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REVIEW

Abiotic Stress-Induced Changes in Antioxidative System and Secondary Metabolites Production in *Andrographis paniculata*

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Andrographis paniculata is an annual herbaceous plant of the family Acanthaceae. Andrographolide (a bicycle diterpene) is the main component of *A. paniculata* and responsible for its bitter taste. Abiotic stress considerably affects the life cycle of plants through morphological, biochemical, and physiological changes. These stresses also act as elicitors for the synthesis of secondary metabolites (SMs) in plants. Secondary metabolites help plants to survive in adverse conditions via alleviating osmotic stress and reducing Reactive Oxygen Species (ROS). In this review, we discuss the response of the antioxidative system and biosynthesis of secondary metabolites in *A. paniculata* under abiotic stress. The mechanism involve in biosynthesis of ent-labdane diterpenoids is also discussed.

Key words: Environmental stress, elicitors, andrographolide, reactive oxygen species, antioxidants

Abbreviation: AACA- Acetyl-CoA Acetyltransferase; ABA - Abscisic acid; AG – Andrographolide; APX - Ascorbate peroxidase; As- Arsenate; CAT – Catalase; Co – Cobalt; Cu – Copper; CYT - Cytochrome oxidase; DDAG – deoxy-11,12-didehydroandrographolide; DXR - 1- deoxyxylulose-5-phosphate synthase; DXS - 1- deoxyxylulose-5-phosphate reductoisomerase; FPP- Farnesyl pyrophosphate; GGPP - Geranylgeranyl diphosphate; GGPS - Geranylgeranyl pyrophosphate synthase; GR - Glutathaione reductase; HMGR - 3-hydroxy-3-methyl glutaryl coenzyme A reductase ; HMGS - 3-hydroxy-3-methyl glutaryl coenzyme A synthase; IPP - Isopentyl pyrophosphate; ISPH - 1-hydroxy-2-methyl-2-(E)-butenyl 4-diphosphate reductase; LP - Lipid peroxidase; MeJA - Methyl jasmonate; MEP - Methyl erythritol phosphate; MVAP - Mevalonic acid pathway; NeoAG – Neoandrographolide; PGRs - Plant growth regulators; POD – Peroxidase; PPO - Polyphenol oxidase; ROS - Reactive oxygen species; SA - Salicylic acid; Sms - Secondary metabolites; Sn – Tin; SOD - Superoxide dimutase; Tfs - Transcription factors

Andrographis paniculata (Burm.f.) Wall. ex Nees (Kalmegh in Hindi) is a useful annual herbaceous medicinal plant related to the family Acanthaceae. It is also known as the king of bitter because of its bitter taste. The bitterness of *A. paniculata* is due to the presence of andrographolide (a bicyclic diterpenoid lactones) (Siripong *et al*., 1992). *A. paniculata* is indigenous in India, Sri Lanka and has a broad range of diversity in some Asian and other countries such as Pakistan, Java, Malaysia (covering Penang, Malacca, & Pangkor Island of Borneo), Indonesia, China, Hong Kong, and Philippines. It is cultivated extensively for traditional herbal medicines in China, Thailand, and some regions of the East and West Indies (Jamaica, Barbados, and Bahamas) (Akbar, 2011; Niranjan *et al*., 2011; Joseph, 2014). In India, *A. paniculata* is found wild through the plains, mostly in Assam, Chhattisgarh, Maharashtra, West Bengal, Uttar Pradesh, Madhya Pradesh, Uttarakhand, Karnataka, and Tamil Nadu (Prajapati *et al*., 2003).

A. paniculata generally propagated through seeds and grows at various areas in pine, evergreen, and deciduous forest and, along the roadside in villages (Mishra *et al.,* 2007). The plant is highly branched, erect, up to 30-70 cm in length, stem herbaceous, quadrangular, dark green with varies in diameter from 2 to 6 mm. Leaves are simple, opposite, lanceolate with acute apex and short petiole, varying in length and breadth from 2-10 cm and 1-2.5 cm respectively, along with unicostate reticulate venation (Patil and Jain, 2021). It possesses terminal, axillary, and panicle type of inflorescence. It has white flowers with violet spots that are complete, bisexual, irregular (zygomorphic), hypogynous, pentamerous, pedicellate, and tubular. Flower are consist of linear 5 small sepals with excess hairs, petals are fuse about 6 mm long, white with a maroon stripe on the upper lip of petals. The plant possesses two stamens with hairy filaments, tricolporate pollen grains, and a bi-celled superior ovary. Seeds are very small, numerous and fruit is capsule (Sareer *et al*., 2014; Sharma *et al*., 2018). The flowering of *A. paniculata* starts from mid-October and it is in full bloom till December (Sharma and Jain, 2015) (Fig. 1).

