Role of Phenolic compounds in plant defense mechanism: An updated review

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Abstract

Being immovable, plants have to face all types of abiotic and biotic stress conditions. In response to various stress conditions, different plants accumulate different phenolic compounds. The phenolic compounds accumulated to counter various stresses depend on the type of stress conditions. In general, light stress induce the synthesis of phenolics and flavonoids; temperature extremes induce the accumulation of osmoprotectant compounds which eventually stimulate the synthesis of antioxidants such as flavonoids, tannins, and phenolics in plants. In nearly all types of stress conditions plants increase the production of reactive oxygen species (ROS) and also to counter this, the plant produces phenolic acids, polyphenols, flavonoids, anthocyanins, and other compounds with similar properties to counter ROS such as (H₂O₂). In case of biological stresses, the plants accumulate phenolics at the infection site to restrict microbes' growth. Sometimes, they also induce the synthesis and accumulation of Salicylic acid (SA) and H₂O₂ at the site of infection. It's important for plants as they develop systemic acquired resistance (SAR). The synthesis and accumulation of phenolic compounds were also recorded immediately after postinfection; indicating their crucial role in plant defense mechanisms against various types of stresses. The present review focuses on current updates on the role of phenolics and their physiological functions as a response to stress conditions and their probable applications in stress counter.

Key words : Abiotic and biotic stress, Phenolic compounds, Plant defense.

Every time, when plants are exposed to any abiotic or biotic stress conditions, these stresses negatively impacted the plant's

growth, development, and yield^{12,13}. During the course of evolutions, plants have developed a variety ofbiochemical or metabolic pathways

to respond to different abiotic and biotic stress conditions, especially through induced biosynthesis of secondary metabolites. These metabolic pathways are important and integral parts of plant growth, survival, development, reproduction, and defense.

During stress conditions, plants divert more energy toward the synthesis of secondary metabolites resulting accumulation of various secondary metabolites in plants^{23,35,132}. These secondary metabolites are essential toregulate the plant's defense mechanism and other developmental processes. Among various plant metabolites, phenolic compounds constitute a special class of natural secondary metabolites synthesized through various pathways likepentose phosphate, shikimate, and phenylpropanoid pathway^{16,29,51}. The plants use these pathways to produce either monomeric phenolic compounds (flavonoids, phenolic acids, and phenylpropanoids) or polymeric phenolic compounds (tannins, lignins, lignans, melanins, etc.). Phenolic compounds show high structural as well as functional diversity. In terms of their occurrence, some phenolic compounds are widely found frequently in many plant species while others are only observed in a fewplant species⁶⁷. Nearly all known phenolic compounds are reported to have a defensive function against abiotic and biotic stress conditions^{36,67}.

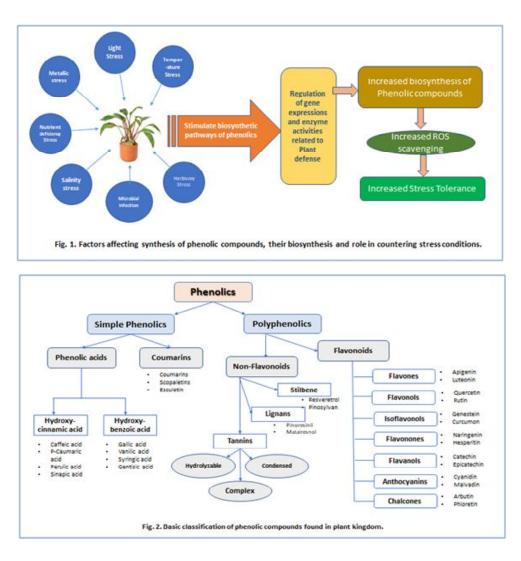
Most common abiotic stress includes extreme environmental conditions such as high or low light conditions and temperature, ultraviolet (UV) radiation, deficiency of nutrients, drought or flood-like conditions, etc. while the biotic stress includes infection by microbial pathogens, attack by herbivorous organisms, nematodes, larvae, etc.

The capability to synthesize specific phenolic compounds in response to particular abiotic or biotic stress is developed by plants through adaptive evolutionary phenomena over a period of time. To respondto different environmental challenges, plants have developed a variety of arrays to synthesize various phenolics to defend against the stresses²⁷. Flavonoids and isoflavones accumulate heavily in plants exposed to very low temperatures, nutrient deficiency, UV- B radiations, pathogenic attack, and herbivorous activities^{87,109,114}. Phenolics were also known to accumulate in plants as a response to metallic stress in the soil^{82,86} and microbial infection^{15,70,127,133}. Fig. 1. is the schematic representation of various types of abiotic stress conditions, which stimulates the biosynthesis of phenolic compounds and later increased accumulation of phenolic compounds helps to counter the abiotic stress conditions.

