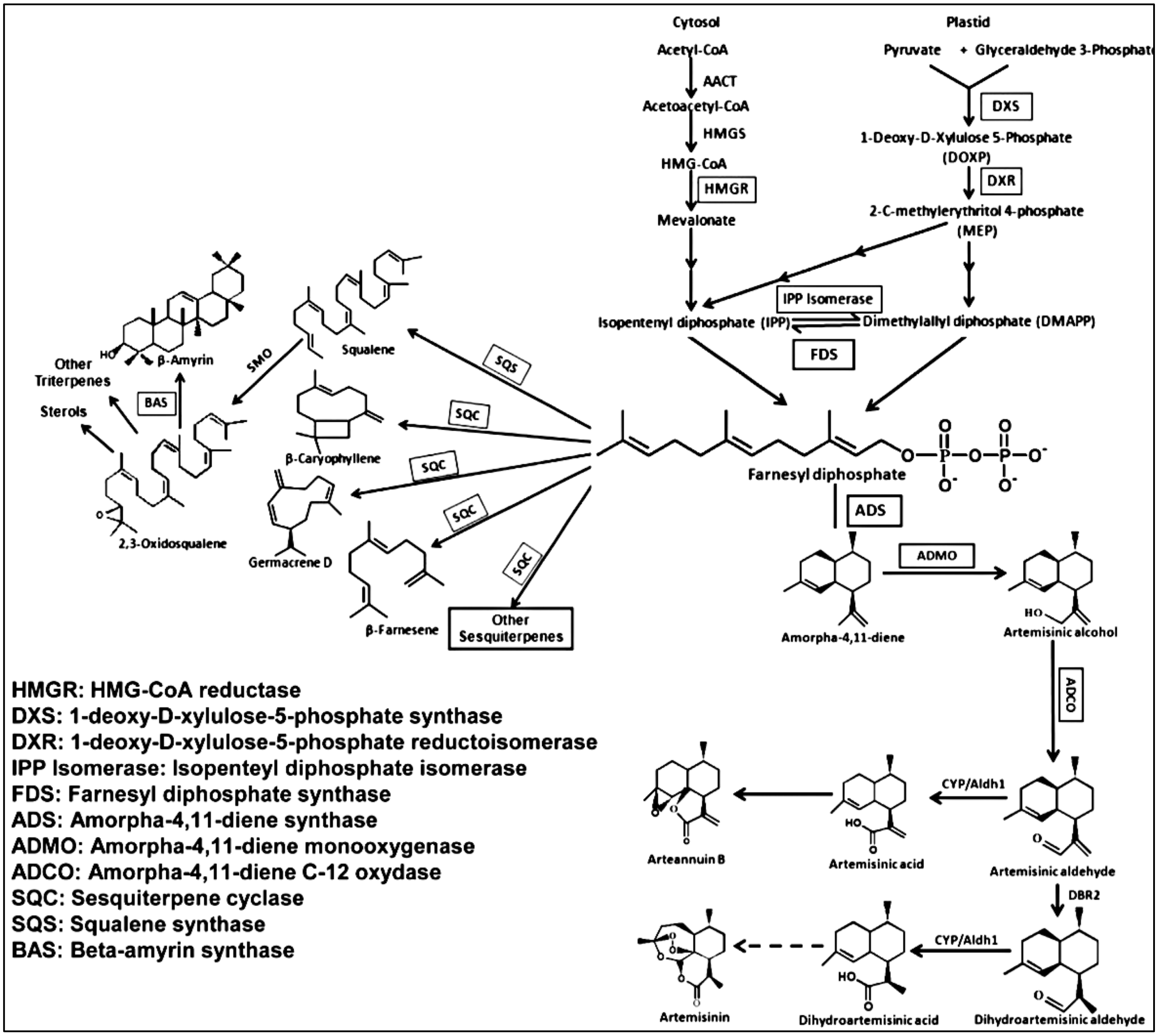

Figure 1. Schematic representation of the biosynthetic pathway of some terpenoids. Observe the two basic pathways at the beginning of the synthesis: the IPP pathway held into cytosol of the cell, and the DMAPP pathway, held in the plastids. Source: Adapted from Yadav et al. (2014).

In some conifers, resins exudation, secondary metabolite belonging to the group of terpenes, is presented as a defense mechanism against fungi and insects (Franceschi et al., 2005), and is used as a raw material for a wide range of industrial products, being one of the most important non-wood forestry products (Hall et al., 2013). Its synthesis can be induced by environmental factors such as high temperatures, radiation and evapotranspiration (Rodríguez-García et al., 2015), by exogenous application of chemical stimulants such as jasmonates (Dar et al., 2015; Moreira et al., 2009, 2012) or by mechanical damage (Ruel et al., 1998). Research has shown that weather conditions can affect resin production of two ways: directly, by changing fluidity of the resin due to higher temperature (Blanche et al., 1992) and indirectly, due of changes in the physiological processes involved in the biosynthesis and secretion of this substance (Genoa et al., 2013).

Effects of some environmental factors on the concentration of terpenes in tomato were revealed, indicating that high temperatures (above 32°C) significantly reduces the amounts of some tetraterpenoids as lycopene, if this stress is induced during late stages of fruit maturation. High temperatures since the vegetative stage, however, show no changes in the composition of these substances in relation to the control treatment, indicating metabolism's acclimation of these plants to high temperatures (Hernández et al., 2015). The influence of controlled water stress, may be related to an increase of lycopene in tomatoes, as evidenced by (Wang et al., 2015a), which reveals the dynamic and complex synthesis of these compounds, dependent on environmental factors.

