



Plant secondary metabolites synthesis and their regulations under biotic and abiotic constraints

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Abstract

Plants being sessile entities are often subjected to varied environmental stresses. They have developed an alternative defense mechanism that involves a vast variety of secondary metabolites to serve as tools to cope up with various stress conditions. The exposure of plant cells to abiotic and biotic stresses initiate multilevel reaction cascades that consequently leads to production and accumulation of various secondary metabolites. Various enzymatic and non-enzymatic molecules comprising the antioxidative defense system comes into play to counteract the undesirable effect of ecological stresses. Energy required as fuel in biosynthesis, transport and storage which comprises the costs for the formation of various transcription factors. When plant experiences stress in combination they express various transcription factors that might help the plant to make flexible signaling cascades to increase plant resistance against one of the stress. Based on this limelight, the present review aims to wrap the influence of different abiotic and biotic factors including salt, drought, heavy metals, UV light, herbivory and pathogenesis on secondary metabolites production and their roles in stress tolerance mechanism in plants.

Keywords Secondary metabolites · Abiotic and biotic stresses · Reactive oxygen species · Antioxidative defense system

Introduction

Plant secondary metabolites (SMs) are natural byproducts of primary metabolic processes. SMs have no direct role in plant growth, metabolism and development but play a significant role in plant defense mechanism, hence labeled as ‘secondary compounds’. The primary function of SMs is to improve the growth and survival of the plants under adverse conditions (Zandalinas et al. 2017). In mutualistic relationships viz. pollination, legume root nodule and antagonistic interactions viz. pathogenesis, herbivory SMs play a very crucial role during communication (Chomel et al. 2016). SMs are diverse group low of molecular weight miscellaneous compounds which are synthesized in low concentration

by large multimodular polyketide synthases (PKSs) and nonribosomal peptide synthetases (NRPSs) or enzymes such as prenyltransferases and dimethylallyl tryptophan synthases (Brakhage 2013; Kasote et al. 2015). Accumulation and production of SMs vary from species to species or within the same plant species growing in different environmental conditions (Radušienė et al. 2012). During the growth of the plant different aspects including physiology, genotype, stages of development and environmental factors determines the concentration and types of SMs synthesis. Biosynthesis of SMs is stimulated when plants are exposed to various potential stresses at the expense of metabolic energy (Eid et al. 2015). Plants are generally exposed to various combinations of biotic and abiotic stresses, such as drought, salinity, heavy metals, UV-irradiation, pathogenesis and herbicides. Various Stresses alters morphology and augments phenolic pigments level, antioxidant activity, electrolyte leakage, flavonoids, proline, tocopherol accumulation hampers plant growth (Brzezinska et al. 2006; Bano et al. 2016, 2017). In response to various biotic and abiotic stress ROS level enhanced in cellular system induces oxidative stress which consequently leads to lipid peroxidation, inactivation of enzymes and DNA damage (Akula and

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Ravishankar 2011). To overcome stress constraints plants adopt many alternative mechanisms that involve a synthesis of wide range of secondary products which serves as resistance tools. An antioxidative defense system and different metabolites help the plant to survive under adverse condition. The timely recognition of the stress by the plant is crucial for a rapid and effective response. Intrinsic basal defense mechanism is activated in plants as a result of stress recognition which in turn initiates complex signaling cascades of defense varying from one stress to another (Chinnusamy et al. 2004; Abou et al. 2009). The interaction and combined exposure to various stresses are also possible. In response to combined stresses, different signaling cascades shared many intermediates compounds and outcomes. This could be advantageous for creating a signaling network which helps to enhanced resistance to abiotic stress under different biotic stress. Hence lack of SMs and antioxidant enzymes synthesis leads to long-term disrupted consequences in plants (Bartwal et al. 2013). Present review focuses on the biosynthesis of SMs, SMs alteration made within plants in the levels

exposed to different abiotic and biotic stresses existing in current environmental conditions.

Biosynthesis of secondary metabolites in plants

Absence of immune system and mobility, plants synthesize a wide range of secondary compounds. Under the unfavorable condition, more than 100,000 SMs are produced in plants from different metabolic pathways. The quantity and quality of these compounds are greatly influenced by the growing environment and temperature (Meena et al. 2017). The biosynthesis of SMs and their interconnections/interrelations with primary metabolism inside the plant cell is shown in Fig. 1. A wide range of SMs are synthesized by alternative mechanisms in plants and some common products are terpenes, phenols, alkaloids etc. (Fig. 1). Two major pathways for the synthesis of terpenes are mevalonic-acid (MVA) pathway and 2-C-methylerythritol 4-phosphate (MEP) pathways