This article is a compiled presentation of various research work related to the synthesis and accumulation of various phenolic compounds by plants exposed to various kinds of stresses and their role in plant defense mechanisms as understood so far.

Fundamentals of Phenolic compounds :

Phenolic compounds are a diverse group of plant chemicals having phenol moiety in their structure. These compounds are basically classified into two categories as simple phenolics and polyphenolics (Fig. 2) which are groups of structurally and functionally allied phenol-containing compounds. They are abundant in plants and found in all parts of



plants. These compounds display a wide variety of biological activities. The most important biological properties of phenolics include antioxidant, antimicrobial, anti-inflammatory etc.^{29,77}.

Role of plant phenolics in countering light stress :

Phenolic compounds in plants play an

important role in growth control and have antioxidant, structural, attractant, signaling, and protective functions. Plants synthesize and accumulate phenolic acids and flavonoids in the vacuoles of mesophyll and epidermal cells in response to light stress conditions¹²⁴. Falcone *et al.*³⁷ noted that after exposure to UV-B radiation the genes P1, B, and PL1 increaseexpression in maize which induces the synthesis of transcription regulators that regulates the activity of protein ZmFLS1 for converting the dihydro-flavanols, dihydroquercetin, and dihydro-kaempferol to flavonols, quercetin, and kaempferol respectively. Radyukina et al., 103 observed the accumulation of flavonoids and anthocyanins in plants exposed to ultraviolet light and salinity stress. Their report suggested that flavonoids protect plants from UV-B radiation and anthocyanins protect them from salinity stress. Manukyan⁸³ reporteda high accumulation of total phenol in Melissa officinalis, Nepeta cataria, and Salvia officinalis after exposure to low UV-B radiation. In Salvia miltiorrhiza, Ma et al.⁸⁰ observed that UV radiation increases the concentration of rosmarinic acid and lithospermic acid. They suggested that methyl jasmonate induces biosynthesis of enzymes tyrosine aminotransferase, cinnamic acid 4-hydroxylase, 4-hydroxyphenylpyruvate reductase, and phenylalanine ammonia-lyase (PAL) that are responsible for he biosynthesis of rosmarinic acid and lithospermic acid. Ghasemzadeh et al.⁴³ reported accumulation of specific phenolic compounds in sweet basil leaves was dependent on the intensity of UV-B radiation. They suggested a direct correlation between synthesized phenolic compounds'reactive oxygen species (ROS) generation due to UV light damage. They observed that some phenolic acids like cinnamic acid, gallic acid, quercetin, ferulic acid, catechin, rutin, luteolin, and kaempferol are precursors for biosynthesis of different flavonoids through phenylpropanoid metabolism that utilizes PAL and chalcone synthase enzymes. when it is exposed to low UV-B light Csepregi et al.³⁴ reportedan increased accumulation of flavonols, quercetin, and kaempferol derivatives in leaves of

Arabidopsis thaliana. Leon-Chan et al.⁷³ observed that the low temperature and UV-B radiation causes the degradation of chlorophyll and accumulation of carotenoids, chlorogenic acid, flavonoids apigenin-7-O-glucoside, and luteolin-7-O-glucoside in leaves of bell pepper. They specifically observed that UV-B radiation increases flavonoid concentration in leaves whereas the combination of low temperature and UV-B radiation increases chlorogenic acid in leaves. They also noted that the luteolin-7-O-glucoside is involved in quenching of the reactive oxygen species (ROS) produced due to low temperature and UV-B radiation stress. Lobiuc et al.78 suggested that the phytochemical content of the basil green cultivar was high in red light whereas of the basil red cultivar was high in blue light when exposed to different proportions of blue and red light. In a comparative study, they observed an increased accumulation of rosmarinic acid, caffeic acid, and anthocyanin when exposed to blue light and white light. Similar reports were made by Taulavuori et al., 125, Stagnari et al., 122, and Nadeem et al., 91. Teerarat¹²⁶ reported an accumulation of phenolic compounds, especially chlorogenic acid and other flavonoids in leaves of Coffea arabica after exposure to UV light.