The principal components of *A. paniculata* are ent-labdane diterpenoids, i.e., andrographolide (AG), neoandrographolide (NeoAG), 14-deoxy-11,12-didehydroandrographolide (DDAG) (Rafi *et al*., 2020), and flavonoids (Song *et al*., 2013). The chemical structure of biochemical components of *A. paniculata* is shown in Fig. 2. It exhibits several medicinal properties such as anticancer, antiviral, antibacterial, antidiabetic, antimalarial, antiinflammatory, liver protective, and cardioprotective (George and Pandalai, 1949; Yao *et al*., 1992; Matsuda *et al*., 1994; Zeha and Rawal, 2001; Chowdhury *et al*., 2012; Subramanian *et al*., 2012; Uttekar *et al*., 2012; Sandborn *et al*., 2013). The plant also used as antipyretic agents for the treatment of common diseases like fever, cold, cough, diarrhea, and inflammatory disease (Chang and But, 1987).

Environmental stresses are adverse or non-ideal conditions for plant that causes changes in morphology, physiology and metabolism of the plant (Kumar, 2020). The effects of stress can lead to reduction in growth, yields, permanent damage and if the environmental stress is more than tolerance limits lead to death (Kumar and Aery, 2011, 2012; Verma *et al*., 2013). Adverse environmental conditions may reduce the performance and yield from 50 to 70% of the crop. Under the stress conditions, decreased length and biomass production of plants are the primary responses. At the cellular levels plants faces oxidative stress and generates ROS. The ROS are toxic to plants and are neutralised by antioxidative system. Antioxidative system includes both enzymatic and nonenzymatic antioxidants which play important role in scavenging of excess ROS (Noctor and foyer, 1998). Enzymatic antioxidant include superoxide dismutase (SOD), Peroxidase (POD), catalase (CAT), gluthatione reductase (GR) and Ascorbate peroxidase (APX) (Arora *et al*., 2002), whereas nonenzymatic antioxidant include tocopherol, ascorbate, carotenoids and phenolics. In plants maintaining antioxidant capacity to remove excess ROS, is associated to enhance tolerance to environment stress (Zaefyzadeh *et al*., 2009). Abiotic stress induced effects and responses of *A. paniculata* is shown in Fig. 3

Plant SMs are synthesized from primary metabolites (e.g., carbohydrates, lipids, and amino acids) by diverse physiological changes in the plant's life cycle. These are unique sources for medicine, flavors, fragrances and industrially useful biochemicals and act as multifunctional metabolites that help the plant to interact with its environment for adaptation and defense against herbivores, pathogens, and stress (Jan *et al*., 2021; Hartmann, 2007). The levels of SMs in plants are also influenced by several abiotic stresses such as nutrient deficiencies, metal ions, wounding, UV radiation, light, salinity, drought, seasonality, and temperature (Gouvea *et al*., 2012; Verma and Shukla, 2015). SMs are classified the basis of chemical structure. The main group of SMs present in plants is alkaloids (nitrogen-containing compounds-caffeine, vinblastine), phenolics, terpenes (alkaloids, cyanogenic glycosides, and glucosinolates), phenolic compounds (tannins, xanthones, flavonoids, iso-flavonoid, and coumarines), terpenes (mono, sesqui, di, tetra and poly terpenes) and saponins (Fang *et al*., 2011; Hussein and El-Anssary, 2019). Here, we review the recent progress in understanding on the production of secondary metabolites and mechanisms of ent-labdane diterpenoids synthesis in *A. paniculata* under abiotic stress.

ABIOTIC STRESS AND PLANT DEFENSE SYSTEM

Abiotic stresses occur mainly by fluctuations in non-biological factors such as environmental and nutritional factors that adversely impact plant growth, physiology, reproduction, and overall life cycle for a short and mild period (Gull *et al*., 2019). Abnormalities in water status (drought and waterlogging), nutrient levels, moisture in wind, temperature (cold, frost, and heat), salinity, and mineral toxicity are some of the types of abiotic stresses in the environment and show impact on growth, development, yield and seed quality of crop and other plants (Mittler, 2006; Gull *et al*. 2019). At the cellular level, due to reduction in turgor pressure the growth of plant decrease as most stress-sensitive process. In higher plants under drought stress, due to disruption of water movement from xylem to the surrounding cells of treachery element, cell elongation is reduced (Nonami, 1998). Under adverse environment, cellular activities such as cell division, cell elongation and expansion are not occurred properly, as per demand of plant that, results in reduction in germination of seeds, height, biomass production, leaf area, and poor establishment of crops and causes reduced yield and quality (Kaya *et al*., 2006; Hussain *et al*., 2008). Heavy metal contamination of agricultural lands limits crop productivity and is also dangerous to human health (Kumar and Aery, 2016). Biochemical and physiological functions are reduced in the plant at stress by changing the functionality of gene/protein at the molecular level (Djanaguiraman *et al*., 2018; Takahashi and Shinozaki, 2019).