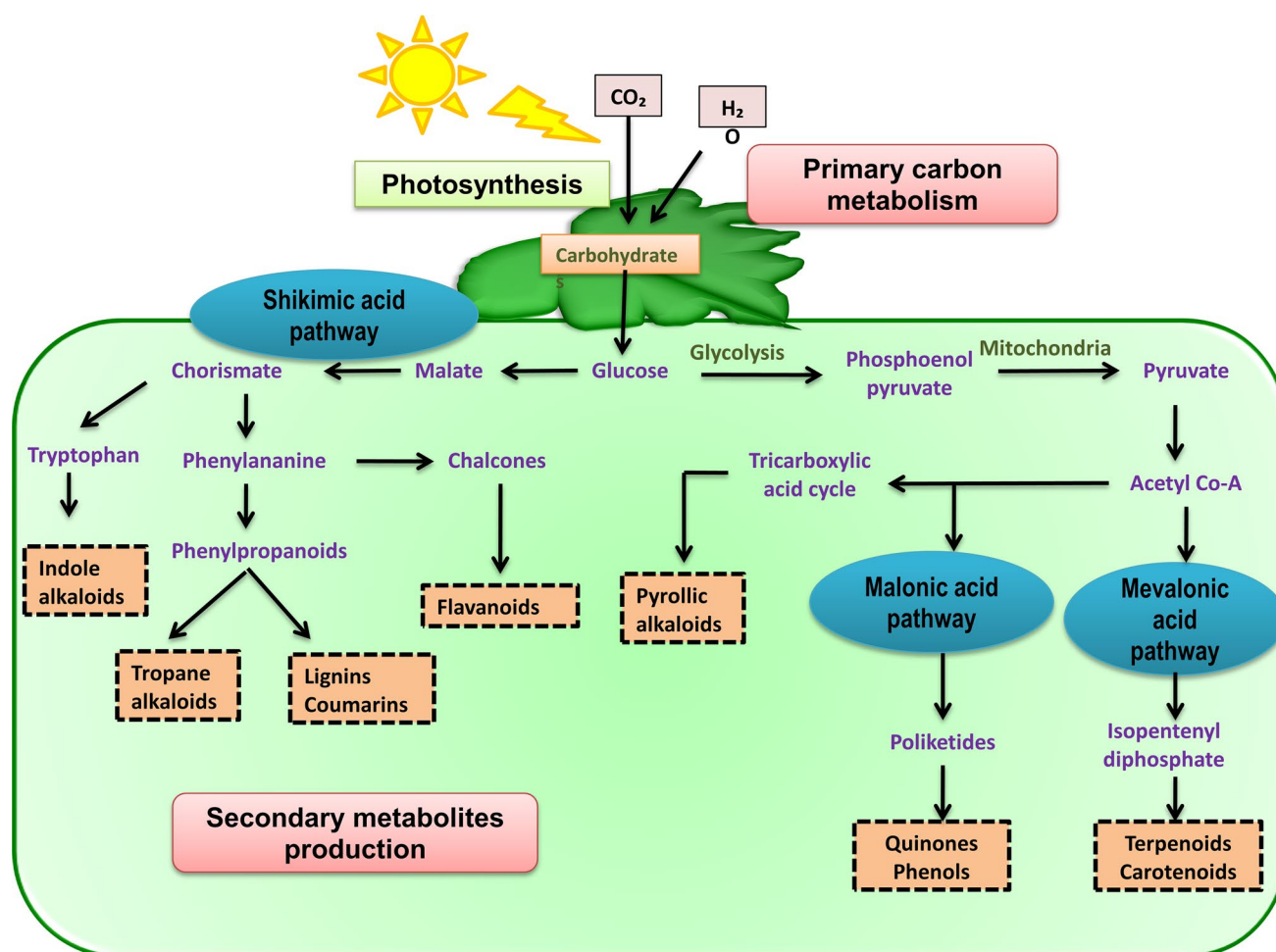


Fig. 1 Biosynthesis of secondary metabolites and their interconnection with primary metabolites

occur in cytosol and plastid, respectively. Product of glycolysis such as pyruvate and glyceraldehyde-3-phosphate is responsible for the synthesis of isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP) which act as a universal precursor for all terpenoids localized in various cellular compartments (Fig. 1). Terpenes synthase enzyme are responsible for the synthesis of terpenes in different cellular compartments. Expression of different transcription factors elevated under various abiotic and biotic stresses such as in *Daucus Carota* and *Bixa orellana*, phytoene synthase and β -lycopene cyclase expression increases the accumulation of carotenoids in response to salt stress (Sankari et al. 2019; Simpson et al. 2018). Some other terpenes with their elevated transcription factors under various biotic and abiotic stresses are mentioned in Table 1. Phenolic compounds are synthesized in plants using shikimic acid pathway and the malonic acid pathway (Ghasemzadeh et al. 2011). Malonic acid pathway has been also reported in fungi and bacteria for the synthesis of phenolics (Cheynier et al. 2013). Phenylalanine ammonia lyase (PAL) and CHS (chalcone synthase) are the soul enzymes regulate phenolic levels under various stress constraints. Function of PAL, C4H (cinnamate 4-hydroxylase), 4CL (4-coumarate:CoA ligase), CHS, CHI (chalcone isomerase), F3H (flavanone 3-hydroxylase), F30H (flavonoid 30-hydroxylase), F3050H (flavonoid 3050-hydroxylase), DFR (dihydroflavonol 4-reductase), FLS (flavonol synthase), IFS (isoflavone synthase), IFR (isoflavone reductase), and UFGT (UDP flavonoid glycosyltransferase) were upregulated with the elevated enzymes concentrations (Sharma et al. 2019). Nitrogen-containing SMs is characterized by the presence of nitrogen molecule in their structure and amino acids such as lysine, tyrosine and tryptophan act as a precursor in their biosynthesis. Tryptophan decarboxylase, WRKY6 and Hyoscyamine 6 β -Hydroxylase are some enzymes and factors responsible for the synthesis of alkaloid under UV-B and salt stress, respectively (Schlutenhofer et al. 2014; Mehrotra et al. 2018). Some other secondary metabolites under various biotic and abiotic stresses are mentioned in Tables 1 and 2.

Mobilization, accumulation and cost of secondary metabolism and their metabolites in plants

A group of SMs are accumulated constitutively in plant tissues during metabolic processes. Vacuoles are reported as a major storage site for various water-soluble SMs. Different trapping mechanisms were used for storage of various metabolites in vacuole such as isoquinoline alkaloids by meconic acid or chelidonic acid in the latex vesicles of *Papaver* or *Chelidonium*, respectively (Roshchina et al. 2012). An adenosine triphosphate (ATP) dependent

transporter used to transport some xenobiotics and conjugated SMs such as glutathione into the vacuole (Wink 2003). Proton gradient was generated by adenosine triphosphatase (ATPase) located in tonoplast which is used as a driving force by a proton antiport mechanism (Falhof et al. 2016). Contrary lipophilic substances usually accumulated in trichomes, resin ducts, glandular hairs, laticifers, thylakoid membranes or on the cuticle and storage can also be tissue and cell specific (Guern et al. 1987; Pagare et al. 2015). Lipophilic compounds and some alkaloids such as berberine are pumped across biomembranes with the help of a diverse range of ABC transporters, a membrane protein driven by ATP (Lv et al. 2016). H^+ -antiporter is used to mediate transport of berberine to vacuoles instead of ABC transporters (Otani et al. 2005). V-ATPase and V-PPase two proton pump transporters located on the vacuolar membrane responsible for uptake of SMs from the cytosol to vacuole by generating membrane potential difference (Roytrakul and Verpoorte 2007).