Several transcription factors of secondary metabolite biosynthesis, suggests that expression of activators or repressors in response to phytohormones and environmental signage is responsible for the synthesis and accumulation of such compounds. Recent research has revealed some of the metabolic pathways are also controlled by posttranscriptional and posttranslational mechanisms (Patra et al., 2013). Recent studies in *Artemisia annua*, a species of Artemisia genus, originating from temperate regions of Asia, revealed that several transcription factors activated by jasmonate phytohormone, leading to artemisinin synthesis, a sesquiterpene widely used in the treatment of malaria (Yu et al., 2012). Studies have shown that drought negatively modulates the production of artemisinin in this plant mainly by reducing the density and size of glandular trichomes, however, the synthesis of some monoterpenes and volatile compounds is induced by water deficit (Yadav et al., 2014).

Jasmonic acid (JA) presents itself as an important signaling molecule of secondary metabolites synthesis, triggering the emission of volatile products such as homoterpenes, like the emission of volatile compounds observed after injury caused by herbivores (Arimura et al., 2000; Hopke et al., 1994; Nabity et al., 2013). Research has revealed that JA is responsible for the increase in secondary metabolites levels in more than thirty species, mainly due to signaling of genes responsible for the synthesis of enzymes such as phenylalanine ammonia-lyase, known to be involved in the chemical plant defense mechanism (Dar et al., 2015; Gundlach et al., 1992). Exogenous applications of JA can act as a tolerance inducer of some plants to salt stress (Qiu et al., 2014), where even in situations of stress of an isolated plant, for example, increasing in concentration of this substance can induce the expression of genes defense in the surrounding plants, even these being from different families (Farmer and Ryan, 1990).

The increase in endogenous concentration of JA is mainly determined by response of plants to environmental stimuli such as high luminosity (Li et al., 2014), low CO_2 levels (Sun et al., 2013.), water stress (Zhang and Huang, 2013) and high levels of toxic substances (Yan et al., 2015). The complexity of the interactions between environmental factors and responses of plants has been stimulating conducting research aimed at obtaining superior genotypes tolerant to adverse climatic conditions, mainly due to prospects of global warming and increases in CO_2 levels, expected for not too distant future.

Phenolic compounds

Plants produce a large variety of secondary metabolites which contain a hydroxyl functional group into an aromatic ring; such substances are known as phenolic compounds. Phenols are a large group of compounds which can be divided into five subgroups: coumarins, lignins, flavonoids, phenolic acids and tannins. Among these, lignins and flavonoids are the most pervasive phenolic compounds in plants (Gumul et al., 2007).

In superior plants, the biosynthesis of phenolic compounds is associated with two basic metabolic pathways: the shikimic acid pathway and the malonic acid pathway. Most of the phenolic compounds are derived from phenylalanine, a product of the shikimic acid pathway, which is converted into cinnamic acid by phenylalanine ammonia-lyase (PAL), perhaps the most studied enzyme in plant secondary metabolism.

In many species, PAL activity regulation becomes complex due the existence of multiple genes that encode this enzyme, some of which are only expressed in specific tissues or under certain environmental conditions, revealing the complex dynamics of signaling and synthesis of secondary metabolites (Cheng et al., 2015; De Jong et al., 2015; Logemann et al., 1995).

Coumarins

Coumarins are benzene and dipirona fused rings with great therapeutic importance. Depending on your configuration has a great ability in regulating cellular routes that can be exploited for cancer prevention (Thakur et al., 2015), besides having great influence on the central nervous system (Skalicka-Woźniak et al., 2015). Despite advances in research with this phenolic compound are not found specific results regarding the influence of environment factors in its synthesis or inhibition.

Lignins

Lignins are very important in plants' sustaining, due to its ability to provide greater rigidity to the cell wall. Although several synthetic polymers are used in a range of applications, the dependence of crude oil for its manufacture has resulted in several environmental impacts, encouraging scientists on finding alternative raw materials for this purpose (Obaid et al., 2016). Lignins, due to its specific structure, it is becoming an environmentally friendly substance with large utilities in the industry as the manufacture of molds, thermoplastic reinforcement and integration with natural fibers to obtain the most varied materials (Saheb et al., 1999).

The synthesis of this substance in plants seems to be related to the presence of sucrose, causing significant intracellular disorder, irregular thickening of the cell wall and lignification. The response to lignification, however, is changed due to the activity of H_2O_2, being lignin synthesis temporarily correlated with the synthesis of this peroxide (Nose et al., 1995). Many are the works evaluating the behavior of different types of lignin, particularly for the thermal behavior, degradation products and processing methods of these substances, but still needs more information that reveals how the interaction between the species and growth environment influences the synthesis of these substances.

Flavonoids

Flavonoids are the major class of plant phenolic compounds. The basic skeleton of these substances contains 15 carbons arranged in two aromatic rings connected by a three-carbon bridge. Besides to promoting pigmentation in flowers, flavonoids are important in protecting plants against UV rays, besides to attracting pollinators and seed dispersers. In addition to the beneficial effect on plants, some research has shown its importance in humans' diet, acting as a potent antioxidant (Winkel, 2004). Flavonoids can be classified into four subgroups, due to the degree of oxidation of the carbon chain, as follows: anthocyanins, flavones, flavonols and isoflavones:

Anthocyanins

Anthocyanins are one of the most important flavonoids studied at the physiology, mainly acting in plant-pollinator-dispersers interaction, due to its ability to provide color to plants. These compounds are essential for the plants being associated with cold and pathogens (Sivankalyani et al., 2016) and when present in the human diet may act as antioxidant (Homoki et al., 2016; Sui et al., 2016).