Role of plant phenolics in countering temperature stress and drought stress :

Extreme temperature conditions usually inhibit plant metabolism and stimulate the production of reactive oxygen species (ROS) which damage the cells^{10,48}. To combat this damaging stress plants accumulate osmoprotective compounds such as soluble sugars, proline, glycine betaine antioxidant enzymes, and other defensive substances which provide protection from oxidative damage^{17,116}. The phenolics, terpenes, and alkaloids also accumulateduring temperature stress to develop stress resistance ability in plants^{52,96}. During temperature stress activity of the enzyme phenylalanine ammonia-lyase (PAL) increases which results in the accumulation of phenolic compounds in plant cells. Rivero et al., 108 suggested that during heat and cold stress, there is a remarkable accumulation of soluble phenolics in watermelon and tomato. Kasuga et al.,60 indicated that cold-induced phenols accumulation in plant cells decreases the freezing point, maintains water potential, and protects cells from disruption. Weidner et al.,130 reported increased content of tannins and soluble phenols in the roots of grapevine after cold treatment. Amarowicz et al.⁵ demonstrated that during cold stress there is increased accumulation of gallic acid, ferulic acid, and caffeic acid in plants. Isshiki et al.55 observed an accumulation of farinose flavonoids in the aerial part of fairy primrosewhen it was exposed to freezing cold stress. Rana and Bhushan¹⁰⁵ suggested that biosynthesis and accumulation of phenolic compounds in plants provide tolerance against cold stress. In the same line, Commisso et al.³² provided evidence that phenolic compounds protect the cytoskeleton of microfilaments from reactive oxygen species. Chalker-Scott and Fuchigami²⁸ reported that cellular injury and stress tolerance capacity in plants is increased by the accumulation of phenolic compounds like suberin or lignin.

When the plant is exposed to drought stress it usually produces reactive oxygen species (ROS) (hydrogen peroxide H₂O₂, singlet oxygen O, superoxide anion O2-, and hydroxyl radical OH) which may cause protein degradation, membrane damage, lipid peroxidation, deoxyribose nucleic acid (DNA) damage andcell mortality^{117,136}. To prevent this damage, plants have a special system of detoxification which is regulated either by enzymes (superoxide dismutase (SOD), ascorbate peroxidase (APX), catalase (CAT), peroxidase (POD)) or by antioxidant molecules (phenols, vitamin C, carotenoids, tocopherol, and glutathione)¹². Kumar et al.⁶⁷ suggested that the overproduction of reactive oxygen species (ROS) during stress is balanced through the production of phenolic compounds and flavonoids using the phenylpropanoid pathway⁶⁷. Akula and Ravishankar¹ observed an accumulation of flavonoids in the leaves of willow plantsduring drought stress. A similar observation was made by Nakabayashi et al.,⁹² in leaves of Arabidopsisthalianain response to drought conditions. An increase in phenylalanine ammonia-lyase (PAL) activity indicates the beginning of the plant's antioxidant defense mechanism and is regulated by the feedback inhibition process through the increase in the accumulation of its own product cinnamic acid²². It regulates the activity of the enzyme and in turn, specific phenolic compounds are synthesized in response to biotic or abiotic stress. Chalcone synthase is an enzyme that shows high activity during drought stress. It is a key enzyme in the flavonoid synthesis pathway that acts on the CoA-ester of cinnamic acid to form chalcone. The chalcone is converted to flavanone by the chalcone flavanone isomerase (CHI) enzyme through isomerization which is a precursor for the synthesis of numerous flavonoid compounds⁶⁷. Hura et al., ⁵⁴ reported the accumulation of ferulic acid and high

activity of PAL enzyme in leaves of maize under water stress conditions. Phimchan et al.¹⁰¹ also reported high PAL activity and ferulic acid accumulation in fruits of capsicum during drought stress. Nakabayashi et al.⁹² observed the high activity of another enzyme chalcone synthase (CHS) in response to drought stress in Arabidopsis. Some workers have observeda high accumulation of phenolic compounds in vegetables, fruits, and cereals under drought stress^{42,121}. Sarker and Oba¹¹² observed a high accumulation of flavonoids in the leaves of Amaranthustricolor during drought stress. Brunetti et al.24 suggested that Moringa oleiferacan serve in water deficit conditions by accumulating flavonoids in leaves. Moayedinezhad et al.,90 indicated that drought stress had a marked influence on the content of various phenolic compounds such as total phenolic content, total as well as individual polyamines, and organic acids in grapevine cultivars. Severe heat stress increases the accumulation of phenolic acids *i.e.*, pcoumaric, syringic, and vanillic acids, and decreasesferulic acid, whereas severe drought had a higher impact on ferulic acid and the total sum of phenolic acids in durum wheat⁶⁹. Park et al.,⁹⁹ also identified drought-responsive phenolic compounds in Ligularia fischeriand studied their biosynthesis and regulation.

