

October 2022

MEDICINAL PLANTS' STRESS FACTORS: EFFECTS ON METABOLITES AND NOVEL PERSPECTIVES FOR TOLERANCE

Mayssaloune ALI kanso

Student, Pharmaceutical Sciences Department, Faculty of Pharmacy, Beirut Arab University, Beirut, Lebanon, mayssalounekanso@yahoo.com

mohamad ali hijazi

Assistant Professor of Pharmacognosy and Medicinal Plants, Pharmaceutical Sciences Department, Faculty of Pharmacy, Beirut Arab University, Beirut, Lebanon, m.hijazi@bau.edu.lb

Maha Aboul Ela Prof.

Professor of Pharmacognosy, Dean of Academic Development and Quality, Faculty of Pharmacy, Beirut Arab University, Beirut, Lebanon, mahaaboulela@bau.edu.lb

Abdalla El-Lakany

Professor of Pharmacy, Head of Pharmacy Practice and Pharmacology & Therapeutics Department, Dean of Faculty of Pharmacy, Beirut Arab University, Beirut, Lebanon, abdalla@bau.edu.lb

Follow this and additional works at: <https://digitalcommons.bau.edu.lb/hwbjournal>



Part of the [Architecture Commons](#), [Business Commons](#), [Life Sciences Commons](#), and the [Medicine and Health Sciences Commons](#)

Recommended Citation

kanso, Mayssaloune ALI; hijazi, mohamad ali; Aboul Ela, Maha Prof.; and El-Lakany, Abdalla (2022) "MEDICINAL PLANTS' STRESS FACTORS: EFFECTS ON METABOLITES AND NOVEL PERSPECTIVES FOR TOLERANCE," *BAU Journal - Health and Wellbeing*: Vol. 5: Iss. 1, Article 6.

DOI: <https://www.doi.org/10.54729/XWWG9154>

Available at: <https://digitalcommons.bau.edu.lb/hwbjournal/vol5/iss1/6>

This Article is brought to you for free and open access by Digital Commons @ BAU. It has been accepted for inclusion in BAU Journal - Health and Wellbeing by an authorized editor of Digital Commons @ BAU. For more information, please contact ibtihal@bau.edu.lb.

MEDICINAL PLANTS' STRESS FACTORS: EFFECTS ON METABOLITES AND NOVEL PERSPECTIVES FOR TOLERANCE

Abstract

Medicinal plants are rich in secondary metabolites representing different chemical classes and synthesized by various biochemical pathways. However, these compounds are susceptible to potential herbal predators and to environmental influences. Several factors induce different biotic and abiotic stresses (drought, cold, salinity, heat) that lead to fluctuations in the biogenesis and accumulation of secondary metabolites by which plants react to overcome the threatening stress conditions. This contribution aims to give an overview of the various medicinal plant defense mechanisms against imminent threats and their impact on secondary metabolites profiles in the most effective medicinal plant species such as the levels of vincristine in *Catharanthus roseus* which is affected by salinity and drought stress, sage (*Salvia officinalis*) that showed fluctuations in terpenes level under drought stress and mineral contents in the soil and *Papaver somniferum* that exhibited a decrease in alkaloids content under cold stress. From a wider perspective, the aim of this study is to present novel tools and strategies used for the preservation of some plant species from extinction by minimizing as much as possible the risk of exogenous influences on phytochemicals levels and on plant bio genome and manipulating the stress factors to ensure plants quality and safety. It also aims to raise awareness about the consumption of herbal medicines without respecting the herbal monographs information about the safe dose, the interactions with drugs, and the side effects, in addition to the necessity of performing toxicity studies by pharmaceutical industries, especially on herbal medicines raised under various stress factors because of the risk of SMs (secondary metabolites) accumulation in these plants at a critical level that may be toxic to consumers.

Keywords

plant metabolites, stress factors, biotic and abiotic stresses, defense mechanisms.

1. INTRODUCTION

Several damaging external factors trigger plants to interact by elaborating alternative defense strategies among which the accumulation of a wide variety of chemical metabolites as tools to fight stress conditions. These secondary metabolites allow the plants to adapt to the changes in the environment such as biotic and abiotic stresses (Ncube et al., 2012) by accumulating in plants organs through regulation and biochemistry mechanisms. More specifically, each plant species has a specific set of mechanisms for regulation of synthesis of SMs (Pavarini et al., 2012). Based on their biosynthetic pathways, there are three major groups of SMs terpenes, (isoprenoids), nitrogen-containing compounds (alkaloids, glucosinolates, and cyanogenic glycosides), and phenolic compounds (flavonoids and phenylpropanoids). In addition to the variations in endogenous levels of secondary metabolites, the abiotic signals cause alterations in ion homeostasis, regulation in protein activity, and gene expression. Genes' regulation at transcription levels is the major control point in the biological systems and this process is mediated by transcription factors and regulators such as cytokinin, jasmonic acid, and salicylic acid. Phytohormones play a crucial role in plant development and growth since they determine the plants' response to stress induced by exogenous factors (Ashraf et al., 2018). Moreover, SMs are singular to each plant populations, their profile and content are also affected by some conditions as season, tissue age, temperature, and time of day. The best example of this effect is *Virola surinamensis* that accommodates to the seasonal cycle in the Amazon forest by the shift in accumulation of terpenes so total monoterpenes content is lower at night during wet winter time (Pavarini et al., 2012). *Medicago sativa* shows the accumulation of saponins mainly medicagenic acid in the older leaves and in summer season (Szakiel et al., 2011). SMs levels undergo fluctuation in plants under biotic and abiotic stresses, while some wounded plant species exhibit accumulation of SMs, others show a decrease in their levels.

Biotic stresses are caused by the attack of living organisms such as fungi, viruses, and nematodes. Since the plants cannot change positions to avoid such stresses, they exhibit tolerance to pathogens by producing Phytoalexins, a SM with antimicrobial properties. Fungal strains of *Lupinus angustifolius* cause significant variation in the levels of endogenous phenolics in plants (Ashraf et al., 2018). Azadirachtin-A is a highly oxidized tetranortriterpenoid, that is synthesized at higher levels in hairy roots of *Azadiracta indica* infected with *Agrobacterium rhizogenes*, a pathogenic soil bacterium (Satdive et al., 2007). Volatile compounds are one of the most studied classes of SMs induced by herbivory attack, these compounds are synthesized by tritrophic ecological interaction, gossypol is an example of a bioactive product that accumulates in the leaves of wounded *Gossypium* spp (Opitz et al., 2008).

The production of SMs after biotic stress is explained by the development of an innate immune system upon the pathogen attack to the plants and it is mediated by basal immunity in which the infected cells recognize the pathogen through the pattern recognition receptors in the host cells and effector-triggered immunity via which the host cells identify the pathogens in response to damages or effectors caused by the toxins of pathogens. The signals perceived from these effectors trigger the metabolic pathways to produce secondary metabolites that decrease in concentration after plant recovery (Ashraf et al., 2018).