By the year 2007, it has been suspected that JA regulates plant metabolism in response to many stressful situations, such as the attack of pathogens or insects, drought, or extreme changes in ambient temperature, triggering a series of gene expression, however, JA transmission mechanism was not known in detail. Research has identified a family of repressor proteins called jasmonate-ZIM-domain proteins (JAZ), that bind to transcription factors of several defense mechanisms and prevents them from acting. When the plant identifies any stress situation (injury, temperature, drought), JA is synthesized as an alarm signal which binds to a receptor and induces degradation of JAZ by ubiquitin-proteasome 26S system, as shown in Figure 2 (Chini et al., 2007; Thines et al., 2007). Genetic engineering techniques have been effective in increasing JA biosynthesis. An example was shown when genes responsible by transcription factors that regulate JA responses were overexpressed, resulting in a greater accumulated amount of terpenoids (Fits and Memelink, 2000).

Low temperatures induce expression of specific genes in the metabolic pathway of synthesis of key enzymes, such as PAL, retarding the degradation of these substances as well as flavonoids and polyphenols (Rouholamin et al., 2015; Zhang et al., 2015). Small RNAs (miRNAs) are important components of a gene-regulatory network, being involved in anthocyanin biosynthesis. Studies using Arabidopsis, has revealed that the expression of genes encoding key enzymes in the biosynthesis of these substances is regulated by specific transcription factors, and its synthesis is induced by JA in the presence of light, but not in dark, being dependent on the phytochrome's response on red-distant light stimuli (LI et al., 2014).

Genetic and physiological evidence has shown that the Myb regulation (Figure 2) by JA triggers an immediate accumulation of anthocyanin and trichomes initiation. Overexpression of MYB75 leads to accumulation of anthocyanin in Arabidopsis *coi1-1* mutants, compared to the wild-type genotype (WT), in the same way that overexpression of GL3 and EGL3 increments the number of trichomes in this plant (Figure 3).

In Arabidopsis, there is an accumulation of anthocyanin mainly at the junction of the rosette and stem. This spatial pattern is controlled by miRNA156, which have a relationship with SPL9, a key regulator of plant development which promotes flowering (Figure 2). When increased activity of miRNA156 occurs, there is an expression of genes that increase the synthesis of anthocyanins; on the other hand, the reduced activity of miRNA156 promotes greater expression of SPL9, resulting in higher levels of flavonoids. This interaction reveals a direct relationship between the transition to flowering stage and secondary metabolism of plants, providing crucial information for handling anthocyanins and flavonoid content in plants (Gou et al., 2011).

Studies with *Potamogeton gramineus* L., an aquatic plant found in irrigation canals in Northern California, has revealed some effects of environmental factors in the synthesis of anthocyanins. Under nitrogen and phosphorus limitation, these substances are inhibited, while the temperature and luminosity slightly increase its content and reduces the chlorophyll content, which seems to be related to the reddish-brown color of this species (Spencer and Ksander, 1990). We saw the complex dynamics of synthesis and inhibition of these compounds in plants and, taking into account the importance of these substances, it is clear the difficulty, particularly regarding the breeders, in finding genotypes with high anthocyanin production and acclimatized in varied environments.