Energy required is contributed by H^+ -ATPase or ABC transporters for the uphill transport across the tonoplast and/or for trapping the metabolite in the vacuole (Buxbaum 2015). It was reported that alkaloid/ H^+ antiporters serve as chief transporter for the transport of many alkaloids. In many studies, it was reported that tannins, alkaloids or glucosinolates stored in specific idioblasts (Mithöfer and Maffei 2016). Moreover, the biosynthesis of SMs, differentiations and maintenance of special anatomical structures (ducts, gland cells, trichomes) and sequestration (the corresponding transcription and translation of related genes and mRNAs) are expensive, required ATP or reduction equivalents, i.e. nicotinamide adenine dinucleotide phosphate (reduced form) ($NADPH_2$) (Wink 2011). In other words, it must be costly for plants to produce defense and signal compounds.

Effect of abiotic and biotic stresses on secondary metabolism of the plants

To cope up from different abiotic and biotic stresses such as drought, salinity, heavy metals, UV-irradiation, herbivory and pathogenesis plant synthesize various SMs as a result of defense mechanism. Alterations in levels of different SMs under abiotic and biotic stresses are mentioned in Tables 1 and 2, respectively.

Effect of salt stress on secondary metabolism of plants

The presence of excessive soluble salts in the soil is one the major reason for the decline in crop yield and productivity worldwide. In spite of availability of water, high concentration of salt causes increase in ionic and osmotic stresses in

Table 1 Different secondary metabolites along with their transcription factors synthesized in plants under abiotic stress

Stress	Secondary metabolites	Source	Transcription factor	Function	References
Drought stress	Flavonoids	<i>Pisum sativum</i>	MYB	Scavenging activity	Larson (2018); Liu et al. (2016)
	Rosmarinic acid	<i>Salvia miltiorrhiza</i>	<i>SmPAL</i> , <i>SmC4H</i>	Significantly decreased both shoot and root dry weight, but increased the root to shoot ratio at later growth cycle	Liu et al. (2011)
	Chlorogenic acid	<i>Helianthus annuum</i>	<i>HaHQT2</i>	Protects against H ₂ O ₂ -induced oxidative stress	Lubaina and Murugan (2013); Chee-varungnapakul et al. (2019)
	Epicatechins	<i>Camellia sinensis</i>	<i>Chalcone synthase 1 and 3</i> , <i>anthocyanidin reductase 1 and 2</i>	Anti-radiation and anti-aging	Zhang et al. (2016)
Salinity stress	Glycosides	<i>Scrophularia ningpoensis</i>		Decreased catalpool, harpagoside, aucubin, harpagide, and cinnamic acid content	Wang et al. (2006)
	Abscissic acid	<i>Glycine max</i>	GmbZIP1	Improved tolerances	Gao et al. (2011)
	Sorbitol	<i>Lycopersicon esculentum</i>	Sorbitol-6-phosphate dehydrogenase (S6PDH)	Cell structure protection and osmotic adaptation	Tari et al. (2010)
	Polyamines	<i>Oryza sativa</i>	SAMDC	Increase in polyphenol content	Berberich et al. (2015); Do et al. (2014)
Heavy metal stress	Glycine betaines	<i>Triticum aestivum</i>	Betaine aldehyde dehydrogenase (BADH)	Reduced membrane permeability lipid peroxidation and H ₂ O ₂	Yadav et al. (2017)
	Tropane alkaloids	<i>Datura innoxia</i>	Hyoscyamine 6 β -Hydroxylase	Increase of scopalamine	Kim et al. (2016); Schlesinger et al. (2019)
	Chlorogenic acid	<i>Helianthus annuum</i>	<i>HaHQT2</i>	Protects against H ₂ O ₂ -induced oxidative stress	Lubaina and Murugan (2013); Chee-varungnapakul et al. (2019)
	Carotenoid	<i>Bixa orellana</i>	β -lycopene cyclase	Act as a scavenger	Sankari et al. (2019)
Heavy metal stress	Carotenoid	<i>Daucus carota</i>	Phytoene synthase	Photoprotective functions	Simpson et al. (2018)
	Rosmarinic acid	<i>Salvia miltiorrhiza</i>	<i>SmPAL</i> , <i>SmC4H</i>	Significantly decreased both shoot and root dry weight, but increased the root to shoot ratio at later growth cycle	Liu et al. (2011)
	Flavonoids	<i>Vitis vinifera</i>	Chalcone synthase (CHS) and flavanone-3-hydroxylase (F3H)	Increased biosynthesis of phenolics	Leng et al. (2015)
	Artemisinin	<i>Artemisia annua</i> L.	3-hydroxy-3-methylglutaryl coenzyme A reductase	Reduced oxidative stress	Rai et al. (2011a, b)
Heavy metal stress	Chlorogenic acid	<i>Zea mays</i>	phenylalanine ammonia lyase (PAL); Chalcone synthase; (CHS)	Reduced oxidative stress	Kisa et al. (2016)
	Essential oils	<i>Mentha pulegium</i> L.	1-Deoxy d-xylulose-5-phosphate synthase (Dxs)	Ameliorates harmful effects	Nazari et al. (2017)
	Apigenin	<i>Chrysanthemum morifolium</i>	Chalcone isomerase (CHI)	Increased phenolic compounds biosynthesis	Hodaiei et al. (2018)

Table 1 (continued)