Due to various environment stresses such as metal toxicity, high temperature, pollutant, UV-radiation, salinity and pathogen infection lead to oxidative stress in plants, and affect many biological processes (Xie *et al*., 2019). Oxidative stress is a complex physiological phenomenon of overproduction and storage of ROS, which causes dysfunction and damage of cell components. In plant, oxygen produce by photolysis of water during photosynthesis is disturbed by unbalance metabolism under stress and results in production of ROS (Asada, 1999). Superoxide radicle (O_2^{-}), singlet oxygen ($^1O_2$), hydrogen peroxide (H_2O_2) and hydroxyl radical ($OH^{\cdot}$**)** are oxygenated and possess at least one unpaired electron, that makes them highly reactive and induce oxidative stress through oxidation of cell components when they are found in excess in the cells and go beyond the cellular defence systems (Demidchik, 2014). Major target for ROS in plant cell are protein and lipid (Xie *et al*., 2019). Antioxidative systems act to decrease the oxidation of proteins, lipids, DNA, and other biomolecules by blocking the oxidation reaction and antioxidants directly scavenge free radicles and prevent damage (Huang *et al*., 2005). Plant defences system sense environmental changes and take action by generating suitable cellular mechanism, after receiving the signal, transferred to the nucleus where transcription machinery activate and respond to stress (Gull *et al*., 2019), by the antioxidative system and metabolic product i.e., Secondary metabolites (SMs).

The SMs significantly improve plant survival under different environmental stresses like drought, salinity, metal stress and therefore act as important metabolites in these adverse conditions (Agostini-Costa *et al*., 2012; Verma and Shukla, 2015; Kurepin *et al*., 2017; Zandalinas *et al*., 2018). Many elicitors such as abiotic or biotic stress enhance the production of SMs and make plants stronger (Jan *et al*., 2021). The mevalonic acid pathway and methyl erythritol phosphate pathway are the main pathway for terpenoid synthesis whereas shikimic acid pathway is the main pathway for phenolic compound under normal as well as stress conditions (Jamwal *et al*., 2018). Plant of different as well as same species differ in endogenous levels of various SMs (Barton, 2007). Several cellular and biochemical factors have an important role in the storage and transportation of SMs.

Generally, SMs are present in plants in normal conditions but the accumulation of SMs increases by various abiotic stress signals or elicitors molecules in response (Akula and Ravishankar, 2011). Salinity in soil and water causes dehydration, and excess removal of water from the cytoplasm that causes cytosolic and vacuolar volumes reduced, resulting in the accumulation of specific secondary metabolites, which adapt to plant in adverse condition (Mahajan and Tuteja, 2005). The production of SMs is also related to heat/temperature, low-temperature decrease, and higher temperature increase SMs production in plants in responses to stress (Morison and Lawlor, 1999; Verma and Shukla, 2015). Unavailability of water and more transpiration rate cause decline in turgidity of cells thereby negatively influencing various physiological processes and altering SMs productions (Lisar *et al*., 2012; Verma and Shukla, 2015).

ANTIOXIDATIVE SYSTEM OF *A. PANICULATA* UNDER ABIOTIC STRESS

Environmental stress is increasing by anthropogenic as well as natural activity. Under these conditions, plants develop several strategies to defend these conditions. Some studies have been conducted on antioxidative system activity of *A. paniculata* that minimize stress.

According to Antony and Nagella (2021) in phosphomolybdate assay, maximum antioxidative activity was observed in 100 mM Co dose treated *A. paniculata* whereas those plants treated with Sn dose also exhibit an increase in antioxidative activity. The highest metal chelating activity was reported in 50 mM Cu treated plant with 57.15% over than 56.55% in control. In DPPH assay antioxidant activity was decline in Cu treatment and raise in Sn treated *A. paniculata*. Arsenate application enhanced the levels of anti-oxidative enzymes like superoxide dismutase (SOD), glutathione reductase (GR) and lipid peroxidase (LP) along with proline content in *A. paniculata.* Both enzymatic and non-enzymatic oxidative stresses were significantly higher in wild plants as compared to cultured plants (Das *et al*., 2021).

Under high light intensity (0.24x103-0.96x103 ìmole.photons.m^{-2}sec^{-1}) peroxidase (POD) activity increased in leaves of *A. paniculata* in all three stages (vegetative, flowering, fruiting). Maximum POD activity was reported in the fruiting stage followed by flowering than the vegetative stage. The irradiance at higher light intensity increased the POD activity by 70% (Kumar *et al.*, 2009).

Under the saline condition, *A. paniculata* accumulates maximum superoxide in 41.10 mM salt-treated leaf (Ismali *et al*., 2015). In *A. paniculata* salinity-induced enhancement of antioxidative enzymes SOD, CAT, POD, cytochrome oxidase (CYT) and polyphenol oxidase (PPO) in roots and leaves was occur with rising salinity (Shao *et al*., 2015). An increase in the catalase (CAT) and ascorbate peroxidase (APX) enzyme activity was observed with increasing NaCl concentration (Kumar *et al*., 2021).

The antioxidative response of antioxidative system of *A. paniculata* to plant growth hormones has also observed. The content of ascorbic acid in *A. paniculata* in PGRs, abscisic acid (ABA), and gibberellic acid (GA_3) treatment. The activity of CAT, APX, and SOD enhance with ABA and GA_3 treated root, stem, and leaves of *A. paniculata*. In ABA and GA_3 treated *A. paniculata,* SOD and CAT activity increases (Anuradha *et al.*, 2010).