Flavones and flavonols

These substances are found in all organs of plants, with

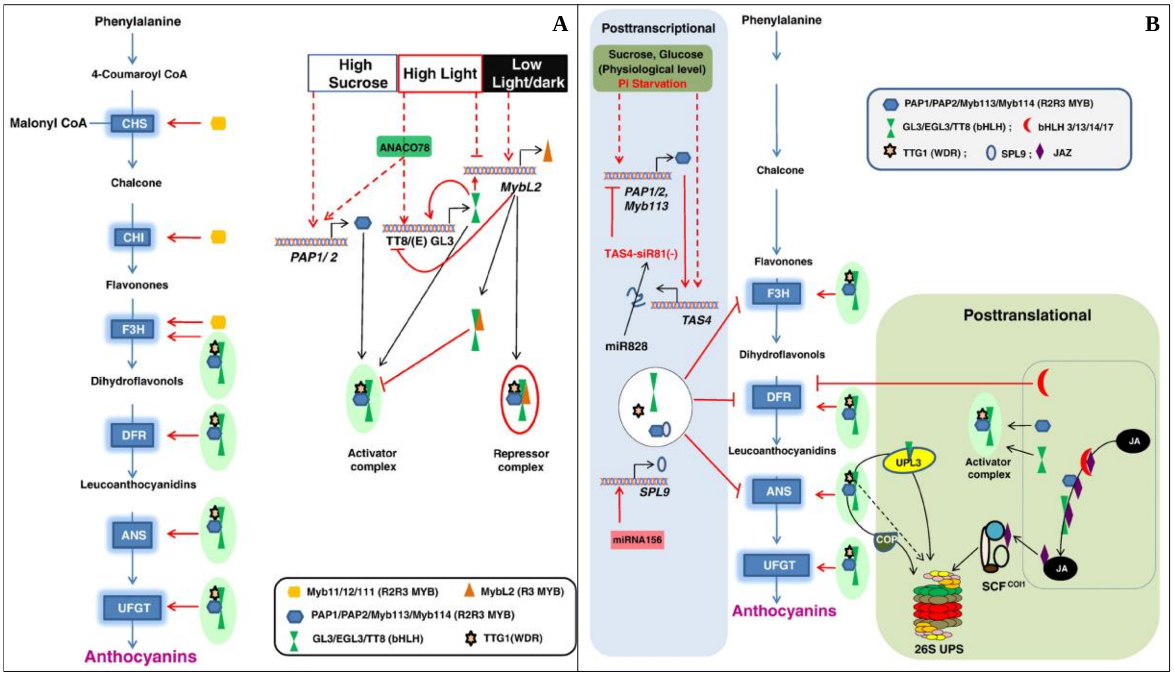

Figure 2. (A) Schematic representation of gene regulation of anthocyanin biosynthesis in response to environmental signals in Arabidopsis. Genes encoding pathway enzymes are represented in blue boxes. solid red arrows and T-bars, represent the direct activation and repression, respectively. Dotted red arrows and T-bars indicate indirect activation and repression, respectively. Half-circle indicates self-activation. The activation of genes by Myb-bHLH-WDR complex (green elliptical circle) and Myb11 / 12/111 (solid yellow rectangle) is shown. The red circle represents the elliptical repressor complex Myb-bHLH-WDR. (B) Schematic representation of posttranscriptional and posttranslational regulation of anthocyanin biosynthesis. The structural genes encoding the enzymes of the route are shown in blue boxes. solid red arrows and T-bars represent the direct repression and activation, respectively. Dotted red arrows and T-bar indicate indirect activation and repression, respectively. The blue shaded area shows the anthocyanin biosynthesis regulated by miRNAs in response to environmental signals and development. The gray shaded area represents a posttranslational degradation of components of the Myb-bHLH-WDR and JAZ proteins by the 26S ubiquitin proteasome system. Source: Adapted from Patra et al. (2013).

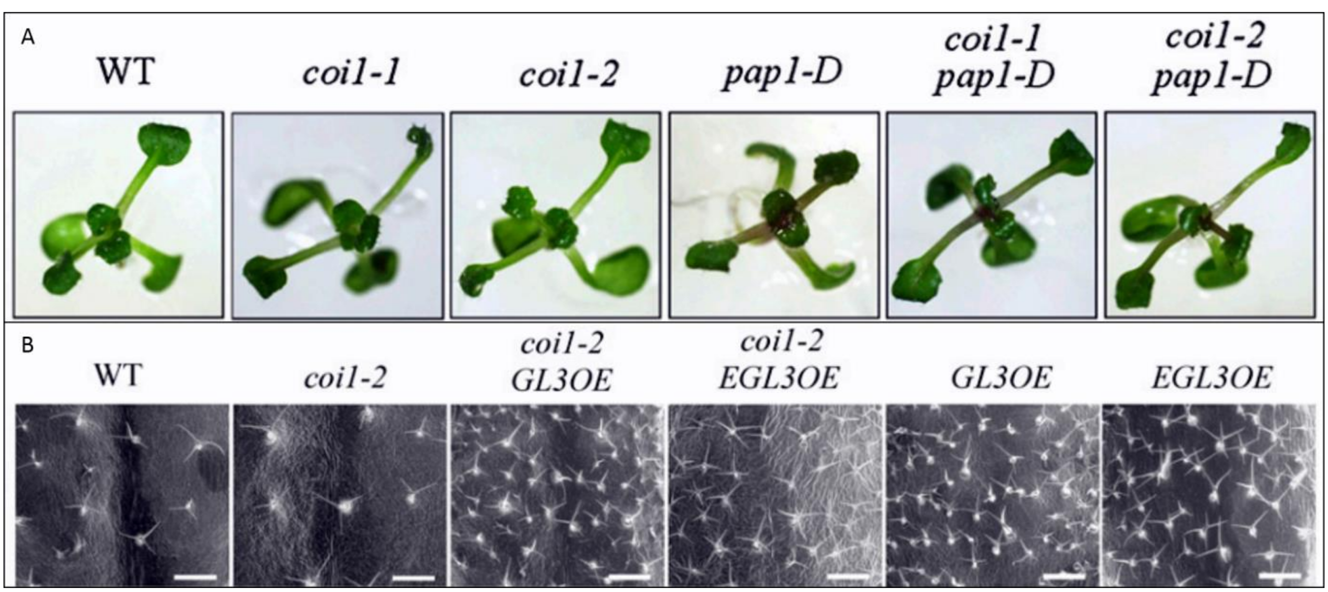

Figure 3. (A) Overexpression of MYB75 in Arabidopsis coi1-1 mutants resulting in increased anthocyanin; (B) Overexpression of GL3 and EGL3, resulting in increased trichome number in coi1-2. Source: Adapted from QiI et al (2011).