Stress	Secondary metabolites	Source	Transcription factor	Function	References
UV-B stress	Terpenes	<i>Vitis vinifera</i>	VvWRKY1	Increased tolerance to osmotic stress	Marchive et al. (2013)
	Terpenoids indole alkaloids	<i>Catharanthus roseus</i>	WRKY6	Transcription factor activity; defense response	Schluttenhofer et al. (2014)
	Phenolic compounds	<i>Clematis terniflora</i>	5-enolpyruvylshikimate-3-phosphate synthase (CtEPSPS)	Elevate phenolics production	Takshak et al. (2019)
	Indole alkaloid	<i>Camptotheca acuminata</i>	Tryptophan decarboxylase	Indole alkaloid biosynthesis	Mehrotra et al. (2018)
	Artemisinin	<i>Artemisia annua</i> L.	1-deoxy-D-xylulose-5-phosphate reducto isomerase (DXR)	Act as scavenger	Pandey and Pandey-Rai (2014)

crops which results in membrane disruption, high production of ROS and ion toxicity (Ashraf et al. 2015). There have been increased levels of tannic acid, flavonoids, and gossypol in cotton plants exposed to salinity (Wang et al. 2015). In safflower, under salt stress elevated levels of flavonoids, proteins and soluble sugars were observed (Gengmao et al. 2015). The tomato and mung bean plants exposed to differential levels of salinity resulted in marked enhancement in carotenoids, phenolics, and flavonoids content (Mahmood et al. 2016; Langi et al. 2018). In *Achillea fragrantissima*, *Catharanthus roseus*, *Oryza sativa* and *Solanum nigrum* higher alkaloid and phenolic content exposed to salt stress which helps in scavenging of harmful ROS (Verma and Shukla 2015; Chunthaburee et al. 2015; Ben Abdallah et al. 2016). Exposure of salt stress to two sugarcane clones, i.e., CP-4333 (salt tolerant) and HSF-240 (salt sensitive) showed decrease in flavones, anthocyanins, and soluble phenolics content although the decrease was more in salt-sensitive HSF-240 clone (Parmar 2016). Essential oil are ameliorating harmful effects and salinity triggered the increased essential oils content in *Salvia officinalis*, *Satureja hortensis*, and *Matricaria recutita* while it decreased in *Mentha suaveolens*, *M. pulegium*, *S. officinalis*, *Matricaria chamomilla*, *Majorana hortensis*, *Origanum vulgare*, *Thymus maroccanus*, *Mentha piperita*, and *Trachyspermum ammi* (Said-Al Ahl and Omer 2011). Under salt stress condition altered levels of SAMDC which enhances polyamine content in roots of *Helianthus annuus* L. (Chiapusio et al. 2016).

Accumulation of various alkaloids like reserpine and vincristine was observed under salt stress conditions in *Rauvolfia tetraphylla* and *Catharanthus roseus*, respectively (Said-Al Ahl and Omer 2011). *Solanum nigrum* seedlings treated with various concentrations of salt viz 0, 50, 100 and 150 mM significantly enhanced the expression of flavonoid genes encoding flavonol synthase, chalcone synthase, and phenylalanine ammonialyase, resulting in enhanced quercetin 3- β -D-glucoside, lutein, and lutein synthesis. Various carotenoids related genes involving β -lycopene cyclase and phytoene synthase 2 were upregulated on exposure to salt stress (Ben Abdallah et al. 2016). ATPase, OSAP1 zinc finger protein, and transcription factor HB1B are some salinity responsive genes expressed more in Pokkalia salt-tolerant rice than in salt-sensitive rice line IR64 (Parihar et al. 2015). GmERF057 and GmCAM4 are transcription factors play a crucial role in tolerating and providing resistance to *R. solanacearum*, *Phytophthora sojae*, *Alternaria tenuissima*, and *Phomopsis longicolla* plants under salt stress (Rao et al. 2014).

Effect of drought stress on secondary metabolism of plants

Plants subjected to water stress decreased water potential to an extent that it affects the normal physiological processes

Table 2 Different secondary metabolites synthesized in plants under biotic stress

Stress	Secondary metabolites	Types	Source	Function	References
Herbivory and pathogenesis	Nicotine	Pyridine alkaloid	<i>Nicotiana</i> sp.	Reduced bacterial diversity and prevent nectar spoilage	Stevenson et al. (2017)
	Vindoline	Alkaloid	<i>Catharanthus roseus</i>	Increase synthesis monoterpene indole alkaloids	DeLuca et al. (1986)
	Cholorogenic acid	Phenol	<i>Vaccinium myrtillus</i>	Hamper growth of lepidopteran larvae	Hernandez-Cumplido et al. (2018)
	Caffeoylquinic acids	Phenylpropanoids	<i>Xanthium pensylvanicum</i>	Act as antioxidants and antibacterial	Miyamae et al. (2011)
	Quinones	Phenol	<i>Glycine max</i>	Defense against noctuid larvae	Felton et al. (1994)
	α -farnesene	Terpene	<i>Malus domestica</i>	Olfactory behaviors and the periodicity of reproduction of codling moth females	Yan et al. (2003)
	Amygdalin	Cyanogenic glycosides	<i>Prunus amygdalus</i>	Cause post-ingestive malaise	Tiedeken et al. (2014)
	Phytoalexin	Diterpenoid	<i>Oryza sativa</i>	Induced resistance to bacterial blight	Kanno et al. (2012)
	Carboxyatractyloside	Diterpene kaurene	<i>Xanthium cavanillesii</i>	Antimalarial	Chen et al. (2015)
	Quercetin	Flavonoid glycosides	<i>Solanum nigrum</i>	Act as prooxidants and are toxic to several species of lepidopteran	Schmidt et al. (2005)