Plants are also exposed to another type of stress, the abiotic stress related to the physical factors affecting the plant's habitat, such as availability of water, soil type and composition, chemical fertilizers, temperature stress, light intensity, and salinity during ontogenic phases. These components should be in the quantities needed by plants so in excessive or deficient amounts they trigger fluctuation in the biosynthesis of SMs (Verma & Shukla, 2015). Several studies were done about this type of stress and showed that UV affects the bioactivity and biosynthesis of phenolics in some plant species such as Umbeliferaceae family (Apiaceae), in which coumarins accumulate in the plant tissue due to UV light in a non-toxic form (Pavarini et al., 2012). Nevertheless, umbeliferones, metabolites of coumarin-type from *Ruta graveolensis* (Rutaceae) are biosynthesized by a UV-inducible gene, so UV enhances umbeliferones levels in the leaves of this plant (Vialart et al., 2012). Resveratrol is a stilbene derivative in *Vitis vinifera*, that accumulates in response to UV radiation exposure (Quiroga et al., 2012). Sunlight favors the accumulation of coumarins in *Mikania glomerata* and a shorter light period decreases the coumarins level in stems and leaves of this plant (Ashraf et al., 2018). Temperature stress is a factor that influences plant growth so it is needed in apposite ranges and high or low temperature

may lead to negative consequences on plant productivity (Yadav, 2010). *Panax quinquefolius* under high temperature reacts to the stress by increasing the production of ginsenosides (Jochum et al., 2007). *Capsicum annuum* plant under low temperature shows inhibition in photosynthesis, and suppression in plant yield and growth (Koç et al., 2010).

Chemical stress is another triggering abiotic stress factor induced by different chemicals such as pesticides, growth regulators, minerals, and trace metals. For example CuSO_4 , ZnSO_4 , and FeSO_4 and it changes the endogenous levels of proteins, phenols, and chlorophyll (Ashraf et al., 2018). Similarly, the flavonoids content in *St. John's wort* is altered by the application of nitrogen and phosphorous fertilizers (Azizi & Dias, 2004). Furthermore facing varying levels of nitrogen, plants undergo changes in gene expression that results in metabolic, physiological, and developmental alterations (Vidal & Gutiérrez, 2008). Phosphorous is also a component that alters the biosynthesis of SMs and is crucial for plant development and growth. Application of phosphorous does not affect only the quality and quantity of essential oils in *Salvia officinalis* but it also causes a significant increase in the rosmarinic acid levels and total phenolics (Nell et al., 2009).

Another abiotic stress factor is salinity, high levels of salt in the growth medium cause osmotic stress making the plants fighting drought, and unable to take water despite water availability. So high levels of salt in soil lead to a decline in growth, in the uptake of nutrients in plants and in photosynthesis (Ashraf et al., 2018). An example is that of *Achillea fragrantissima*, *Solanum nigrum*, and *C. roseus* in which salinity stress caused an increase in the alkaloid's levels and of endogenous phenolic content in *A. fragrantissima* (Verma & Shukla, 2015). In another study, *Mentha pulegium* and *Nigella sativa* under the salinity stress showed a significant increase in phenols (Ashraf et al., 2018; Oueslati et al., 2010).

Furthermore, drought stress is also a factor affecting plant growth and SMs content, unavailability of sufficient amounts of water causes suppression in photosynthesis and affects the productivity of important cereals and some plant species such as *Hypericum perforatum*, *Artemisia annua* and *C. roseus* under drought stress showed rise in photosynthetic pigments and phenolics (Azhar et al., 2011). Water stress is also a factor causing physiological adaptations, it can induce osmotic shift and biosynthesis of purine alkaloids (Pavarini et al., 2012). Some studies showed that irradiation is one of the triggering stress factors, *Ocimum basilicum* under irradiation showed a greater accumulation of RA (rosmarinic acid) in upper leaves than in lower leaves and a continuous white light exposure lead to a high RA content (Shiga et al., 2009). Moreover, heavy metal stress is due to some heavy metals in the environment such as redox metals (Cu, Cr, and Mn) and non-redox active metals (Ni, Zn, and Al) that have the capacity at toxic levels to damage the plants and cause excessive augmentation in ROS (reactive oxygen species). Facing this stress, the plants develop defense strategies to tolerate heavy metals intoxication by the biosynthesis of chelators as spermine, nicotianamine, flavonoids, phenolic compounds that act as scavengers of free radicals (Emamverdian et al., 2015). According to several reports heavy metal stresses cause an increase of secondary metabolites levels in medicinal plants. However, because of the ability of these plants to accumulate heavy metals in their edible parts, therefore, before consumption they should abide by the maximum allowable limits of heavy metals according to the strict regulations implemented by WHO (2005) (Asgari Lajayer et al., 2017).

So, plant responses to stress factors are very complex with specific characteristics for various species, and metabolomic, proteomic approaches become very powerful tools in the study of plants' reaction to any stimuli (Gani et al., 2021). Moreover, the biosynthetic pathways of SMs involved in plants adaptation are specific for example, phenyl acylated flavonols (saiginols) play an essential role in protecting the plant against UV-B irradiation mainly in northern regions, and the synthesis pathway of glucosinolates a tryptophan-derived indole is involved in the protection of Brassicaceae species from microbes (Hiruma, 2019).

This article aims to review the key factors affecting the accumulation and biosynthesis of secondary metabolites in plants. In addition to highlighting the most promising medicinal plant species and their defense strategies in response to specific exogenous influences. Our purpose is to protect these important species from extinction by encouraging the rational development of novel tools to obtain stress tolerant crops.

2. METHODS

The article was built by collecting data over the past twenty years, from reliable sources such as PubMed, google scholar and gathering information published on abiotic and biotic factors and their impact on the accumulation of SMs. The results are summarized in table 1 that reports the levels of secondary metabolites in response to the various abiotic factors and in table 2 that summarizes the strategies adopted through genetic engineering for enhancing abiotic stress tolerance in plants.

3. RESULTS

Table 1: Stress factors effects on the SMs levels of some plant species

Plant/family	Effect on SMs	Response mechanism	Plant part	Ref
Low temperature /cold stress				
<i>Artemisia spp.</i> Asteraceae	Higher levels of artemisin	Induction of the following transcription factors: C-repeat binding factor expression-1, C-repeat binding factors, myeloblasts and mitogen-activated protein kinase	Whole plant	(Wallaart et al., 2000; Yadav, 2010)
<i>Nicotiana tabacum</i> Solanaceae	Higher levels of anthocyanins		Juvenile leaves	(Huang et al., 2012)
<i>Camellia sinensis</i> L/ Theaceae	Change in polyphenols metabolism		Leaves	(Upadhyaya, 2012)
<i>Papaver somniferum</i> Papaveraceae	Decrease in alkaloids content		Flowers and seeds	(Yang et al., 2018)
<i>Camellia japonica</i> Theaceae	Increase in fatty acids α -linolenic acid, Jasmonic acid		Leaf	(Y. Li et al., 2020)
<i>Vitis vinifera</i> L./Vitaceae	Decrease in the concentration of phenolics		Roots and leaves	(Ashraf et al., 2018)
<i>Capsicum annum</i> Solanaceae	Significant increase in the endogenous levels of phenolic compound, proline, and total soluble proteins, whereas chlorophyll contents decreased		Seeds	(Koç et al., 2010)
<i>Zingiber officinale</i> /Zingiberaceae	Metabolic decomposition and decrease in zingiberene Gingerols, geranial, geranyl acetate content	Rhizomes	(Zehra et al., 2019)	
High temperature				
<i>Quercus rubra</i> /Fagaceae	Increase terpenes content	Induction of HsfA1b and HsfA2 expression, the response of ROS and the network of hormones	Leaves	(Yang et al., 2018)
<i>Daucus carota</i> Apiaceae	Decrease α -terpinolene content and increase in β -caryophyllene and α -farnesene content		Roots	(Yang et al., 2018)
<i>Astragalus compactus</i> /Fabaceae	Increase in phenolics		Roots, leaf and flowers	(Y. Li et al., 2020)
<i>Chrysanthemum</i> Asteraceae	Decrease in Anthocyanins		Whole plant	(Y. Li et al., 2020; Qu et al., 2013)
Long light exposure				
<i>Panax quinquefolius</i> /Araliaceae	Higher levels of ginsenosides	Induction of jasmonate-response genes	Roots	(Fournier et al., 2003)
<i>Ipomoea batatas</i> Convolvulaceae	Increase in the content of flavonoids and phenolic acids	Activation of Flavonoid biosynthesis pathway	Leaves	(Yang et al., 2018)
Continuous solar radiation				