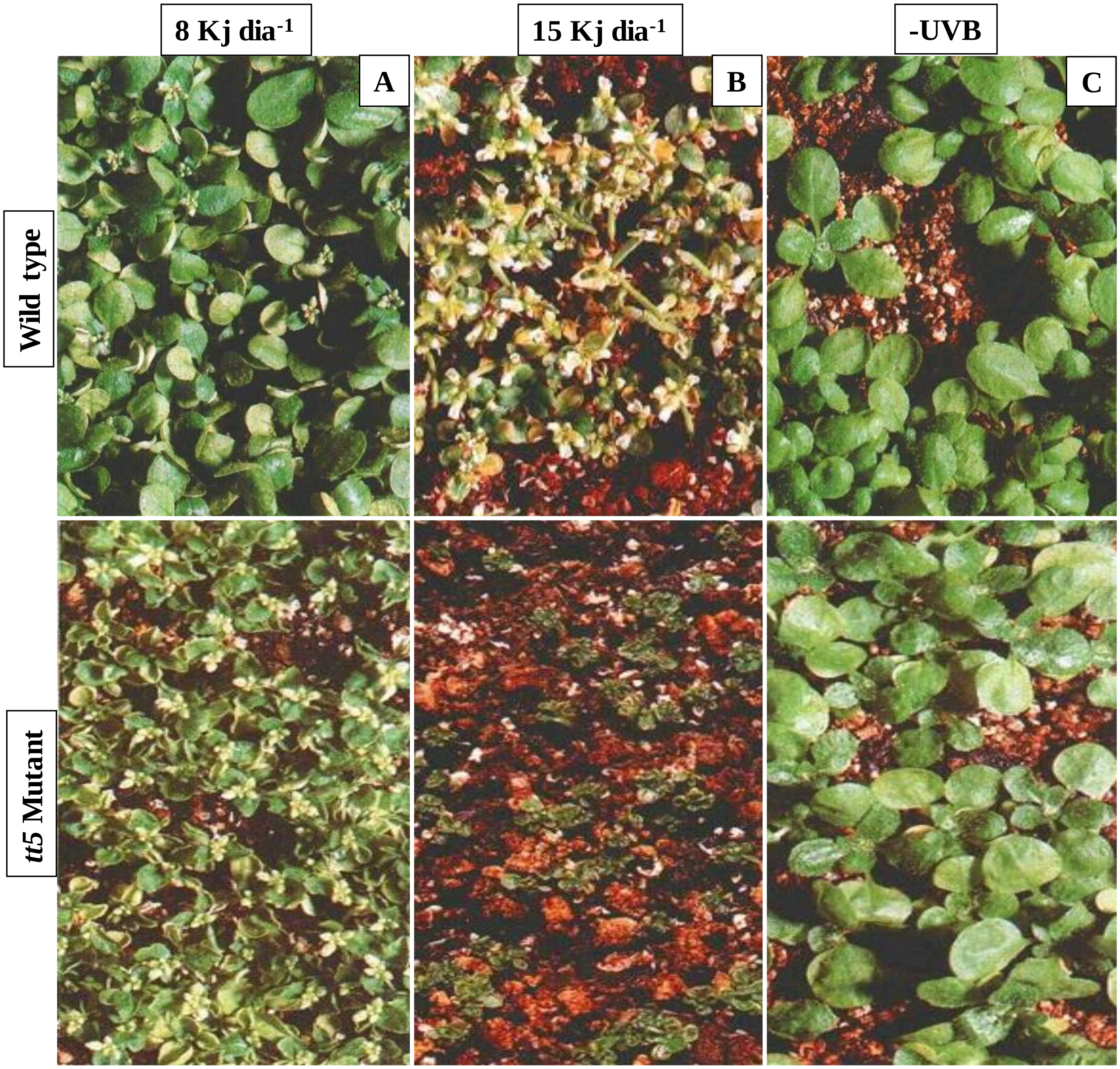

Figure 4. Growth of Arabidopsis *tt5* mutants and wild types under 8 kj day^{-1} (a), 15 kj day^{-1} (B) and on without UVB radiation wavelength (C). Source: Adapted from Li et al. (1993).

special importance for the flowers. Usually, these substances absorb light-long waves that are lower to the visual ability of human beings. However, insects like bees, which are responsive to light in the ultraviolet range, are attracted by these colorations.

Flavones and flavonols have great importance to plants, due to their ability to protect plants against damage from ultra-violet light (280-320 nm) mainly due be presents in the epidermis of leaves and stem, absorbing light at this wavelength (Taiz and Zeiger, 2010).

In Arabidopsis mutant for the synthesis of these compounds, plants are hypersensitive to UVB radiation, grown less under normal condition. When protected, these plants have similar growth to the wild-type genotype. Figure 4 clarifies the role of this sub-group of phenolic compounds. Incident radiation with the presence of UVB, even at low density, causes the standstill of growth in Genotypes TT5 mutants, as compared to the wild-type. When the incident light has no radiation in the UVB wavelength, both the wild type as mutant for the synthesis of flavones and flavonols, have similar growth.

It is visible the influence of radiation in the mutant plants for synthesis of these substances. Thus, a challenge to be achieved is to obtain genotypes that have high concentrations of these protective substances, thus avoiding a reduction in the growth and development due to the inhibitory effect of radiation, especially with the prospect of ozone layer depletion, an important molecule responsible for filtering the vast majority of incident UV radiation.

Isoflavones

These substances are mainly found in Fabaceae species. With 745 genera and over 19,500 species, these legumes are the third largest family of plants. Among several biological activities of these substances, we can mention the beneficial effect on the initial growth of *Trachinotus ovatus*, a species of fish of Carangidae family (Zhou et al., 2015), increase in cell antioxidant activity (Al-Qudah et al., 2015), as well as a reduction of up to 27% in anti-*Tobacco Mosaic Virus* (Li et al., 2015).