Antioxidant enzymes functions in sequentially manner- first of all, SOD catalyses the conversion of superoxide radicles to H_2O_2, by electron transport, further CAT, POD, and APX act upon H_2O_2 and convert it into H_2O. GR acts as an important enzyme, it maintains reduced/oxidized glutathione inside the cell (Yaghoubian *et al*., 2014) (Fig. 4).

Table 1: Effect of different abiotic stress on the biosynthesis of secondary metabolites in *A. paniculata*.

S. No.	**Abiotic stress**	**Secondary Metabolites**	**Response**	**References**
1	Heavy metals (Copper, Tin)	Andrographolide	Increased	Antony and Nagella (2021)
2	$CuSO_4$	Andrographolide	Four fold overproduction	Dawande and Sahay (2020)
3	$AgNO_3$	Andrographolide	Seven-fold overproduction of andrographolide	Das and Bandyopadhyay (2020)
4	As	Andrographolide, neoandrographolide, didehydroandrographolide	Increased	Das *et al*. (2020)
5	Sodium Azide	Andrographolide, andrographonin	Increased	Chandran and Pillai (2018)
6	High Sulphur plus low /high nitrogen	Andrographolide, dehydroanddrographolide	Increased	Jian *et al.* (2021)
7	Salinity	Andrographolide, neoandrographolide	Increased	Kumar *et al.* (2021)
8	Salinity	Andrographolide, deoxyandrographolide and dehydroandrographolide	All increased	Shao *et al*. (2015)
9	Salinity	Andrographolide, neoandrographolide	Tolerant plants accumulate higher amounts than sensitive plants	Talei *et al.* (2013); Talei *et al*. (2015)
10	Salinity	Andrographolide	Increased	Gandi *et al*. (2012)
11	Drought	Andrographolide, 14-deoxy-11,12 didehydroandrographolide	Increased	Chen *et al*. (2020)
12	Drought	Andrographolide	Increased in leaves but decreased in stems	Saravanan *et al.* (2009)
13	Light	Flavonoid	Increased	Kumar *et al*. (2012)
14	Shading and fertiliser	Andrographolide	Increased	Purwanto *et al*. (2011)
15	Salicylic acid and chitosan	Andrographolide	18.5 and 59.5 fold overproduction in SA and chitosan treatment	Vakil and Mendhulkar (2013)
16	Methyl jasmonate (MeJA)	Andrographolide	5.25 fold overproduction	Sharma *et al*. (2014)
17	Jasmonic acid and salicyclic acid	Andrographolide	3.3 and 3.4 fold overproduction in JA and SA	Zaheer and Giri (2015)
18	Aspartic acid and methyl jasmonate	Andrographolide	Three-fold overproduction	Das and Bandyopadhyay (2020)
19	Methyl-jasmonate	Andrographolide	Increased	Sharma *et al*. (2015)

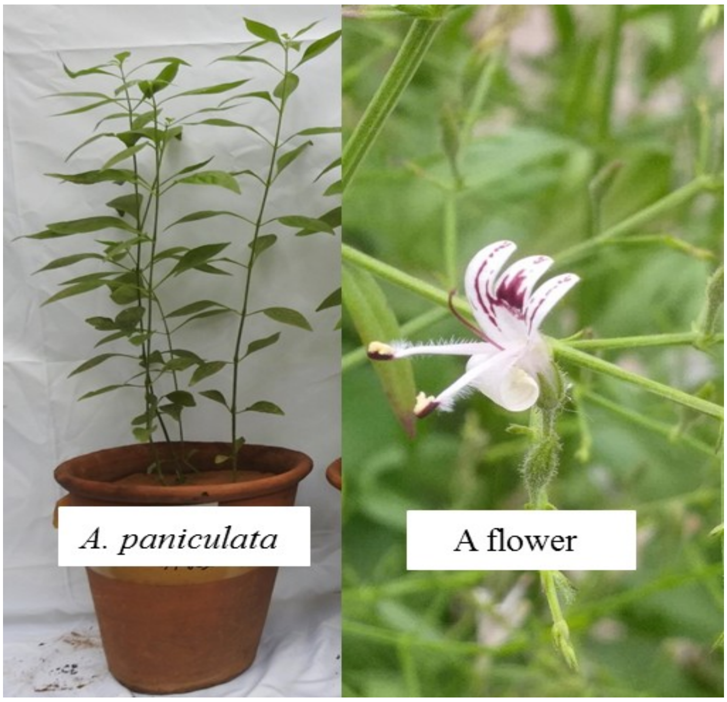
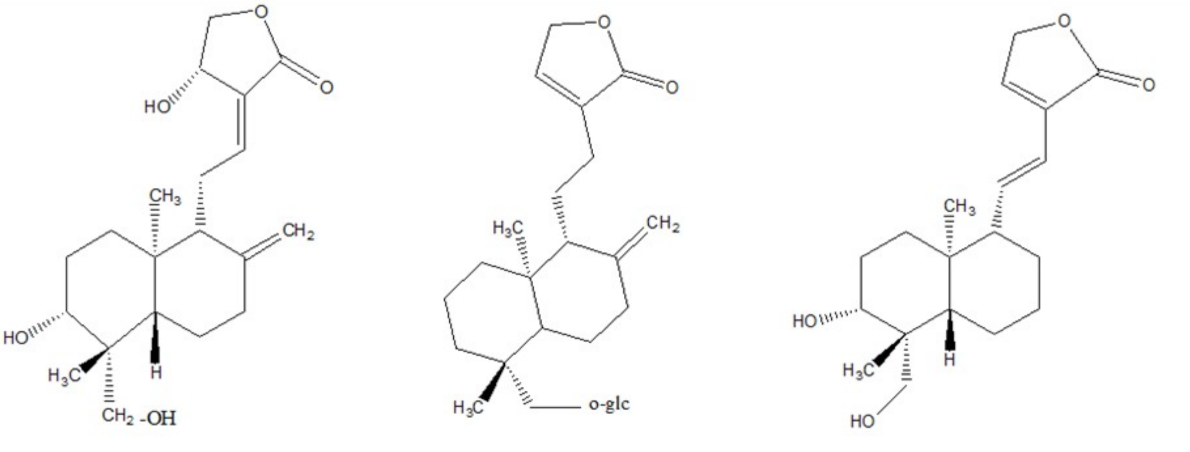