Plant/family	Effect on SMs	Response mechanism	Plant part	Ref
<i>Vaccinium myrtillus</i> / Ericaceae	Increase in flavonoids content	Activation of Flavonoid biosynthesis pathway	Leaves	(Jaakola et al., 2004; Pavarini et al., 2012)
Exposure to red light				
<i>Ocimum basilicum</i> / Lamiaceae	Rosmarinic acid accumulation	-	Seeds	(Pavarini et al., 2012; Shiga et al., 2009)
Exposure to UV				
<i>Catharanthus roseus</i> / Apocynaceae	Enhanced production of catharanthine	Induction of transcription of genes encoding tryptophan decarboxylase (Tdc) and strictosidine synthase (Str).	Cell culture	(Ramani & Chelliah, 2007; Shiga et al., 2009)
High Altitude				
<i>Leontodon autumnalis</i> / Asteraceae	Shifting flavonoids contents	Induction of low temperature and cold stress mechanism	Flowering heads and leaves	(Pavarini et al., 2012)
<i>Matricaria chamomilla</i> / Asteraceae	Higher flavonoids and phenolic acids contents		Flowering heads	(Ganzera et al., 2008)
Drought stress				
<i>Quercus ilex</i> /Fagaceae	Lower monoterpene emissions	-Alteration of the activity of key-enzymes within the specific biosynthesis pathway of the accumulating SMs - Alteration of the availability of basic substrates entering this pathway -Changes in the expression of many genes contributing in the synthesis pathway of accumulating SMs	Leaves	(Lavoir et al., 2009; Pavarini et al., 2012)
<i>Achillea filipendulina</i> / Asteraceae	Increase in total phenolic and flavonoid contents under both moderate and severe drought stress		Leaves	(Ashraf et al., 2018)
<i>Soybean</i> /Fabaceae	Increase in total phenolics and lignin		Seeds	(Bellaloui, 2012)
<i>Camellia sinensis</i> / Theaceae	Higher content of Epicatechins			(Selmar & Kleinwächter, 2013)
<i>Mentha × piperita ssp</i> / Lamiaceae	Significant increase in essential oils		Leaves	(Selmar & Kleinwächter, 2013; Zehra et al., 2019)
<i>Salvia officinalis</i> /Lamiaceae	Strong increase in monoterpenes		Aerial parts	(Selmar & Kleinwächter, 2013)
<i>Bupleurum chinense</i> /Apiaceae	Strong increase in Saikosaponin		Roots	(Selmar & Kleinwächter, 2013)
<i>Hypericum brasiliense</i> / Hypericaceae	Increase in total phenolics		Shoots and roots	(Y. Li et al., 2020)
High conditions of Cu and Mn nutrition				
<i>Eugenia uniflora</i> /Myrtaceae	Lower both tannins and flavonoids contents	Cu and Mn in particular, are cofactors of enzymes involved in phenol degradation and lignin biosynthesis.	Leaves	(Santos et al., 2011)
Salinity stress				
<i>Lepidium sativum</i> / Brassicaceae	Increase under moderate salinity levels of flavonols, flavonoids, and phenolic	Induction of specific enzymes involved in the biosynthesis of accumulating SMs	-	(Ashraf et al., 2018)
<i>Rosmarinus officinalis</i> /Lamiaceae	Increase in the phenolics content		-	(Ashraf et al., 2018)
<i>Salvia mirzayanii</i> /Lamiaceae	Increase in the phenolic contents and volatile components		Aerial parts	(Valifard et al., 2014)
<i>Catharanthus roseus</i> /Apocynaceae	Increase in vincristine content		Leaves and roots	(Misra & Gupta, 2006)

Plant/family	Effect on SMs	Response mechanism	Plant part	Ref
<i>Rauvolfia tetraphylla</i> / Apocynaceae	Increase in the endogenous levels of reserpine		-	(Ashraf et al., 2018)
<i>Plantago ovata</i> / Plantaginaceae	Increase in tannins, saponins, flavonoids alkaloids content		Root and shoot	(Y. Li et al., 2020)
Heavy metal stress				
<i>Artemisia annua</i> / Asteraceae	Enhanced artemisinin production in As treated plants	upregulation of the transcripts of the genes 3-hydroxy-3-methylglutaryl coenzyme A reductase, amorpha-4,11-diene synthase, cytochrome P450 mono oxygenase and farnesyl diphosphate involved in artemisinin biosynthesis	Leaves	(Asgari Lajayer et al., 2017; Zehra et al., 2019)
<i>Hypericum perforatum</i> / Hypericaceae.	Enhanced production of total hypericin in Cr treated plants	Upregulation of anthranoid metabolism pathway	Fruits	(Asgari Lajayer et al., 2017)
<i>Matricaria chamomilla</i> / Asteraceae	Accumulation of chlorogenic acid, an important antioxidant molecule, was increased by Ni treatment	Enhancement of enzymes responsible for biosynthesis of accumulating SMs	Leaves	(Asgari Lajayer et al., 2017; Zehra et al., 2019)
<i>Withania somnifera</i> L./ Solanaceae	Total phenolic contents increased with increasing concentration of Cu		Roots	(Asgari Lajayer et al., 2017; Zehra et al., 2019)
<i>Ocimum basilicum</i> L/ Lamiaceae	Increased production of methyl chavicol and decreased content of linalool		Roots, stems leaves	(Asgari Lajayer et al., 2017)
<i>Matricaria chamomilla</i> L./ Asteraceae	Increase in the production of phenolics mainly chlorogenic acid		Leaves	(Asgari Lajayer et al., 2017; Zehra et al., 2019)
<i>Vaccinium corymbosum</i> L/ Ericaceae	Increase in the production of phenolic compounds mainly chlorogenic acid		Plantlets	(Manquían-Cerda et al., 2016)
Synergistic stress factors				
High Temperature; UV-B light irradiation				
<i>Malus spp</i> / Rosaceae	Lower levels of anthocyanins	Reduction in the expression of the R2R3 MYB transcription factor (MYB10) responsible for coordinative regulation for red skin colour, as well as expression of other genes in the transcriptional activation complex.	Fruits	(Lin-Wang et al., 2011)
<i>Populus × canescens</i> / Salicaceae	Increase in terpene levels	Shifts on transcript levels of terpene biosynthesis-related genes	Tree	(Pavarini et al., 2012)
Higher altitudes and lower temperatures				
<i>Arnica montana</i> / Asteraceae	Increase in the ratio of B-ring ortho-diphenolic (quercetin) compared to B-ring monophenolic (kaempferol) flavonols	-	Flowering heads	(Albert et al., 2009)