Role of plant phenolics in countering salinity stress :

Usually, salinity stress induces the production of reactive oxygen species (ROS) in plants resulting oxidative stress. To counter this oxidative damage plants produce antioxidative metabolites such as polyphenols, flavonoids, anthocyanins, pro-anthocyanidins,

phenolic acids, and phenolic terpenes which quench the singlet oxygen, neutralize or absorb free radicals and decompose peroxides⁹⁶. Yang *et al.*,¹³⁴ suggested the accumulation of specific phenolic compounds in plants during salinity stress. Parida et al.,98 earlier reported that there was a significant increase in polyphenols content in plants of Aegiceras corniculatum after 250 mM NaCl treatment. Ksouri et al.,⁶⁶ suggested that there was a significant increase in polyphenols in jerboa plants after treatment with 100 mM and 400 mM NaCl. Hanen et al.,45 suggested that the phenol content in a leaf of the plant Cynara cardunculus increases in response to 50 mM NaCl treatment. Lim et al.,⁷⁶ suggested that the accumulation of phenolic compounds in response to salinity stress in Fagopyrum esculentum is due to the increased content of compounds such as vitexin, iso-orientin, rutin, and orientin. Similar reports were presented by Petridis et al.,¹⁰⁰ and Borgognone et al.,²¹.

Another mechanism acquired by plants to resist salinity stress is through salicylic acid which is an endogenous growth regulator and signaling molecule. It is a phenolic phytohormone that controls stress by decreasing H₂O₂ levels and reducing oxidative damage in plants⁷². It enhances growth, development, and productivity in plants during stress conditions¹⁰⁴. Many research studies have suggested the function of salicylic acid in increasing salinity tolerance in plants. Jini and Joseph⁵⁸ and Khan et al., 62 suggested that salicylic acid strengthens the salinity tolerance in plants such as Medicago sativa, Vicia faba, Brassica juncea, and Vigna radiata. Jayakannan et al.,57 observed that exogenous salicylic treatment increased

water content and growth of shoots in Arabidopsis plants growing under saline conditions. Various studies of mutant plants have suggested the function of salicylic acid in providing salinity tolerance to plants^{11,26,47,89}. Various studies on the exogenous application of salicylic acid to salinity-stressed plants have also confirmed that salicylic acid alleviates the toxic effect of salt and increases the resistance of plants against salinity^{9,12,61,97}. Hanifah and Purvestri⁴⁶ reported that there is an increase in the accumulation of Phenolic compounds, total flavonoid, and antioxidant activity with the increase of saline concentration.Kiana et al. (2021) reported the vigorous antioxidant activity and robust accumulation of phenolic compounds in the leaves of Triticum vulgare and Aegilops cylindrica.

Role of plant phenolics in countering heavy metal stress :

The plants take up heavy metals through their roots which get accumulated inside the cell wall by the apoplastic system. These heavy metals may cause harm to plants by hindering biochemical metabolisms such as cell division, cell elongation, photosynthesis, nitrogen metabolism, respiration, mineral nutrient utilization, and water transportation^{31,123}. It was noted that heavy metals inactivate essential enzymes by binding to their active sites, it also induces the biosynthesis of reactive oxygen species, and exchange metal ions from biomolecules¹¹⁵. Under heavy metal stress conditions, plants synthesize phenols and flavonoids to scavenge the harmful reactive oxygen species (ROS) which donates their electron to peroxidase enzymes to detoxify hydrogen peroxide produced by heavy metals¹¹¹.