Figure 1 Showing habit of *A. paniculata* growing in pot and enlarged single flower.



Andrographolide ($C_{20}H_{30}O_5$) **Neoandrographolide ($C_{26}H_{40}O_8$)** **14- deoxy,11,12 didehydro andrographolide ($C_{20}H_{28}O_4$)**

Figure 2 Showing the chemical structure of important biochemical components of *A. paniculata*.

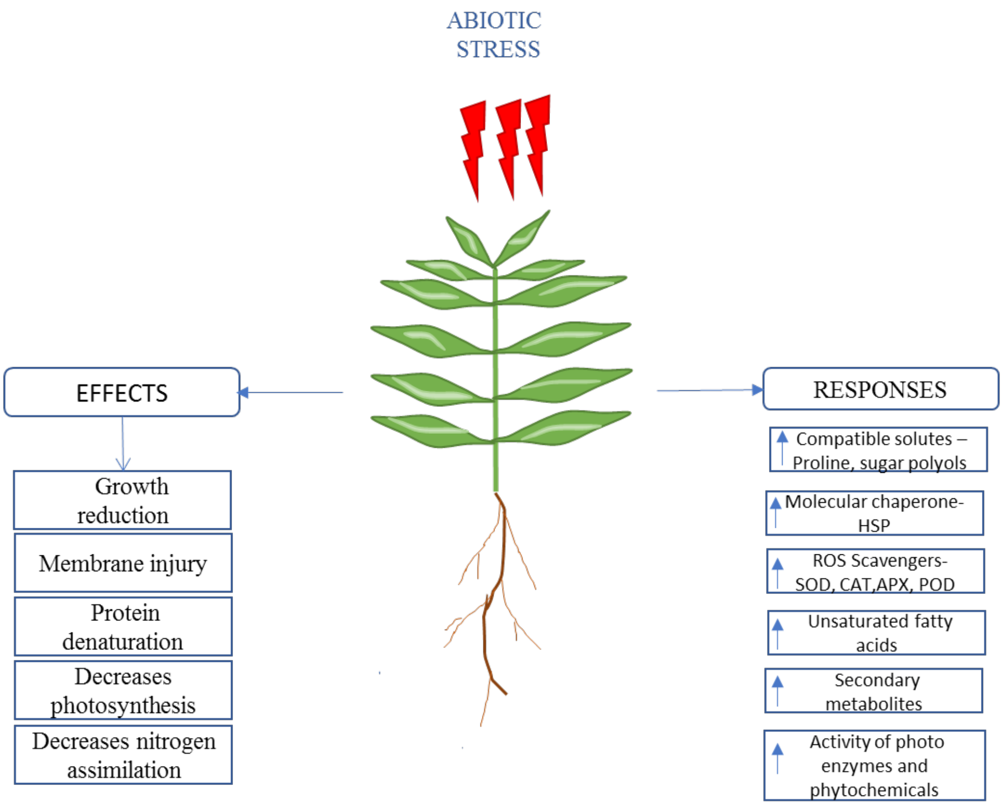


Figure 3 Showing abiotic stress induced effects and responses of *A. paniculata*.