(Salehi-lisar et al. 2012). Drought has a significant impact on biochemical physiognomies of plants that affect plant growth and development, photosynthesis, cellular dehydration and other metabolic processes. (Fig. 2) (Xu et al. 2010; Iqbal et al. 2011). Plants show a variety of responses related to drought stress tolerance. In willow leaves, drought causes oxidative stress which results in enhanced flavonoids and phenolic acids contents (Larson 2018). The chlorophyll contents decreased in cotton and *Catharanthus roseus* exposed to drought stress (Akula and Ravishankar 2011). Saponin contents in *Chenopodium quinoa* decreased in plants growing under low and severe water stress. It has been reported that anthocyanins accumulate in plant tissues and provide resistance against drought conditions (Morales et al. 2017). In the root of *Scutellaria baicalensis* Georigi the expression of several flavonoids biosynthesis genes elevated under drought stress (Yuan et al. 2012). In *Antirrhinum majus* increased flavonoids accumulation resulted in the intense purple coloration of both flesh and peel of fruit due to overexpression of a basic helix-loop-helix (bHLH) transcription factor gene AmDEL gene (Butelli et al., 2008). *Arabidopsis* plants and wild type (WT) plants were exposed to drought stress for 4 weeks and resulted in a higher content of total flavonoids in the tolerant transgenic plants in comparison

with WT plants due to increased AmDEL expression (Wang et al. 2016).

Biosynthesis of SMs in medicinal plants like *Artemisia annua*, *Hypericum perforatum* and *C. roseus* increased several folds under water stress condition (Katz and Baltz 2016). *Trachyspermum ammi* grown in water limiting fields showed a reduction in plant fresh and dry weight and increased total phenolic content and pigments (Azhar et al. 2011). Drought stress showed elevated activity of antioxidant enzymes (Amist et al. 2014, 2015) and enzyme activity of proline metabolism in wheat plants (Amist and Singh 2014, 2015, 2017).

Under various stresses, including drought overexpression of four basic leucine zipper (bZIP) gene family members, *GmbZIP44*, *GmbZIP46*, *GmbZIP62*, and *GmbZIP78*, were reported to enhance drought tolerance (Xie et al. 2009). Overexpression of *GmbZIP1* in BS93 a variety of Chinese wheat under drought stress was used as an excellent resource for genetic engineering of abiotic stress tolerance in crop plants (Gao et al. 2011). Expression of some other genes including *GmNAC002*, *GmNAC010*, *GmNAC012*, *GmNAC013*, *GmNAC015* and *GmNAC028* is induced in an ABA-independent manner (Tran et al. 2009). In *Lactuca sativa* the PAL gene activated under drought stress and

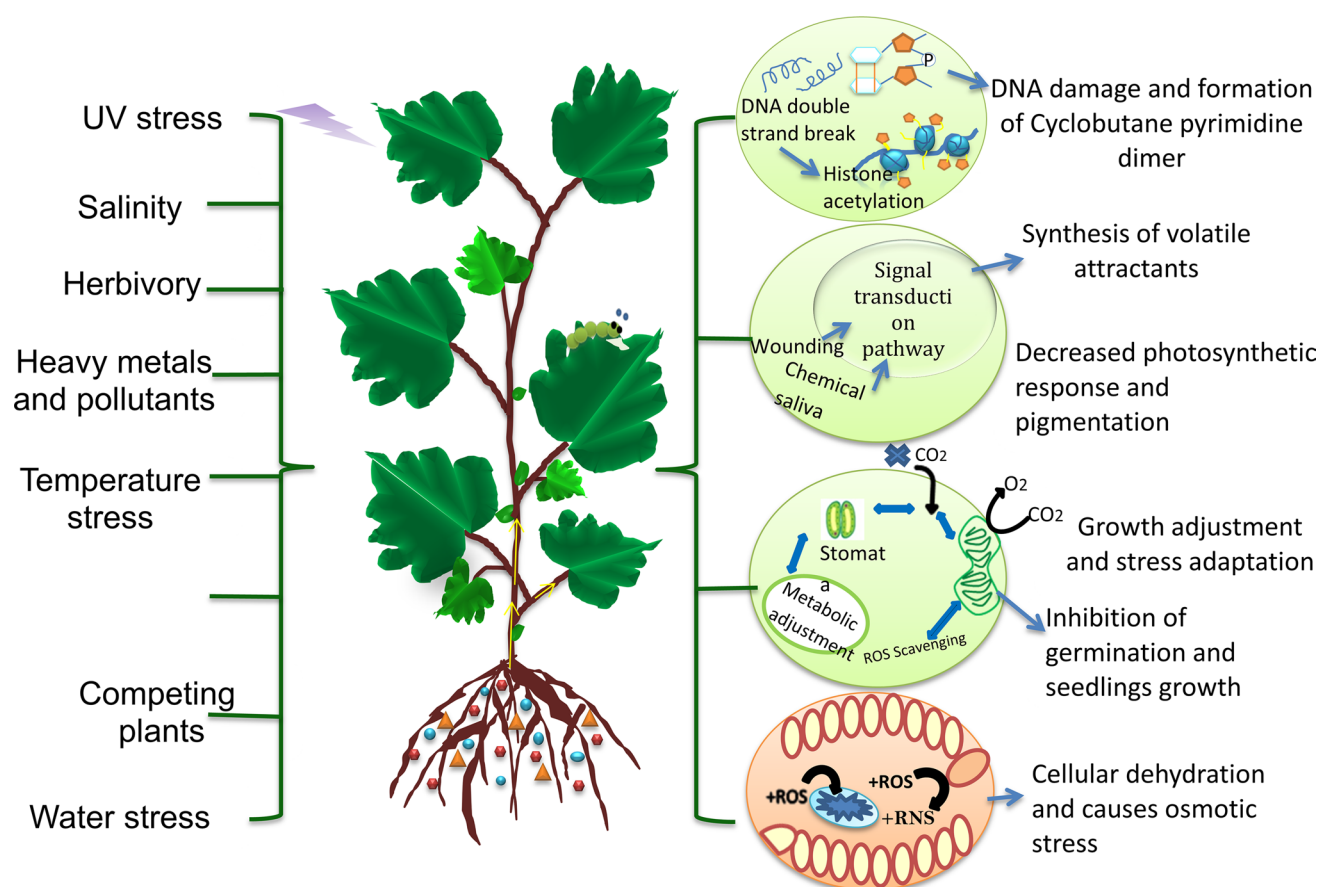


Fig. 2 Physiological changes in the plant under the influence of various abiotic and biotic stresses