Table 2: Genetic engineering strategies for better abiotic stress tolerance in plants

Strategies	Target	Phenotype	Reference
Engineering transcriptional regulators	Transcription factors	Abiotic stress tolerance with or without pleiotropic effects	(Cabello et al., 2014)
Manipulating single traits	Genes involved in ROS metabolism and osmoregulation chaperones	Abiotic stress tolerance	(Lisch & Bennetzen, 2011)
Challenging homeostasis hormones	Genes involved in hormone biosynthesis hormones catabolism and hormone signaling	Abiotic stress tolerance with or without pleiotropic effects	(Chamoli & Verma, 2014)
Post-transcriptional control	miRNAs	Drought tolerance	(Khraiwesh et al., 2012)
Epigenetic regulation	DNA methylation And histone modification	Salinity stress	(Cabello et al., 2014)

As shown in the previous table, SMs are distributed in different organs of the plants (fruits and seeds, roots and stems, flowers, leaves), their biosynthesis begins from the basic pathways such as shikimic acid or glycolysis pathways then diversifies according to the type of cells and development stage. Therefore, different tissues in the medicinal plants may produce different properties according to the development stage. Moreover, the accumulation of SMs in plants is altered by different environmental conditions as a response of the plants to such changes and trying to adapt since the expression of genes during SMs pathways are affected by these stresses (Y. Li et al., 2020). Many articles have discussed the mechanisms that lead to alteration in the levels of SMs. High levels of salt in soils induce hyperosmotic stress, decline in photosynthesis, and in the uptake of nutrients (Banerjee & Roychoudhury, 2017). So, this stress factor may cause a decrease or increase in the SMs concentrations and it induces alterations in molecular responses, as well as changes in the plant metabolome, proteome, transcriptome and some transcription factors such as bZIP, NAC, MYB, AP2, ERF, and WRKY which have higher correlations with salinity (Kumar et al., 2017). Therefore, the introgression of salt-tolerant genes in medical plants helps to maintain the SMs yield to get the best beneficial effects and the best stress acclimatization.

Light is essential for photosynthesis in plants and affects the accumulation and quality of SMs so in some instances, the high irradiance is associated with better plant growth and higher SMs yield for example in *Erigeron breviscapus* the amount of scutellarin was showed to be higher in leaves growing under sun than in those under shade (Zhou et al., 2016). But some articles reported the opposite situation in *Flourensia cernua*, the levels of sabinene, camphene, borneol were in higher levels in the plants cultivated under partial shade than those fully irradiated (Estell et al., 2016). Therefore, light intensity has different impacts on the SMs accumulation in plants and this can be beneficial in improving the yield in medicinal plants, since different species of plants have their own light sets in quality and quantity that should be managed to elicit maximal SMs yields (Zhou et al., 2016). UV light regulates the transcriptional level and expression of the genes regulating SMs, for example exposure to low dose UV-B in *Artemisia annua* induces high artemisinin accumulation due to upregulation of ADS, CYP71AV1, IPPi, FPS, HMGR, ED1, and DXR gene transcripts and transcription levels of cytochrome P450 monooxygenase and amorpha4,11-diene synthase (ADS) genes (Y. Li et al., 2020). In most cases, the UV light exposure has positive impact on SMs production but in case of high doses of UV-C and UV-B plant growth and photosynthesis are negatively affected (Katerova et al., 2017).

The temperature in high or low levels directly affects plant growth but the SMs levels decrease or increase in response to high-temperature stress. Low temperature induces cold acclimation phenomenon that helps the plants to survive and adapt with low-temperature stress, it involves different molecular and physiochemical processes (metabolic reactions, cellular dehydration, and water uptake) (Ashraf et al., 2018). High temperature causes alterations in biochemical processes through changes in gene expression which lead to heat tolerance by

adaptation of plants to the high temperature (Hasanuzzaman et al., 2017). The proteins involved in heat stress response are divided into two groups, the first one includes functional genes and the second one the signaling components such as transcription factors and protein kinases. Therefore, because of temperature stress, many changes occur at the transcriptional level and this explains the fact of reduction in the total content of anthocyanins in *Vitis vinifera* under high temperature and in other plants as *Petunia* hybrid and *Citrus sinensis*, but it is the low temperature that induced anthocyanins accumulation in leaves and stems of *Arabidopsis thaliana* (Yang et al., 2018). Thus, because of global warming causing billions of losses in crops and because heat stress induces oxidative and osmotic secondary stresses, the regulation of transcription genes is essential for plants adaptation and to benefit from the maximum yield of plants SMs especially in medicinal plants (Qu et al., 2013).

Drought is one of the stress factors that affects SMs content in plants, mainly flavonoids, and phenolics whose level is related to the balance between sinks and carbohydrate sources. Many reports have shown that the accumulation of carbohydrates in plants is related to the low transport of soluble sugars because of water stress (Jaafar et al., 2012). In addition to the expression of several genes participating in the synthetic pathways of phenolics as phenylalanine ammonia-lyase (PAL) that are increased in low drought conditions but in severe conditions these processes are limited. In addition to the expression of some key enzymes 4-coumarate-coA ligase (4CL), phenylalanine ammonia-lyase (PAL), cinnamate-4-hydroxylase (C4H), and chalcone synthase (CHS) during baicalin biosynthesis pathway in *Scutellaria baicalensis* under water stress (Y. Li et al., 2020).

Heavy metal toxicity such as Cd also is a factor that increases oxidative damage, reduces water and nutrients uptake, and disrupts plant metabolism. Plant adaptation to Cd exposure is related to stress-signaling molecules such as salicylic acid, nitric oxide, and jasmonic acid. The mechanisms of dealing with this stress factor involve the hyperaccumulation that consists in uptake and distribution of Cd and some plants increase the antioxidant potential against ROS to protect the cells from the destruction caused by Cd, in addition to the formation of metallothioneins (MTs) or phytochelatins (PCs) at the intercellular level for the removal of heavy metal ions and sequestration of ligand-metal compounds from vacuoles (Haider et al., 2021). So, the use of exogenous materials is crucial to protect plants against heavy metal toxicity such as the use of biochar to soil contaminated with Cd to prevent its accumulation and toxicity of the plants. Moreover, the application of N (nitrogen) in high doses can solve the problem by soil acidification, thus enhancing the bioavailability and solubility of toxic metal as Cd in the soil. In addition to the use of bioremediation, phytoremediation, plant growth regulators, organic manure and compost, and the use of chemical methods as barium acetate to coagulate Cd. Furthermore, the application of nitric oxide and salicylic acid have protective effects against heavy metals impact (Haider et al., 2021). In addition to the use of compounds as proline that has metal detoxification potential, and the technique of symbiotic association with AM (arbuscular mycorrhizal fungi) that works by binding metal ions to the cell wall and thus immobilizing heavy metals (Haider et al., 2021).