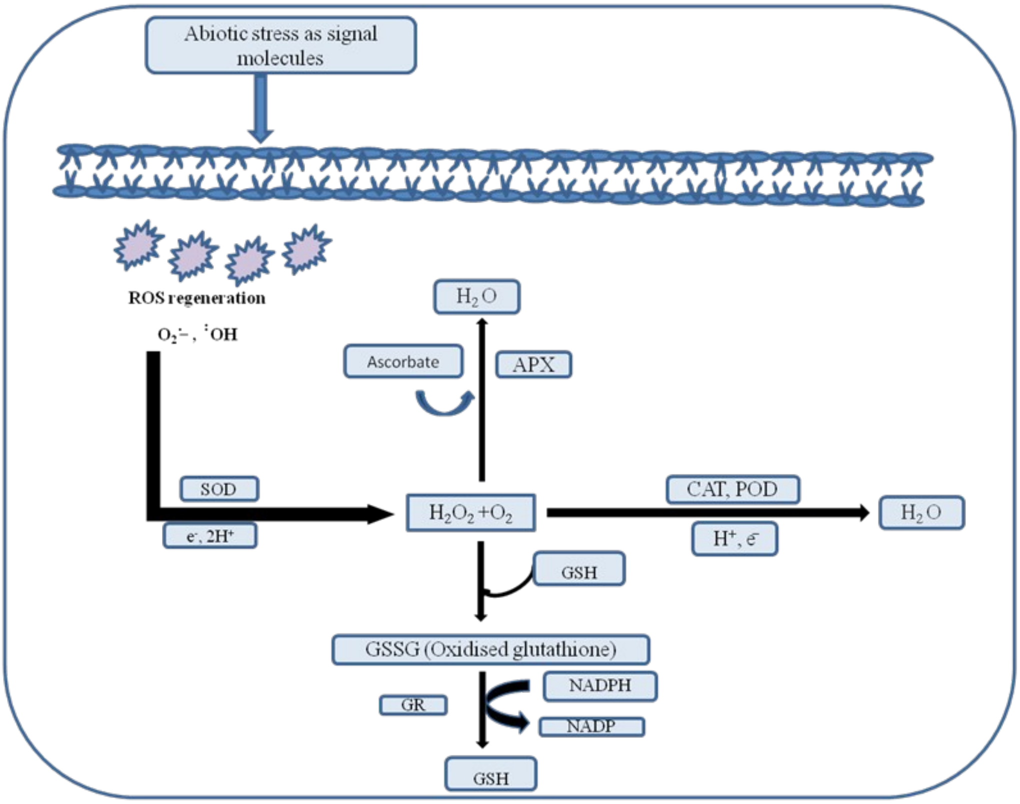


Figure 4 Showing mechanism of ROS scavenging by different antioxidant enzymes produced under abiotic stress.