involved in the biosynthesis of various phenolics and flavonoids (Rajabbeigi et al. 2013). Exposure of *C. acuminata*, *P. somniferum camptothecin* seedlings to water limiting condition enhances indole alkaloids such as narkotine, morphine and codeine (Yang et al. 2018). In *Catharanthus.roseus* alkaloid accumulation in shoot and root both increases due to oxidative stress as compared with control plants (Jaleel et al. 2007). Underwater deficit condition in *C. roseus*, enhance expression of betaine aldehyde dehydrogenase which simultaneously uplifts glycine betaine (GB), synthesis an osmolytes which play a protective role in the plant under stress condition (Jaleel et al. 2007).

Effects of heavy metals on secondary metabolism of plants

Heavy metals stress is one of the main abiotic constraints due to its high bioaccumulation and toxicity. Nowadays heavy metals are frequently used in agarotechnics and various developing industries. Heavy metals affect the quality and efficacy of natural products produced by plants. Heavy metals stress impaired photosynthetic apparatus by

interact with protein of Light-harvesting complex II and alter its conformation. Heavy metals stimulate senescence by increasing ethylene synthesis followed by jasmonic acid signaling pathway (Keunen et al. 2016). Artemisinin is a sesquiterpenes synthesized in *Artemisia annua* L., when treatment of As (0–4500 $\mu\text{g L}^{-1}$) was given. Furthermore, it leads to synthesis and up regulation of various genes transcripts such as 3-hydroxy-3-methylglutaryl coenzyme A reductase, amorpha-4,11-diene synthase, cytochrome P450 monooxygenase and farnesyl diphosphate involved in artemisinin production (Rai et al. 2011a, b). *Mentha pulegium* L. treated with 0–25 mg kg^{-1} Cu and 0–50 mg kg^{-1} Zn concentrations increased synthesis of major components of essential oils including pulegone, *cis*-isopulegone, α -pinene, sabinene, 1,8-cineol, and thymol (Lajayer et al. 2017). *Panax ginseng* Meyer and *Withania somnifera* L. Dunal at different concentrations of Cu increased production of phenolic and lignin compounds (Ali et al. 2006; Khatun et al. 2008). *Trigonella foenum-graecum* L. when treated with Cd and Co arouse production of diosgenin, whereas, Cr and Ni deter the biosynthesis of diosgenin (Thomas et al. 2011). *Hypericum perforatum* L. exposed to high concentrations of Ni i.e., 0.25

and 50 μM resulted in inhibition of pseudohypericin and hypericin synthesis and on the other hand at low concentrations of Cr (VI) i.e., 0.01 and 0.1 μM biosynthesis of total hypericin was upregulated (Murch et al. 2003; Tirillini et al. 2006).

Effect of UV stress on secondary metabolism of plants

The UV-B wavelengths are potentially harmful and cause deleterious effects on both plants and animals. Anthropogenic activities increased UV-B rays which cause DNA damage and the formation of cyclobutane pyrimidine dimer in plants (Fig. 2). Plants also respond to small molecules of different origin, known as elicitors that activate the same response in the plant-like other stress conditions. These elicitors introduced in a cell in minute concentrations are capable of redirecting the metabolism, causing increased formation of particular SMs (Singla and Garg 2017). It has been shown that in *Catharanthus roseus* exposed to UV-B light induced the synthesis of dimeric terpenoids, *strictosidine synthase*, indole alkaloids and tryptophan decarboxylase mRNA accumulation (Ramani and Jayabaskaran 2008). In grapevine cell cultures the outcome of UV irradiation on stilbene content is lesser known (Tůmová and Tůma 2011). Accumulation of stilbene in callus of grapevine treated with UV light resulted in higher production of stilbene (including *trans*-resveratrol) and it is found that only actively growing callus was capable of producing stilbenes, whereas old callus had lost this ability (Tůmová and Tůma 2011). *Clematis terniflora* exposed to 120.8 Mw cm^{-2} UV-B dose following 36 h of dark showed an elevation in levels of genes involved in shikimate pathways such as shikimate kinase (CtSK), 5-enolpyruvylshikimate-3-phosphate synthase (CtEPSPS), chorismate synthase (CtCS), L-tryptophan synthase (L-CtTS), and L-SERINE DEAMINASE (L-CtSD) (Gao et al. 2016).

Under high UV radiation exposure in *Clematis terniflora* the genes and enzymes concerned with alkaloid biosynthesis were upregulated to a greater extent in comparison to control. 10-hydroxygeraniol oxidoreductase (10-HGO) was increased up to twofolds, the expression levels of mRNA of 6–17-odeacetyl-vindoline O-acetyltransferase (dat), tabersonine 16-hydroxylase (t16h), deacetoxyvindoline 4-hydroxylase (d4h), octadecanoid-derivative responsive catharanthus AP2-domain protein 3 (ORCA3), strictosidine synthase (str), geraniol-10-hydroxylase (g10h), and 10-hydroxygeraniol oxidoreductase (10-hgo) were over expressed with t16h ORCA3 and str were enhanced up to approximately fourfold (Gao et al. 2016). mRNA levels of strictosidine β -glucosidase (sgd), secologanin synthase (sls), and tryptophan decarboxylase (tdc) were upregulated upon 30 min of UV-B irradiation, but prolonged exposure of up to 60 min caused declination in their levels. Recently it

was reported that in vitro propagated *A. annua* seedlings in response to low UV-B dose (2.8 Wm^{-2}), showed up-regulation in genes like *HMGR*, 1-deoxy-D-xylulose-5-phosphate reductoisomerase (*DXR*) (Table 1), Isopentenyl pyrophosphate isomerase (*IPPi*), farnesyl diphosphate synthase (*FPS*), *ADS*, cytochrome P450 dependent monooxygenase/hydroxylase (*CYP71AV1*) and dihydroartemisininaldehyde reductase (*RED1*) leading to enhanced artemisinin accumulation (Pandey and Pandey-Rai 2014).