In summary, light stress factor affects plant species belonging to the families Araliaceae, Pinaceae, Rutaceae, Brassicaceae, Asteraceae, Rosaceae, Rhamnaceae, Lamiaceae, Ericaceae, and Apocynaceae. This factor has shown impact on levels of the following SMs luteolin, apigenin, flavonoids, phenolic acids, phytosterols, flavonol glycosides, hydroxycinnamic acids, tannins, terpenoids, alkaloids, artemisinin, glycoalkaloids. On the other hand, moisture affects mostly *Pteridium arachnoideum*, *Artemisia annua*, *Pachypodium saundersii*, *Achnatherum inebrians* with an impact on the concentrations of the following SMs phenolic compounds, lipophilic resins, artemisinin, tannins, isoprene, anthocyanins, alkaloids. Besides the effect of temperature stress on plants belonging to some families as Asteraceae, Araliaceae, Theaceae, Papaveraceae, Solanaceae, Apiaceae, Fabaceae, Fagaceae by affecting the phenolic compounds, isoprene anthocyanins, alkaloids, flavonoids, tannins levels. Soil nutrients affect mainly *Ceratonia siliqua*, *Lithospermum erythrorhizon*, *Rhodiola sachalinensis*, *Betula* spp., *Eucalyptus cladocalyx*, *Aradopsis thaliana*, by causing alteration in the content of the shikonin, cyanogenic glycosides, phenolic compounds, condensed tannins, Salidroside, gallotannins in these species. Moreover, ozone affects mainly, the tannins, phenolic acids, phenolic compounds levels inside the following plants *Petroselinum crispum*, *Pinus taeda*, *Ginkgo biloba*, and *Betula pendula* (Ncube et al., 2012). Therefore, special care should be done with the medicinal plants belonging

to the families mentioned above especially that some of them were proven beneficial in protection from COVID- 19 virus such as *Artemisia annua*, *Camellia sinensis*, *Bupleurum Chinensis*, *Withania somnifera*, and *Vitis vinifera* (Cheng et al., 2006; Fuzimoto & Isidoro, 2020; Tripathi et al., 2020), to protect them from stress factors and improve their defense mechanisms and preserve them from extinction being rich in bioactive compounds that are used in the novel drugs discovery. Therefore, there is a crucial need for developing tools and strategies serving the above goals.

4. DISCUSSION

Besides the beneficial effects of accumulation of SMs as a defense of the plants under stress, at critical levels, SMs could cause cytotoxicity to the consumer and to the plant itself. For that, cellular strategies like storage in specific sites such as vacuoles to tackle the cytotoxic SMs are noticed and under stress conditions, studies showed the transfer of metabolites inside the plants. For example, in *Nicotiana* species, the nicotine is synthesized in the roots under herbivory attack, and is transported to the aerial part in the plant to function as insect neurotoxin to defend the plant. Moreover, studies have demonstrated that trafficking of SMs such as phytohormones, from one organ to another is achieved by transporters that function as enzymes acting specifically on a particular compound or chemical ligand (Gani et al., 2021). Thus, knowledge about the transporters responsible for the transport of SMs inside the plants is essential to establish biotechnological interventions to produce high-value molecules from medicinal plants. The major transport mechanisms are multidrug and toxic compound extrusion (MATE) and ATP (adenosine triphosphate) binding cassette (ABC). An example is the knockdown of CrTPT2 (a unique catharanthine transporter) that led to the increase of catharanthine level in the internal leaves and the decrease of this metabolite at the leaf surface. Another case is that of co-expression of crocin (a type of carotenoid) transporter and carotenoid cleavage dioxygenase (CsCCD2) that led to enhanced crocin level in *N. benthamiana* (Gani et al., 2021).

The previously discussed mechanisms of plant adaptation to stress factors demonstrated that the major control points are related at transcription levels to the regulation of genes. Because of the crucial need to get the maximum SMs yield from medicinal plants, different tools are available to support the adaptation of the plants exposed to stress like phytoremediation that adopts different strategies such as growth regulators. Many studies showed the importance of plant hormones such as ethylene, jasmonic acid (JA), salicylic acid (SA), abscisic acid (ABA), gibberellic acid (GA), auxins, nitric oxide, strigolactones, brassinosteroids, polyamines, and cytokinin. These hormones play a crucial role in plant development by determining plant responses to various abiotic and biotic stresses. So, plants to which plant hormones are administered for a longer period showed wider alterations in gene expression (Ashraf et al., 2018). For example, GAs diterpenoid plant hormones, when used are involved in diverse developmental events as seed germination, stem elongation, and pollen maturation so they are determinants of plant defense response and permit the plant growth despite the environmental stresses (Olszewski et al., 2002). Brassinosteroids are also plant hormones that inhibit lipids degradation resulting from reactive oxygen species overproduction when plants are under stress conditions, they also promote the synthesis of phytochelatins responsible for metal detoxification and higher the antioxidants activity. Therefore, the application of brassinosteroids in phytoremediation is desired because they are capable of modifying some agronomic traits in plants (Rajewska et al., 2016). Phytoremediation involves different mechanisms as, rhizome-filtration, Phyto-extraction, Phyto-volatilization, and Phyto-stabilization. For the selection of the best phytoremediation strategy, many factors should be taken into consideration such as the root system, the degree of harm in the plant, the rate of growth in the presence of the pollutants, and the time needed to reach the remediation desired (Haider et al., 2021).

Recently, bioremediation is adopted, since phytohormones are also produced by root-associated microbes and proved as important targets in metabolic engineering for helping plants tolerance to stresses and improving the medicinal plant's yield. Several studies were done on different plant species exhibiting the biosynthesis of phytohormones by microbes in its roots such as *Sulla carnosa* under salt stress, which showed the release of IAA (indole-3acetic acid) phytohormone with the help of *Pseudomonas* sp., *Bacillus* s. Besides, the plant *Helianthus annuus*, under drought stress, showed the presence of salicylic acid from *Achromobacter xylosoxidans* and

Bacillus pumilus (Egamberdieva et al., 2017) . Furthermore, *Cicer arietinum* L., under Nutrient stress, exhibited the IAA release by *Serratia* sp. Another example is that of *Solanum lycopersicum* L., under Cd stress, that also showed IAA release by *Burkholderia* sp. Therefore, the exogenous application of microbes inducing phytohormones is one of the crucial strategies adopted to increase the plant's tolerance facing biotic and abiotic stresses providing its applications under extreme or changing environmental conditions (Egamberdieva et al., 2017) . Certain fungi species (i.e., *Trichoderma* spp and *Piriformospora indica*) are considered versatile because of their adaptation to soils contaminated with high concentration (Haider et al., 2021). Endophytic bacterium *Bacillus subtilis* (BERA 71) has shown helpful in the stimulation of chickpea plants growth and increasing the phenol content because this bacteria enhanced minerals contents in the plant and lowered sodium accumulation, moreover, it causes inhibition of lipid peroxidation and ROS generation and proline accumulation (Abd-Allah et al., 2018).