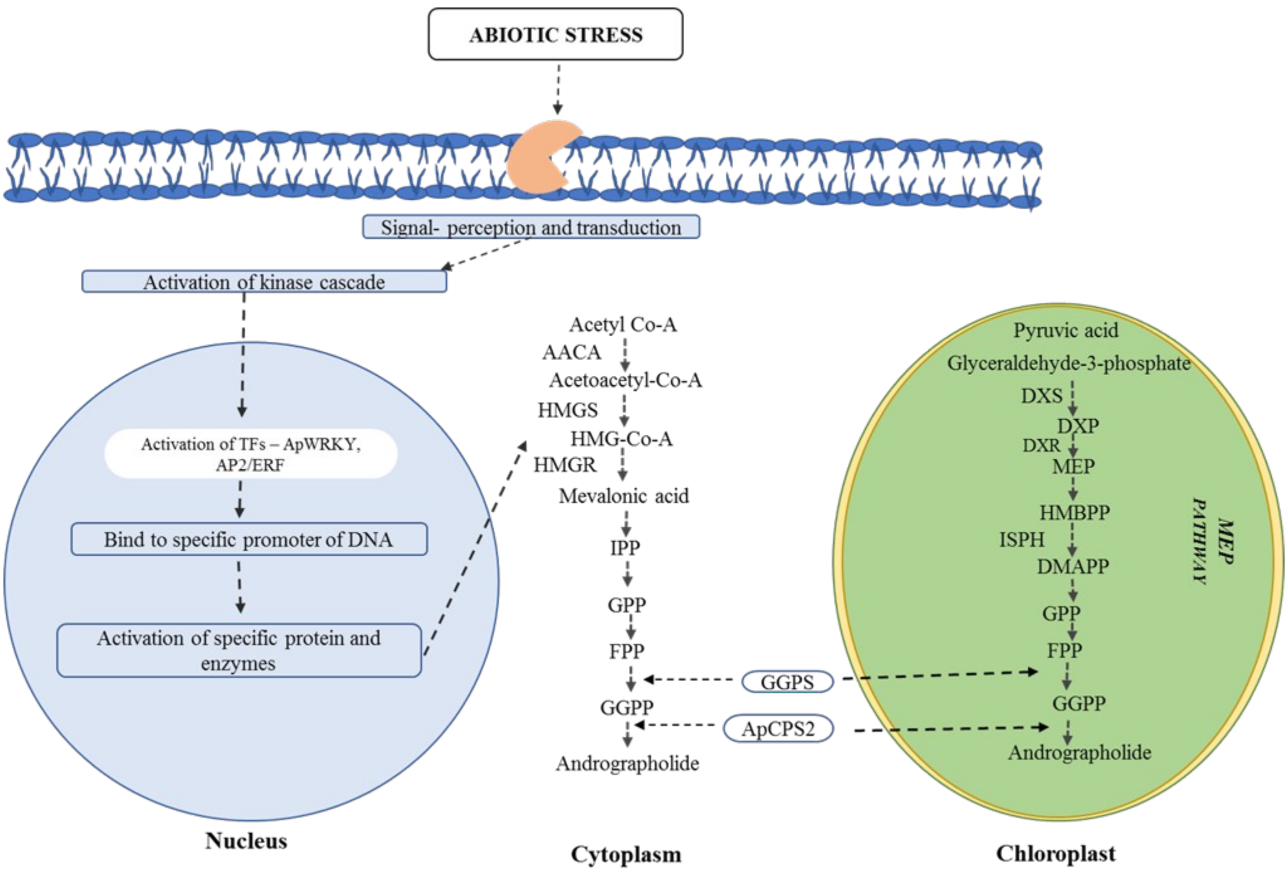


Figure 5 Mechanism of SMs production in response to abiotic stress in *A. paniculata*.

ABIOTIC STRESS AS AN ELICITOR OF SECONDARY METABOLITES

Abiotic stresses are diverse types of adverse conditions that plants face in their life cycle. Several studies have been undertaken to use these stresses as elicitors of SMs production. Heavy metals have a positive role in the AG content in *A. paniculata*. The improved level of AG was observed in 50 mM Cu and Sn (Antony and Nagella, 2021). Among different salts of metal, 5 mM Cd has strong effect on AG production and is produced about five times compared to control. The order of AG biosynthesis in different salts was found to be $CdCl_2$ > $CuCl_2$ > $AgNO_3$ > $HgCl_2$ (Gandi *et al*., 2012). In a study conducted by Dawande and Sahay (2020), fourfold elevation in the AG content was reported after treatment with Cu at 100 to 500 μM concentrations. In *A. paniculata,* AG production was seven-fold increase in tissues when treated with Ag and three-fold overproduction of AG occur in seedlings treated with L-aspartic acid and methyl jasmonate (Das and Bandyopadhyay, 2020). Main terpenes NeoAG, DDAG, AG, and flavonoid 5,7,2,3-tetra-methoxy-flavanone enhanced in leaves of *A. paniculata* treated with As (Das *et al*., 2021). Treatment of 0.01% sodium azide resulted in maximum amount of andrographonin (0.004%) and andrographolide (0.06%) (Chandran and Pillai, 2018). The concentration of total diterpene lactones (AG and dehydroandrographolide) was significantly increased with high sulphur at both high and low nitrogen levels. A higher quantitative concentration of total diterpene lactones was reported in leaves of *A. paniculata* (Jian *et al*., 2021).

In *A. paniculata* highest AG content (17,600 μg g^{-1}) was observed in the 100 mM salt dose whereas maximum NeoAG content (12,600 μg g^{-1}) was observed in 50 mM salinity treated plants (Kumar *et al*., 2021). The sodium chloride (12 dS m^{-1}) led to a significant increase in AG quantity up to 11.18%. AG content in *A. paniculata* varied from 1.48% to 2.55% (Talei *et al*., 2015). An enhancement in the quantity of anti-cancerous phytochemicals AG, NeoAG, and DDAG was reported in *A. paniculata* under salinity of 12 dSm^{-1}. The tolerant accessions accumulate higher amount of AG and NeoAG than the sensitive accessions (Talei *et al*., 2013). In *A. paniculata* AG, deoxy-AG and dehydro-AG were increased significantly with moderate salt concentration 143.7 mM salt. The maximum rise in the quantities of AG, dehydroandrographolide and total lactone were reported at 143.7 mM were 31.5, 39.8, and 30.8% respectively. The quantity of deoxy-AG was maximum (60.7%) at 92.4 mM salinity than other salt concentrations. At 193.4 mM NaCl, there were no significant changes reported in bicycle terpenes (Shao *et al.,* 2015).

AG content in leaves of *A. paniculata* increased (2.85-3.30%) under water-stressed plants (Saravanan *et al.* 2009). The effect of drought stress on *A. paniculata* is dependent on the quantity and time of water. AG content was significantly affected by prolonged treatment of drought. Severe and moderate drought-induced increase of AG, DDAG in *A. paniculata* has been reported by Chen *et al*. (2020).