Effects of herbivory on secondary metabolism of plants

Production of SMs that accumulate in plant tissues govern a variety of diverse functions but principally for defense against herbivores, fungi and bacteria and as plant signals (Mithofer and Wilhelm 2012). Plants can have two ways to avoid being eaten. First, they can avoid being selected for oviposition or herbivory by synthesizing substances which repel-ovipositing herbivores and attract enemies, including predatory and parasitic insects by killing plant-feeding insects which will reduce further damage. Secondly, by producing chemicals responsible for the mortality of herbivores (Mithofer and Boland 2012). SMs regulates defense systems in their interactions with insect herbivores, especially as toxins or repellents, has been well established through decades of research. Out of many SMs terpenes play a significant role against herbivory such as conifers induce some additional quantities of monoterpenes in response to bark beetle infestation (Fig. 2) (Xu et al. 2010). Pyrethroids (monoterpene ester) and pyrethrins are strong insecticides found in leaves and flowers of *Chrysanthemum* species and *Tanacetum cinerariifolium*, respectively, and are slightly harmful to mammals with their low tenacity in the environment (Xu et al. 2010). Recent research has revealed an interesting twist on the role of the volatile terpenes where they play significant roles in rice, cotton, wheat, sorghum and other species by inducing certain monoterpenes and sesquiterpenes after insect feeding (Smith 2005). Outward projection of glandular hairs from the epidermis having essential oil (a mixture of volatile monoterpenes and sesquiterpenes) “advertise” the toxicity of the plant and even a trial bite can reduce the potential of herbivores. Azadirachtin is the most potent feeding deterrent and it exerts a wide range of lethal effects to herbivores (Saydee 2015).

Nectar and pollen SMs in many plants and their effect on honey bees were studied: High nectar concentrations of gelsemine (terpenoidal alkaloids) found in *Gelsemium sempervirens* (nectar) associated with reduced pollen receipt (Stevenson et al. 2017). Pollination of caffeinated flowers enhanced with the production of caffeine due to better recruitment and foraging on caffeinated food sources (Thomson et al. 2015). Damage on *Glycine max* foliage infected

with spider and mite elevate lipid peroxidation, lipoxygenase (LOX), and peroxidase (POX), but the levels of the antioxidant enzymes catalase (CAT) and superoxide dismutase (SOD) were not affected (Heath et al. 2013). Nicotine, the antagonist of nicotinic acetylcholine receptors (nAChRs) found in nectar and is involved in fast neurotransmission between neurons (Moffat et al. 2016). Herbivores inhibit the synthesis of toxic isothiocyanates from glucosinolates by elevating the concentration of nitrile-specifier proteins and sulfatases (NSPs) (Jeschke et al. 2015). However, the outcome of these tactics is the breakdown of deactivated products that cannot be used for self-defense. By consequence, inhibition of hydrolysis and non-disruptive feeding had done by glucosinolate-sequestering insects by adapting strategies to stabilize the toxins (Winde and Wittstock 2011).

In *Chrysomela populi*, ATP-binding cassette (ABC) transporter (CpMRP) were identified expressing in defensive glands and are involved in invitro transportation of plant-derived phenolglucoside salicin (Strauss et al. 2013). A recent research on *Spodoptera littoralis* moths found that the herbivory-induced homoterpene (*E*)-4,8-dimethyl-1,3,7-nonatriene (DMNT) inhibit moth responses and reduce volatile organic compounds (VOC) emissions from green leaves (Hatano et al. 2015). Sometimes a single compound such as 1-hexanol added to floral VOC bouquets and showed resistance against *Bombus* sp. (Wright and Schiestl 2009).

Effect of pathogenesis on secondary metabolism of plant

Recognition of a variety of different pathogens, followed by a diverse defense mechanism, plays a vital factor for plant survival. The defensive mechanisms induced by pathogen attack lead to an increased translocation of carbon skeletons from source to site of infection which causes accumulation, production and/or degradation of conjugates and/or de novo synthesis of the SMs with protective or allelopathic activity (Ayala et al. 2014).

For pathogenic interactions, SMs play crucial roles as virulence factors, which can be observed for fungi infecting animals as well as plants. Not only the role of SMs in pathogenicity make them interesting to study, but many SMs, including penicillin, statins, and cyclosporines, have been found to have medical applications (Macheleidt et al. 2016). Against invading pathogens one of the most effective and observable portions of defense mechanisms in nature is hypersensitive reaction (HR) (Singh 2013). Persistence and establishment of plants are greatly influenced by the accumulation of secondary products in response to invading pathogens (Rejeb et al. 2014). In fungi alteration in levels of cyclic amino monophosphate (cAMP) regulatory elements greatly affects SMs synthesis with an enhanced rate of PKA phosphorylation cause increase in sterigmatocystin

production in *Aspergillus nidulans* and orthologous pathway mediates the biosynthesis of aflatoxin in *A. parasiticus* and *A. flavus* (Thieme et al. 2018). Limonoids a nonvolatile, bitter triterpenoids compounds found in citrus fruit, shows lethal consequences by disrupting molting and other developmental processes of insects when ingested (Rao et al. 2017). Glucosinolates give characteristic smell and taste to vegetables belonging to family Brassicaceae such as cabbage, broccoli, radish etc. and also show antimicrobial activity (Taiz and Zeiger 2006). Antiherbivore defenses due to alkaloids and cyanogenic glycosides are well documented (Mithöfer and Maffei 2016).

bZIP and winged helix proteins are less frequently found in fungi which often link stress response and SMs formation (Hong et al. 2013). The winged-helix TF CPC1 involved in, arthrospore formation and cephalosporin C production, thus links SMs synthesis and morphological development (Macheleidt et al. 2016). In fungi, loss of LaeA and SMs gene clusters causes a reduction in SMs production (Macheleidt et al. 2016). The tight regulation of light-dependent sexual development and SMs formation shown in filamentous fungi (Bayram and Braus 2012) is accomplished by spatial compartmentalization of the velvet complex subunits i.e., VelB and VeA (light-dependent), both can migrate between the nucleus and the cytoplasm (Bayram and Braus 2012). Under darkness, VeA-VelB heterodimer is formed and VeA moves to nucleus (Stinnett et al. 2007). The constitutive nuclear localization of LaeA assists functional velvet complex assembly only in the absence of light because light suppresses the velvet-dependent functions in sporulation, secondary metabolism and development (Brakhage 2013).