It is evident that manipulation of various parameters is essential to obtain the maximum SMs yield from medicinal plants especially that it is evident that resistance to pathogens in plants can be enhanced or attenuated by multiple stress factors (Bai et al., 2018). These parameters are specific to each plant species and for getting the best level of SMs, we must investigate the synergistic impacts of multiple stress factors affecting medicinal plants. An example of the synergism between various environmental factors is the case of sage (*Salvia officinalis*), when exposed to moderate drought stress it exhibits accumulation of total monoterpenes higher than in the well-watered plants. When these plants are cultivated under high CO₂ levels in parallel, the elevation in monoterpene synthesis related to drought stress is compensated (Selmar & Kleinwächter, 2013). Vincristine a very potential secondary metabolite that requires a high salt level for its accumulation in *C. roseus*, and little water since drought stress induces a rise in the levels of vincristine (Ashraf et al., 2018). Artemisinin concentration in *Artemisia annua* is increased by heavy metal stress, drought stress, and exposure to a low dose of UV-B (Asgari Lajayer et al., 2017; Azhar et al., 2011; Y. Li et al., 2020). Based on these considerations, and to increase the medicinal plants' quality, putative applications may be applied by manipulating several exogenous factors as described above (Selmar & Kleinwächter, 2013). Moreover, breeding strategies by modulation of multiple transcription factors are helpful in achieving robustness of medicinal plants under combined stress combinations (Bai et al., 2018). Furthermore, several other strategies are adopted such as silicon to regulate abiotic-induced oxidative stress in crop plants because silicon activates the defense systems in the plants (Kim et al., 2017). Also, a novel technique to restore the drought stress tolerance in rice, is adopted by using exogenous reagent OsADR3 that induces ROS-scavenging effect associated with ABA (abscisic acid) signaling pathway (J. Li et al., 2021).

Genetic engineering programs are developed to enhance tolerance to abiotic stress because of the limitations of all the strategies discussed previously such as the probability of obtaining undesired pleiotropic effects like developmental alterations or growth handicap, in addition to the fact that the expression up-regulation or direct-action genes activity are beneficial in individual stress conditions (Cabello et al., 2014) .

Finally, to preserve many plant crops from extinction and especially medicinal plants such as *Caesalpinaceae*, *Solanaceae*, *Apocynaceae*, *Liliaceae*, *Asteraceae*, *Ranunculaceae*, *Apiaceae*, *Sapotaceae*, *Rutaceae*, *Piperaceae* that have a great pharmacological potential being rich in bioactive compounds useful in the discovery of drugs and especially those with no alternatives such as the anti-cancer taxol yielding plants Pacific yew tree (*Taxus brevifolia*), manipulation of various stress factors threatening the plant should be done but great care should be given to the optimum levels of accumulated SMs that should not reach the toxic dose. Therefore, toxicity studies should be performed to ensure the safety of medicinal plants grown under different stressful conditions and consumers should be aware of the necessity to abide by the official information in the herbal monographs especially those related to the side effects, herb-drug interactions, adulterations, and the safe plant organs to be used.

5. CONCLUSION

In response to diverse biotic/abiotic stresses, plants develop defense mechanisms, in which many biological processes and molecules are induced such as ROS cascade. Then signals through specific mediators are transduced to the transcription factors (TFs) that regulate gene expression and SMs biosynthesis. Some secondary metabolites directly inhibit the plant infection and others

act as ROS scavengers by maintaining redox balance and confer stress tolerance to plants. The data collected showed various responses either increase or decrease in the SMs levels and sometimes shift of these metabolites from one organ to the other. Thus, the optimum accumulation of SMs will make the balance between the defense and growth of plants because accumulation of SMs at critical levels may be cytotoxic to plants and to consumers, and the best approach to produce safe and high value medicinal plants, consists in engineering the suitable transporters of SMs. However, the concurrence of various types of stresses becomes more common. Therefore, it will be beneficial to understand the response networks inside plants under various stresses and to cultivate plant breeds that are stress-resistant under multiple exogenous factors. This article highlighted the complex relations between the plant's metabolic system and external factors in addition to offering an overview about the strategies adopted to improve plant stress tolerance and the use of novel regulatory targets helping in modulation plant stress responses, such as small RNAs, hormonal networks, post-transcriptional modifications. In this context, integration of approaches and tools based on synthetic biology into programs relying on genetic engineering will provide the capacity of getting the optimal yield of SMs from medicinal plants having significant pharmacological potential especially after the demand and need for the supply of safe medicinal plants of uniform quality attributes.

REFERENCES

- Abd-Allah, E. F., Alqarawi, A. A., Hashem, A., Radhakrishnan, R., Al-Huqail, A. A., Al-Otibi, F. O. N., Malik, J. A., Alharbi, R. I., & Egamberdieva, D. (2018). Endophytic bacterium *Bacillus subtilis* (BERA 71) improves salt tolerance in chickpea plants by regulating the plant defense mechanisms. *Journal of Plant Interactions*, 13(1), 37–44.
- Albert, A., Sareedenchai, V., Heller, W., Seidlitz, H. K., & Zidorn, C. (2009). Temperature is the key to altitudinal variation of phenolics in *Arnica montana* L. cv. ARBO. *Oecologia*, 160(1), 1–8.
- Asgari Lajayer, B., Ghorbanpour, M., & Nikabadi, S. (2017). Heavy metals in contaminated environment: Destiny of secondary metabolite biosynthesis, oxidative status and phytoextraction in medicinal plants. In *Ecotoxicology and Environmental Safety* (Vol. 145, pp. 377–390). Academic Press.
- Ashraf, M. A., Iqbal, M., Rasheed, R., Hussain, I., Riaz, M., & Arif, M. S. (2018). Environmental Stress and Secondary Metabolites in Plants: An Overview. In *Plant Metabolites and Regulation under Environmental Stress*. Elsevier Inc. <https://doi.org/10.1016/B978-0-12-812689-9.00008-X>
- Azhar, N., Hussain, B., Yasin Ashraf, M., & Yar Abbasi, K. (2011). Medicinal Plants: Conservation & Sustainable use) WATER STRESS MEDIATED CHANGES IN GROWTH, PHYSIOLOGY AND SECONDARY METABOLITES OF DESI AJWAIN (*TRACHYSPERMUM AMMI* L. In Special Issue (Vol. 43).
- Azizi, M., & Dias, A. (2004). Nitrogen and Phosphorus Fertilizers Affect Flavonoids Contents of St. John's Wort (*Hypericum perforatum* L.). *Proceedings of The Fourth International Iran & Russia Conference*, November 2014, 458–462.
- Bai, Y., Kissoudis, C., Yan, Z., Visser, R. G. F., & van der Linden, G. (2018). Plant behaviour under combined stress: tomato responses to combined salinity and pathogen stress. *Plant Journal*, 93(4), 781–793.
- Banerjee, A., & Roychoudhury, A. (2017). Effect of salinity stress on growth and physiology of medicinal plants. In *Medicinal Plants and Environmental Challenges* (pp. 177–188). Springer International Publishing.
- Bellaloui, N. (2012). Soybean Seed Phenol, Lignin, and Isoflavones and Sugars Composition Altered by Foliar Boron Application in Soybean under Water Stress. *Food and Nutrition Sciences*, 03(04), 579–590.
- Cabello, J. V., Lodeyro, A. F., & Zurbriggen, M. D. (2014). Novel perspectives for the engineering of abiotic stress tolerance in plants. *Current Opinion in Biotechnology*, 26, 62–70.
- Chamoli, S., & Verma, A. K. (2014). Targeting of Metabolic Pathways for Genetic Engineering to Combat Abiotic Stress Tolerance in Crop Plants.
- Cheng, P. W., Ng, L. T., Chiang, L. C., & Lin, C. C. (2006). Antiviral effects of saikosaponins on human coronavirus 229E in vitro. *Clinical and Experimental Pharmacology and Physiology*, 33(7), 612–616.