Recent research has aroused the interest of isoflavones for their action as phytoalexins. These compounds are generally absent in healthy plants, and its synthesis is induced by plant responses to biotic factors, including infection by fungi and bacteria (Budovská et al., 2013; Ejike et al., 2013), or abiotic factors, such as physical injury (Darvill and Albersheim, 1984). Studies have also shown that there is a possibility of increasing the resistance of plants to diseases based on an additional external application of phytoalexins (Stuiver and Custers, 2001).

One of the first studies evaluating the influence of the environment factors in response to the synthesis of these substances has revealed that when plants are adapted to metalliferous environments, their response to biotic stress (fungi) is more intense, resulting in increased production of phytoalexins (Martellini et al., 2014). This example of positive interaction between biotic and abiotic stimuli can arouse the interest of researchers, particularly regarding the production of plants with higher levels of phytoalexins.

Phenolic acids

These phenolic compounds are characterized by being formed by a benzene ring, a carboxyl group and one or more hydroxyl groups in their molecules, giving them antioxidant properties, both for the foods, as for the bodies, being indicated for treatment and prevention of a number of diseases, among them cancer (Chang et al., 2015; Espinosa et al., 2015; Heleno et al., 2015; Kurth et al., 2015; Milner, 2002; Taofiq et al., 2015).

Salicylic acid

It is known the effect of salicylic acid in some plant functions, such as reducing ethylene levels and increasing capsaicin content of peppers (Sudha and Ravishankar, 2003), as well the increasing anthocyanin production in carrots (Rajendran et al., 1992). However, this substance is basically related signaling of plant resistance to pathogens.

Localized attack by a pathogen induces acquired resistance, mainly due to the accumulation of salicylic acid, which induces the accumulation of proteins related to the elimination of pathogens. Research has proved the efficiency of induced resistance in plants through genetic modification techniques and has demonstrated the ability of a leaf (resistant) promote long-distance signaling and induce resistance in the surrounding plants. This process is basically related to the interaction of ‘resistant’ leaf with a derived-lipid molecule (Maldonado et al., 2002) and with methyl silicate production, a volatile liquid synthesized from salicylic acid (Shulaev et al., 1997).

Few are studies about the influence of environmental factors in synthesis or inhibition of these compounds. Breeding programs have indicated that a large diversity of phenolic acids is found in more than 60 varieties of vegetables and wild relatives. The heritability estimates for these substances have relatively high (> 0.5), indicating that selection for higher levels of phenolic acids can be effective without major environmental influences (Prohens et al., 2007). With the advancement of plant breeding techniques, genetic tools such as transposon handling and gene silencing also have been shown to be effective in increasing the synthesis of phenolic acids in plants, without effects on the levels of other compounds. This suggests the possibility of improvement in antioxidant capacity and plant resistance, without changes in agronomic traits of the species (Kaushik et al., 2015; Niggeweg et al., 2004).

Tannins

Tannins along with lignin are considered one of the most important groups of secondary metabolites in the defense of plants, mainly due to their biochemical and molecular properties (Adamczyk et al., 2013; Zucker, 1983). There are basically two categories, namely condensed tannins, compounds formed by the addition of flavonoid constituents of woody plants and the water-soluble tannins, polymers that present phenolic acids and simple sugars (Taiz and Zeiger, 2010).

Herbivores such as cattle, deer, monkeys and birds avoid plants or parts of them that have higher tannin levels. Studies have shown that interaction of these substances with proteins, for example, determines the selectivity of some herbivores in plant feeding (Clausen et al., 1990; Zungu and Downs, 2015).

The plant defense strategies are intrinsically related to the organ in which the tannins are synthesized. Studies with *Medinilla magnifica*, known as rose grape, revealed the cells that synthesize tannins show distribution patterns defined in plant organs with a preference for accumulation around or near the vascular tissues. In leaves, these substances tend to accumulate in mesophyll region and surrounding tissues, with the highest concentration in the apical region. Roots and stems tend to have lower levels of these substances, yet still found in small quantities.

The concentration of tannins in reproductive structures and fruit maturity was also relatively high, reducing the extent which fruit maturing (Robil and Tolentino, 2015). This specific distribution both spatially and temporally may indicate its role in protecting vital structures of plants and also an obvious adaptation to make more palatable fruit only when they are physiologically mature and presenting viable seeds, leading to success in the spread of species.

In addition to its role in herbivores food selectivity, these compounds may also have antibiotic activity. A condensed tannin isolated from *Gossypium hirsutum* flower, known as Mexican cotton, was presented as an antibiotic component of this plant, comprising about 3.4% of the dry weight of the flower. Its use in the diet of *Heliothis virescens*, tobacco caterpillar, retarded growth of the larvae in 84% (Chan et al., 1978). However, recent studies have revealed that addition of specific isolates of these substances in flour for cooking, improves their properties, primarily due to increased hydrogen bonding, improving the interactions between proteins and carbohydrates, resulting in a more compact gluten (Wang et al., 2015b).

There are few studies that reveal how the environment provides changes in synthesis of these compounds, however, some research has shown that tannins can significantly influence the soil changes. The addition of these substances decreases carbon mineralization and nitrogen nitrification, significantly affecting the complexation of nitrogen compounds and consequently the availability of nitrogen (Adamczyk et al., 2013).

Nitrogen compounds

A great variety of secondary metabolites has nitrogen in their structures. The main nitrogenous compounds found in plants are alkaloids, glycosides, and non-protein amino acids: these are usually synthesized from the common amino acids (Taiz and Zeiger, 2010). In this session will be addressed the main types of nitrogenous compounds produced by the plants, their biological properties and how environmental factors can influence their synthesis.