Cross talk signaling between biotic and abiotic stress

There is a great association between abiotic and biotic stress, biotic stress can enhance the resistance to abiotic stress (Abou et al. 2009). Transcription factors (TFs) play an essential role in the stress response by directly regulating the expression levels of various stress-related genes. In addition, to their ability for transcriptional regulation, TFs play a key role in integrating diverse signaling pathways in response to biotic and abiotic stresses. A number of genes belonging to APETALA2/ethylene response factor (AP2/ERF), MYB, WRKY, plant homeodomain (PHD), NAC, bZIP and GT transcription factor (GT-1 binding site related element binding factors) families in various model systems have been demonstrated to play a pivotal role in influencing stress-mediated cross talk in rice and *Arabidopsis* (Mengiste et al. 2003; Vannini et al. 2006; Cao et al. 2006; Nakashima et al. 2007; Chen et al. 2010; Zhu et al. 2010; Liu et al. 2013; Xiao et al. 2013; Lindemose

et al. 2013). *GmDREB2* transcripts belonging to A5 gene subclass were expressed in high salt, drought, cold and ABA treatment (Gupta et al. 2016). When *GmDREB2* transcripts overexpressed in *Arabidopsis* under the control of constitutive CaMV35S promoter or stress-inducible responsive to dehydration 29A (RD29A) promoter, the transgenic plants can survive up to a concentration of 200 mM salt and drought stress and this effect is detectable when plants are under pathogen attack (Shin et al. 2019). Pathogen infection may cause stomatal closure to obstruct the entrance of pathogen and as a result reduction in water loss is observed and leads to an improved plant resistance under abiotic stress (Atkinson et al. 2015). In tomato plants, wounding enhances plant tolerance to salt stress (Hu et al. 2017). In tobacco plants, ectopic expression of *GmERF057* not only enhanced salt tolerance but also increased resistance against bacterial pathogen *Ralstonia solanacearum* (Gupta et al. 2016).

The seedlings of *Solanum lycopersicum* infected by *Pseudomonas syringae* pv. tomato (*Pst*) caused complete resistance against insect *Helicoverpa zea* (Rejeb et al. 2014). Underwater deficit condition infection of tomato by *Botrytis cinerea* and *Oidium neolyopersici* were reduced (Rejeb et al. 2014). When stresses are given in combination common components and outputs are shared by different signaling cascades which could help plants to make flexible signaling network and minimize energy costs (Rasmussen et al. 2013; Koornneef and Pieterse 2014). Xu and colleagues (2008) observed that plants infected with virus showed resistance against drought stress.

The expression of several TFs belonging to MYB family along with stress-responsive genes such as *AZF1*, *STZ*, *RHL41/ZAT12*, and *DREB2A* and ABA signaling components (*LTP3*, *LTP4*, *PAD3*, and *UGT71B6*) were raised in transgenic plants (Xie et al. 2009). Overexpression of each of these genes in *Arabidopsis* significantly improved plant tolerance to drought, cold, and salinity stress. The plants of *Arabidopsis* infected with *Verticillium* showed enhanced tolerance towards drought due to expression of genes like vascular-related no apical meristem. Cup-shaped cotyledon (NAC) domain (VND) in de novo xylem development involved transcription factor VND7 which ensure water storage ability in plants (Reusche et al. 2012). Ectopic expression of *GmbZIP44*, *GmbZIP62*, and *GmbZIP78* in *Arabidopsis* results in reduced sensitivity toward ABA compared with WT plants at the germination stage (Gupta et al. 2016). Combined stress of heavy metals and pathogens enhances the expression of defense enzymes such as glucanases, chitinases or proteinases (Mithöfer and Wilhelm 2012). Mittra et al. (2004) observed that plant showed resistance against fungal and viral infection when pre-exposed to mild concentrations of Cd.

Conclusion and future prospective

SMs are natural products induced in plants exposed to various potential enemies. These compounds serve to meet the secondary requirements of the producing organisms. Growth and productivity of crop plants were adversely affected by various biotic and abiotic stresses. These secondary compounds play defensive roles in plants under various abiotic and biotic constraints and play a promising role in adapting plants to their local environment. They mediate a variety of defensive functions by elevating the synthesis of various enzymes responsible for SMs production and enhance the expressions of various genes involving in resistance mechanism of the plants. Ecological factors which influence SMs production and elevate their potential to over produce useful phytochemicals for varied applications. In vitro plant cell culture used for the production of synthetic biochemicals and drugs has made new footsteps in the world of natural products. A Recombinant DNA technology is used for commercial production of SMs on the basis of the regulated pathway of secondary metabolism via genetical tools. For substantial interest in plant harvesting, large-scale plant cell culture technology will be used for the utilization of SMs due to its medicinal properties and supply concerns. Moreover, molecular understanding will help to understand different stress responses useful in plant development with enhanced adaptation and efficiency. Although various researches have been done but it is interesting to focus our future studies on understanding how different ecological signals affect biosynthesis of various SMs. Future research in the field of bioinformatics could help to decode the production of various SMs at cellular and molecular levels.

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