- Egamberdieva, D., Wirth, S. J., Alqarawi, A. A., Abd-Allah, E. F., & Hashem, A. (2017). Phytohormones and beneficial microbes: Essential components for plants to balance stress and fitness. *Frontiers in Microbiology*, 8(OCT), 1–14.
- Emamverdian, A., Ding, Y., Mokhberdorani, F., & Xie, Y. (2015). Heavy metal stress and some mechanisms of plant defense response. In *Scientific World Journal* (Vol. 2015). Hindawi Publishing Corporation.
- Estell, R. E., Fredrickson, E. L., & James, D. K. (2016). Effect of light intensity and wavelength on concentration of plant secondary metabolites in the leaves of *Flourensia cernua*. *Biochemical Systematics and Ecology*, 65, 108–114.
- Fournier, A. R., Proctor, J. T. A., Gauthier, L., Khanizadeh, S., Bélanger, A., Gosselin, A., & Dorais, M. (2003). Understory light and root ginsenosides in forest-grown *Panax quinquefolius*. *Phytochemistry*, 63(7), 777–782.
- Fuzimoto, A. D., & Isidoro, C. (2020). The antiviral and coronavirus-host protein pathways inhibiting properties of herbs and natural compounds - Additional weapons in the fight against the COVID-19 pandemic? *Journal of Traditional and Complementary Medicine*, 10(4), 405–419.
- Gani, U., Vishwakarma, R. A., & Misra, P. (2021). Membrane transporters: the key drivers of transport of secondary metabolites in plants. *Plant Cell Reports*, 40(1).
- Ganzera, M., Guggenberger, M., Stuppner, H., & Zidorn, C. (2008). Altitudinal variation of secondary metabolite profiles in flowering heads of *Matricaria chamomilla* cv. BONA. *Planta Medica*, 74(4), 453–457.
- Haider, F. U., Liqun, C., Coulter, J. A., Cheema, S. A., Wu, J., Zhang, R., Wenjun, M., & Farooq, M. (2021). Cadmium toxicity in plants: Impacts and remediation strategies. *Ecotoxicology and Environmental Safety*, 211, 111887.
- Hasanuzzaman, M., Nahar, K., Anee, T. I., & Fujita, M. (2017). Glutathione in plants: biosynthesis and physiological role in environmental stress tolerance. In *Physiology and Molecular Biology of Plants* (Vol. 23, Issue 2, pp. 249–268). Springer India.
- Hiruma, K. (2019). Roles of plant-derived secondary metabolites during interactions with pathogenic and beneficial microbes under conditions of environmental stress. In *Microorganisms* (Vol. 7, Issue 9, p. 362). MDPI AG.
- Huang, Z. A., Zhao, T., Fan, H. J., Wang, N., Zheng, S. S., & Ling, H. Q. (2012). The Upregulation of NtAN2 Expression at Low Temperature is Required for Anthocyanin Accumulation in Juvenile Leaves of Lc-transgenic Tobacco (*Nicotiana tabacum* L.). *Journal of Genetics and Genomics*, 39(3), 149–156.
- Jaafar, H. Z. E., Ibrahim, M. H., & Fakri, N. F. M. (2012). Impact of soil field water capacity on secondary metabolites, phenylalanine ammonia-lyase (PAL), malondialdehyde (MDA) and photosynthetic responses of Malaysian Kacip Fatimah (*Labisia pumila* Benth). *Molecules*, 17(6), 7305–7322.
- Jaakola, L., Määttä-Riihinen, K., Kärenlampi, S., & Hohtola, A. (2004). Activation of flavonoid biosynthesis by solar radiation in bilberry (*Vaccinium myrtillus* L.) leaves. *Planta*, 218(5), 721–728.
- Jochum, G. M., Mudge, K. W., & Thomas, R. B. (2007). Elevated temperatures increase leaf senescence and root secondary metabolite concentrations in the understory herb *Panax quinquefolius* (Araliaceae). *American Journal of Botany*, 94(5), 819–826.
- Katerova, Z., Todorova, D., & Sergiev, I. (2017). Plant secondary metabolites and some plant growth regulators elicited by UV irradiation, light and/or shade. In *Medicinal Plants and Environmental Challenges* (pp. 97–121). Springer International Publishing.
- Khraiwesh, B., Zhu, J. K., & Zhu, J. (2012). Role of miRNAs and siRNAs in biotic and abiotic stress responses of plants. *Biochimica et Biophysica Acta - Gene Regulatory Mechanisms*, 1819(2), 137–148.
- Kim, Y. H., Khan, A. L., Waqas, M., & Lee, I. J. (2017). Silicon regulates antioxidant activities of crop plants under abiotic-induced oxidative stress: A review. *Frontiers in Plant Science*, 8(April), 1–7.
- Koç, E., Dşlek, C., & Üstün, As. (2010). Effect of Cold on Protein, Proline, Phenolic Compounds and Chlorophyll Content of Two Pepper (*Capsicum annum* L.) Varieties. In *Journal of Science* (Vol. 23, Issue 1). www.gujs.org
- Kumar, J., Singh, S., Singh, M., Srivastava, P. K., Mishra, R. K., Singh, V. P., & Prasad, S. M. (2017). Transcriptional regulation of salinity stress in plants: A short review. *Plant Gene*, 11, 160–169.