Alkaloids

Alkaloids are a large group with more than 15,000 substances, being found in about 20% of the vascular species. These compounds are generally characterized by the occurrence of a nitrogen atom in oxidative state into a heterocyclic ring. Unlike other secondary metabolites, many alkaloids have independent biosynthetic pathways, may be originated from different amino acids (De Luca and Laflamme, 2001). With this, it is not surprising enzymes acting on alkaloid synthesis, while also performing functions in primary metabolism (Facchini, 2001).

The roles of the alkaloids in plants have been the subject of several types of research. It was believed that these substances are responsible for nitrogen secretion (like urea and uric acid in animals); however, this hypothesis is not accepted due to few concrete results. It is believed that most of the alkaloids present defense function in plants, due to their general toxicity their and ability to inhibit feeding (Wink, 1988).

Virtually all alkaloids are toxic to humans if ingested in sufficient quantities, however, many of these compounds are medicinally used, moving a worldwide volume of approximately 4 billion dollars (Julsing et al., 2006). Figure 5 shows some important alkaloids, such as morphine, berberine, vinblastine and scopolamine, which have medicinal properties and others such as cocaine, caffeine and nicotine, which have no medical use but is widely used as stimulants or sedatives (Facchini et al., 2004).

The alkaloid biosynthesis in plants requires the differentiation of specific cell types in response to specific environmental signals. For example, the N-methyltransferase enzyme, responsible for the chemical changes in the molecules of several nitrogenous compounds, has its activity increased by about 30% when etiolated plants of *Catharanthus roseus*, known as Vinca, were exposed too light (De Luca et al., 1988).

Few studies have shown specifically as changes in weather elements may affect the synthesis of this substance, but the most widely accepted hypothesis is that mainly light through phytochrome, modulates the regulation of protein and key enzymes involved in the metabolic pathways of these substances (Aerts and De Luca, 1992). Increases in alkaloids production of *C. roseus* were found with an increase of CO_2, mainly in a greater supply of nitrogen (Singh et al., 2015), indicating the relationship between plant metabolic responses and environmental factors.

Glycosides

Besides the alkaloids, glycosides also act as protective substances in plants. These substances can be divided into two types: cyanogenic glycosides, and glucosinolates. These metabolites are in wide varieties of plants. Alkaloids are not toxic in its natural state. For example, in crops such as sorghum and cassava, these substances are stored in the vacuole of the epidermal cells, whereas the enzymes responsible for the poisonous gas synthesis are in mesophyll (Poulton, 1990). When the plant is

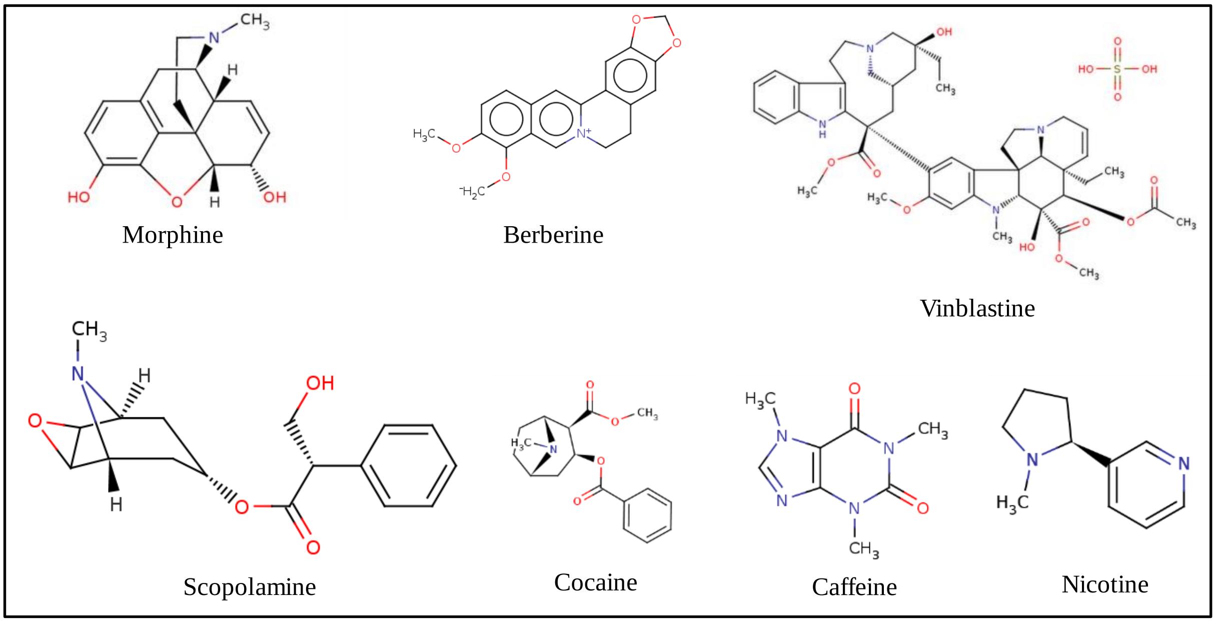

Figure 5. Some alkaloids of economic importance used by humans.

physically injured, cyanogenic glycosides (present in vacuole) are mixed, with hydrolytic enzymes (present in mesophyll), producing volatile poisons such as hydrogen cyanide (Taiz and Zeiger, 2010). Plant breeding programs aimed at reducing these compounds in crops of interest has been done. In cassava, for example, when fragments of CYP79D1 / D2 genes (responsible for the synthesis linamarin a cyanogenic glycoside) were silenced, it was observed the reduction of about 60-94% of these substances in leaves and surprisingly, 99% in roots (Siritunga and Sayre, 2004).