Zaheer and Giri (2015) reported that the treatment of jasmonic acid (JA) and salicylic acid (SA) has enhancive effect on andrographolide content in *A. paniculata*. JA at 25 µM increases highest (3.3 fold) andrographolide than 1.0 µM (2.6 fold) and 50 µM (3.0 fold). SA at 10, 20, and 50 µM concentrations resulted in 3.0, 3.4, and 3.1 fold AG content, respectively (Zaheer and Giri, 2015). Among the various concentrations 2.5, 5.0, 10.0 µM of Methyl-jasmonate (MeJA) applied to *A. paniculata*, the accumulation of andrographolide was 1.86, 5.25, 2.1 fold higher after 24 hours of treatment. These observations reveal the stimulatory role of MeJA on the biosynthesis of andrographolide (Sharma *et al.*, 2015). In *A. paniculata* SA (0.05 mM) and chitosan influenced elicitation of andrographolide content when expose for different duration has been observed. In SA and chitosan treatment for 24 and 48 hours increases the andrographolide content 18.5 fold (37.0 $\mu g\ g^{-1}$) and 59.5 fold (119.0 $\mu g\ g^{-1}$), respectively (Vakil and Mendhulkar, 2013).

The maximum percentage 2.43% of the andrographolide was recorded in the leaves of sunlight-grown plants during the vegetative stage. It was also reported that the plants grown under sunlight conditions showed the highest concentration of the alkaloid compared to that of shade conditions (Kumar *et al.*, 2012). According to Purwanto *et al*. (2012) AG content increased under 50% shading level and straw compost fertilizer application.

In addition to stress, some PGRs are also studied as elicitor of secondary metabolite production. ABA and GA_3 enhances AG content in *A. paniculata* tissues 30.20 $mg\ g^{-1}$ and 29.35 $mg\ g^{-1}$, respectively (Anuradha *et al.*, 2010). According to Gudhate *et al.* (2009) all the plant growth regulator treatments (GA_3, IAA, NAA, and BAP) resulted in increased andrographolide content. Among the all PGRs, IAA 50 $mg\ l^{-1}$ had a pronounced effect on the andrographolide content followed by NAA. GA3 and BAP showed slight increase in andrographolide content in *A. paniculata* (Gudhate *et al*., 2009).

MECHANISM OF ENT-LABDANE DITERPENOIDS ELICITATION UNDER STRESS

Transcription factors (TFs), play important role in the regulation of plant secondary metabolism by regulating the expression of genes that encode biosynthetic enzymes at the transcriptional level (Hao *et al*., 2020; Deng *et al*., 2020). Genes liable for SMs synthesis in different plant species under stress are regulated by transcription factors such as WRKY, MYB, AP2/ERF, bZIP, and bHLH (Jan *et al*., 2021). Among these TFs, WRKY and AP2/ERF have broadly participated in stress responses via regulation of plant SMs (Phukan *et al*., 2016; Wasternack and Song, 2017; Jan *et al*., 2021). The mechanism of TFs and subsequent gene expression response under abiotic stress is given in Fig. 4. In *A. paniculata* most WRKY genes are upregulated and WRKY transcripts induce in stem and root while depress in the leaves under stress (Wang *et al*., 2021). According to Yao *et al*. (2020) AP2/ERF genes are expressed along with CPS2, which encodes key enzymes liable for the synthesis of active compounds AG of *A. paniculata*.

Plant SMs synthesized by the mevalonic acid pathway (MVAP) and methyl-ethritol-phosphate (MEP) pathway, occurs in the cytosol and plastid respectively, are used for the synthesis of central precursors of isoprenoids, isopentenyl diphosphate (IPP), and dimethylallyl diphosphate (DMAPP) (Lange *et al*., 2001, Rodríguez-Concepción and Boronat, 2002) (Fig. 4).

The synthesis of AG correlates with the expression of regulatory genes such as HMGS, HMGR, DXS, DXR, GGPS and ISPH in association with MVAP and MEP pathways (Sharma *et al*. 2015). In *A. paniculata*, ent-copalyl-diphosphate synthase (ApCPS2) involve in ent-labdane-diterpens (ent-LRDs) synthesis process, it catalysed conversion of GGPP to ent-Copalyl-diphosphate(ent-CPP) (Misra *et al*., 2015; Garg *et al*., 2015; Das *et al*., 2021). These gene expression levels are influenced by abiotic stress or elicitors and enhance SMs (ent-labdane-diterpens) elicitation directly or indirectly. Therefore, high transcript-level expression of these genes significantly coordinates to the elicitation of AG and other ent-LRDs under elicitors or abiotic stress (Ho *et al*., 2020).

CONCLUSION AND FUTURE PROSPECTIVE

Abiotic stress is a major worldwide problem and is continuously increasing by anthropogenic activities. *A. paniculata* is a medicinal plant and has extensive possibilities of various compounds of medicinal purpose. The morphology, biochemistry, and physiology of *A. paniculata* alter under abiotic stress. Under environmental stress, the growth of *A. paniculata* reduces but high amount of secondary metabolites are produced. These metabolites play a significant role as a reservoir of key phytochemicals protecting plants against multiple environmental constraints. However, several reports are indicating the increased biosynthesis of SMs in *A. paniculata* under stress but the exact mechanism is yet to be studied. Using various combinations of stress can synthesize novel terpenoids and flavonoids of importance in medical science. Further, the effect of combined abiotic stresses on the growth performance and efficiency of SMs synthesis is not studied.

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CONFLICTS OF INTEREST

The authors declare that they have no potential conflicts of interest.

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