- Lavoit, A.-V., Staudt, M., Schnitzler, J. P., Landais, D., Massol, F., Rocheteau, A., Rodriguez, R., Zimmer, I., & Rambal, S. (2009). Drought reduced monoterpene emissions from *Quercus ilex* trees: results from a throughfall displacement experiment within a forest ecosystem. *Biogeosciences Discussions*, 6(1), 863–893.
- Li, J., Zhang, M., Yang, L., Mao, X., Li, J., Li, L., Wang, J., Liu, H., Zheng, H., Li, Z., Zhao, H., Li, X., Lei, L., Sun, J., & Zou, D. (2021). OsADR3 increases drought stress tolerance by inducing antioxidant defense mechanisms and regulating OsGPX1 in rice (*Oryza sativa* L.). *Crop Journal*, xxxx.
- Li, Y., Kong, D., Fu, Y., Sussman, M. R., & Wu, H. (2020). The effect of developmental and environmental factors on secondary metabolites in medicinal plants. *Plant Physiology and Biochemistry*, 148(June 2019), 80–89.
- Lin-Wang, K., Micheletti, D., Palmer, J., Volz, R., Lozano, L., Espley, R., Hellens, R. P., Chagnè, D., Rowan, D. D., Troggio, M., Iglesias, I., & Allan, A. C. (2011). High temperature reduces apple fruit colour via modulation of the anthocyanin regulatory complex. *Plant, Cell and Environment*, 34(7), 1176–1190.
- Lisch, D., & Bennetzen, J. L. (2011). Transposable element origins of epigenetic gene regulation. *Current Opinion in Plant Biology*, 14(2), 156–161.
- Manquían-Cerda, K., Escudey, M., Zúñiga, G., Arancibia-Miranda, N., Molina, M., & Cruces, E. (2016). Effect of cadmium on phenolic compounds, antioxidant enzyme activity and oxidative stress in blueberry (*Vaccinium corymbosum* L.) plantlets grown in vitro. *Ecotoxicology and Environmental Safety*, 133, 316–326.
- Misra, N., & Gupta, A. K. (2006). Effect of salinity and different nitrogen sources on the activity of antioxidant enzymes and indole alkaloid content in *Catharanthus roseus* seedlings. *Journal of Plant Physiology*, 163(1), 11–18.
- Ncube, B., Finnie, J. F., & Van Staden, J. (2012). Quality from the field: The impact of environmental factors as quality determinants in medicinal plants. *South African Journal of Botany*, 82, 11–20.
- Nell, M., Vötsch, M., Vierheilig, H., Steinkellner, S., Zitterl-Eglseer, K., Franz, C., & Novak, J. (2009). Effect of phosphorus uptake on growth and secondary metabolites of garden sage (*Salvia officinalis* L.). *Journal of the Science of Food and Agriculture*, 89(6), 1090–1096.
- Olszewski, N., Sun, T. P., & Gubler, F. (2002). Gibberellin signaling: Biosynthesis, catabolism, and response pathways. *Plant Cell*, 14(SUPPL.), S61–S80.
- Opitz, S., Kunert, G., & Gershenzon, J. (2008). Increased terpenoid accumulation in cotton (*Gossypium hirsutum*) foliage is a general wound response. *Journal of Chemical Ecology*, 34(4), 508–522.
- Oueslati, S., Karray-Bourouai, N., Attia, H., Rabhi, M., Ksouri, R., & Lachaal, M. (2010). Physiological and antioxidant responses of *Mentha pulegium* (Pennyroyal) to salt stress. *Acta Physiologiae Plantarum*, 32(2), 289–296.
- Pavarini, D. P., Pavarini, S. P., Niehues, M., & Lopes, N. P. (2012). Exogenous influences on plant secondary metabolite levels. *Animal Feed Science and Technology*, 176(1–4), 5–16.
- Qu, A. L., Ding, Y. F., Jiang, Q., & Zhu, C. (2013). Molecular mechanisms of the plant heat stress response. *Biochemical and Biophysical Research Communications*, 432(2), 203–207.
- Quiroga, A. M., Deis, L., Cavagnaro, J. B., Bottini, R., & Silva, M. F. (2012). Water stress and abscisic acid exogenous supply produce differential enhancements in the concentration of selected phenolic compounds in Cabernet Sauvignon. *Journal of Berry Research*, 2(1), 33–44.
- Rajewska, I., Talarek, M., & Bajguz, A. (2016). Brassinosteroids and Response of Plants to Heavy Metals Action. *Frontiers in Plant Science*, 7(May), 1–5.
- Ramani, S., & Chelliah, J. (2007). UV-B-induced signaling events leading to enhanced-production of catharanthine in *Catharanthus roseus* cell suspension cultures. *BMC Plant Biology*, 7(1), 1–17.
- Santos, R. M., Fortes, G. A. C., Ferri, P. H., & Santos, S. C. (2011). Influence of foliar nutrients on phenol levels in leaves of *Eugenia uniflora*. *Revista Brasileira de Farmacognosia*, 21(4), 581–586.
- Satdive, R. K., Fulzele, D. P., & Eapen, S. (2007). Enhanced production of azadirachtin by hairy root cultures of *Azadirachta indica* A. Juss by elicitation and media optimization. *Journal of Biotechnology*, 128(2), 281–289.
- Selmar, D., & Kleinwächter, M. (2013). Influencing the product quality by deliberately applying drought stress during the cultivation of medicinal plants. *Industrial Crops and Products*, 42(1), 558–566.

- Shiga, T., Shoji, K., Shimada, H., Hashida, S. N., Goto, F., & Yoshihara, T. (2009). Effect of light quality on rosmarinic acid content and antioxidant activity of sweet basil, *Ocimum basilicum* L. *Plant Biotechnology*, 26(2), 255–259. <https://doi.org/10.5511/plantbiotechnology.26.255>
- Szakiel, A., Pączkowski, C., & Henry, M. (2011). Influence of environmental biotic factors on the content of saponins in plants. *Phytochemistry Reviews*, 10(4), 493–502.
- Tripathi, M. K., Singh, P., Sharma, S., Singh, T. P., Ethayathulla, A. S., & Kaur, P. (2020). Identification of bioactive molecule from *Withania somnifera* (Ashwagandha) as SARS-CoV-2 main protease inhibitor. *Journal of Biomolecular Structure and Dynamics*, 0(0), 1–14.
- Upadhyaya, H. (2012). Changes in Antioxidative Responses to Low Temperature in Tea [*Camellia sinensis* (L) O. Kuntze] Cultivars. *International Journal of Modern Botany*, 2012(4), 83–87.
- Valifard, M., Mohsenzadeh, S., Kholdebarin, B., & Rowshan, V. (2014). Effects of salt stress on volatile compounds, total phenolic content and antioxidant activities of *Salvia mirzayanii*. *South African Journal of Botany*, 93, 92–97.
- Verma, N., & Shukla, S. (2015). Impact of various factors responsible for fluctuation in plant secondary metabolites. *Journal of Applied Research on Medicinal and Aromatic Plants*, 2(4), 105–113. <https://doi.org/10.1016/j.jarmap.2015.09.002>
- Vialart, G., Hehn, A., Olry, A., Ito, K., Krieger, C., Larbat, R., Paris, C., Shimizu, B. I., Sugimoto, Y., Mizutani, M., & Bourgaud, F. (2012). A 2-oxoglutarate-dependent dioxygenase from *Ruta graveolens* L. Exhibits p-coumaroyl CoA 2-hydroxylase activity (C2H): A missing step in the synthesis of umbelliferone in plants. *Plant Journal*, 70(3), 460–470.
- Vidal, E. A., & Gutiérrez, R. A. (2008). A systems view of nitrogen nutrient and metabolite responses in *Arabidopsis*. In *Current Opinion in Plant Biology* (Vol. 11, Issue 5, pp. 521–529). Elsevier Current Trends.
- Wallaart, T. E., Pras, N., Beekman, A. C., & Quax, W. J. (2000). Seasonal variation of artemisinin and its biosynthetic precursors in plants of *Artemisia annua* of different geographical origin: Proof for the existence of chemotypes. *Planta Medica*, 66(1), 57–62.
- Yadav, S. K. (2010). Cold stress tolerance mechanisms in plants. A review. In *Agronomy for Sustainable Development* (Vol. 30, Issue 3, pp. 515–527). EDP Sciences.
- Yang, L., Wen, K. S., Ruan, X., Zhao, Y. X., Wei, F., & Wang, Q. (2018). Response of plant secondary metabolites to environmental factors. *Molecules*, 23(4), 1–26.
- Zehra, A., Choudhary, S., Naeem, M., Masroor Khan, M. A., Khan, A., Aftab, T., Tariq Aftab, C., & Masroor, M. A. (2019). A review of medicinal and aromatic plants and their secondary metabolites status under abiotic stress *Plant Micronutrients: Deficiency and Toxicity Management View project Research project View project A review of medicinal and aromatic plants and their secondary metabolites status under abiotic stress*. Article in *Journal of Medicinal Plants Studies*, 7(3), 99–106. <https://www.researchgate.net/publication/334710110>
- Zhou, R., Su, W. H., Zhang, G. F., Zhang, Y. N., & Guo, X. R. (2016). Relationship between flavonoids and photoprotection in shade-developed *Erigeron breviscapus* transferred to sunlight. *Photosynthetica*, 54(2), 201–209.