The influence of climatological variables in glycosidic compounds is significant. Studies in stevia, a small evergreen shrub with high sweetening capacity, has revealed that the transcript levels of 15 genes involved in vital pathways of steviol glycosides synthesis, were maximum at the temperature at 25^{o}C, while the transcription of 12 of the 15 genes was inhibited both at low temperatures (15°C) as at high temperatures (35°C). Most genes exhibited low transcription levels under water deficit, while the photoperiod did not significantly influence its transcriptions (Yang et al., 2015). These responses, however, cannot be generalized to all species, due to genetic specificity of each, and its adaptation to specific environments. This can be a stimulus for performing local research with cultures that have an economic interest.

Non-protein amino acids

Plants and animals incorporate the same 20 amino acids in their proteins. However, non-protein amino acids, which are not incorporated into proteins and roam freely, acting as protection substances in plants. Among some, may be cited the 2,4-diaminobutyric acid, 2,3-Diaminopropionic acid, L-3-Amino-2-(oxalylamino) propanoic acid and 2-amino-6n-oxalylureidopropionic acid (oxalylalbizziine) which are present in certain fodder and has been causing toxicity in ruminants (Mcsweeney et al., 2008).

Diaminobutyric acid can act as a competitive inhibitor of gamma-aminobutyric acid (GABA), an important regulator of neuronal excitability. A study with synaptosomal fraction isolated from mouse brains has revealed that diaminobutyric acid causes a competitive inhibition with the site of GABA absorption in a short time; for more prolonged periods, this inhibition was not competitive, being the effectiveness of this inhibitor, dependent on sodium levels and the temperature sensitive. (Simon and Martin, 1973).

Final considerations

The evidence presented here indicates that the synthesis and inhibition of plant's secondary metabolites are dependent upon its primary metabolism, and are subject to great influence by environmental factors, primarily due changes in the transcription factors responsible for its synthesis. Environmental factors such as extreme temperatures, radiation, CO2 levels and water availability are presented as potential factors in changing the pathways of several secondary metabolites in plants. The same can be said for biotic factors such as plant damage caused by pathogens or herbivores. The plants have

Table 1. Limitations and challenges to be achieved upon the control of secondary metabolite synthesis in plants.

Limitations	Challenges
Terpenes	
Dynamic and complex synthesis of terpenes in response to environmental factors in important crops such as watermelon, Gac, papaya and tomato are still limited.	To identify the pathways responsible for synthesis of these compounds that are influenced by environmental factors.
Reduction in endogenous concentrations of JA under increased CO_2 levels.	Obtaining superior genotypes with high JA synthesis in presence of elevated CO_2 levels.
Phenolic compounds	
Multiple-gene regulation of PAL enzyme's activity.	To identify PAL genes in important crops responsible for role in the defense responses, under different environmental stimuli.
Information about how the environmental factors acts on coumarins' synthesis are still limited.	To reveal the pathways modified by environmental factors aimed at production of responsive plants with greater therapeutic importance.
Little information about how the environmental factors acts on Lignin's synthesis and the response to lignification related to presence of peroxides.	To identify how environmental factors act on its synthesis or inhibition, aiming to obtain superior genotypes with greater or lesser lignin content.
The pleiotropy for miRNA156, controlling the synthesis of anthocyanin and flavonoids and its relationship with SPL9, a key regulator of plant development which promotes flowering in Arabidopsis.	To identify the kind of pleiotropy acting in this crop, and to perform studies with economical-important crops in order to clarify the genome-wide significant associations with plant complex traits.
The complex interaction between soil and environmental factors on the synthesis of anthocyanin.	To create genotypes with high anthocyanin production and acclimatized in varied environments.
Hyper sensibility to UVB radiation in plants mutants or with little synthesis of flavones and flavonols.	To increase endogenous concentration of flavones and flavonols in crops in order to mitigate the effects of the reduction of ozone layer.
Little information about the interaction of biotic and abiotic stimuli on Isoflavones synthesis and plant's resistance.	To identify the pathways altered by environmental factors in order to produce more resistant plants.
Nitrogen compounds	
Research evaluating the influence of environmental factors on alkaloids' synthesis are still limited.	Due its medicinal importance, is highly encouraged the realization of research aiming at evaluating the influence of environmental factor in its synthesis.
Limited information about dynamic of cyanogenic glycosides in plants such as cassava and sweet potato.	To use genomic tolls in order to silence genes responsible for glycosides' synthesis in economical-important crops.
Toxicity in ruminants caused for non-protein amino-acids.	To balance the lesser concentration of toxic compounds such non-protein amino acids with the maintenance of plants' defense against herbivores.

created protection strategies which allowed them higher levels of evolutionary fitness. Scientific advances in molecular biology over the past years have been useful in understanding the dynamics of secondary metabolite synthesis in plants. Recent techniques in gene editing have been useful and can be used by breeders aiming to exert greater control over the expression or inhibition of these substances. A synthesis of limitations and the challenges to be achieved upon the control of secondary metabolite synthesis in plants is shown in Table 1.

Conflict of Interests

The authors have not declared any conflict of interests.

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