Under cadmium stress, maize accumulates phenolic compounds in roots¹¹⁸. Ali et al.,⁴ observed high activity of enzymes responsible for the biosynthesis of phenols and flavonoids in roots of Panax ginseng exposed to copper sulfate. Kovacik et al.,65 reported that when Matricaria chamomillawas exposed to nickel, the activity of the polyphenol oxidase enzyme decreased and there was an increase in total phenolics content. There was a remarkable increase in the activity of phenylalanine ammonia-lyase (PAL) and shikimate dehydrogenase enzymes with an accumulation of chlorogenic acid, protocatechuic acid, and caffeic acid. Marguez-Garcia et al.,⁸⁴ observed that when Erica and evalensis are exposed to cadmium, the concentration of rutin, cinnamic acid derivatives, and epigallocatechin increases. They suggested that increased cadmium exposure decreases the concentration of phenolic compounds in plants to reduce the deleterious effect of produced phenoxyl radicals. Malcovska et al.,⁸¹ suggested the production of phenolic compounds increases in plant cells when plants are under heavy metal stress as phenols are reactive oxygen species (ROS) scavengers and metal chelators. Kisa et al.,⁶³ observed that when Zey maize plants are exposed to cadmium and lead, the phenolic compounds (chlorogenic acid and rutin) increased in leaves whereas there was a decrease of caffeic acid and ferulic acid. Later in 2019, Kisa et al.,64 reported the changes in phenolics compounds in tomatoes in relation to heavy metal stress. Janczak-Pieniązeket al.,⁵⁶ studied the pattern and correlated the metal stress with an accumulation of phenolic compounds in winter wheat varieties.

Role of plant phenolics in countering microbial pathogens :

Plant growth and development are directly influenced by a variety of abiotic and biotic stresses. The plants mechanize their defense in two stages, first there is a rapid accumulation of phenols at the infection site that slowdowns the growth of invading pathogens. In the second step, it biosynthesizes specific stress-related substances (simple phenols, phenolic phytoalexins, hydroxycinnamic acids, etc.). These compounds restrict the pathogen from invasion. The sequence of plant defense mechanisms includes the accumulation of phenolic compounds, necrosis, host cell death, modification of cell wall through phenolic compounds deposition or development of some kind of barriers, and at last synthesis of specific toxic compounds to eradicate the pathogens⁹⁵. Pattern recognition receptors (PRRs) are the proteins present in the cell membrane of plants. They recognize conserved pathogen-associated molecular patterns (PAMPs) of microorganisms and givea signal to synthesize specific phenolic compounds, through a defense mechanism known as PAMPs-induced immunity^{20,50,94,102,138}.

In some cases, plants induce multicomponent defense response after a pathogen attack which includes the reprogramming of genetic resources, expression of a large number of defense-related genes, and encoding of enzymes that catalyze the biosynthesis of defense metabolites (phytoalexins). The process is regulated by transcriptional factors responsible for the accumulation of specific phytoalexins in plants. Salicylic acid also plays a crucial role in resisting pathogen attacks in plants. During pathogenic infection, there is a remarkable accumulation of pathogenesisrelated (PR) protein at the location distant from the infection site and to regulate systemic acquired resistance (SAR) in plants salicylic acid and H_2O_2 play a vital role^{14,59}.

Some plants possess innate immunity against pathogenic bacterial species. They have developed metabolic mechanisms to resist pathogenic bacteria through the accumulation of phenolic compounds. Postel and Kemmerling¹⁰² reported that plants recognize bacterial pathogens through pathogen-associated molecular patterns (PAMPs). In walnut plantsinfected by Xanthomonas arboricola bacteria, Mikulic Petkovsek et al.,⁸⁸ observed an accumulation of hydroxycinnamic acid, gallic acid, quercetins and catechin. Cho and Lee³⁰ identifiedan accumulation of sakuranetin in rice plants infected by Xanthomonas oryzae and Burkholderiaglumae. Wang et al.,¹²⁹ suggested that polyphenols inhibit bacterial species such as Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus, Salmonella choleraesuis, Bacillus subtilis, Serratia marcescens, and Pseudomonas aeruginosa.

Earlier studies suggested that phenolic compounds eliminate fungal pathogens by altering the permeability of cell membrane, the integrity of the cell wall, the formation of free radicals and suppression of enzymes activity, damage of DNA, and suppression the expression of virulence genes^{6,39,93,102}. Gallego-Giraldo *et al.*,⁴¹ reported the suppression of lignin biosynthesis genes (HCT) leads to the accumulation of salicylic acid which in turn increases the transcription level of some pathogenesis-related (PR) genes to improve the immunity of plants. Widodo *et al.*,¹³¹ suggested that

coumarins inhibit the growth of fungi by altering the thickness of the mitochondrial matrix, inducing apoptosis. Al-Barwani and Eltayeb³ observed the antifungal activity of psoralen and furanocoumarin against fungi Alternaria brassicicola, Sclerotinia sclerotiorum and Cercospora carotae. Some other similar reports includes that of Al-Amiery et. al.,², Serpa et al.¹¹⁶ and Zuzarte et al.,¹³⁹. Belofsky et. al.,¹⁸ suggested that the isoflavone sedonan A isolated from plant Dalea formosa prevents from infection caused by Candida albicans and Candida glabrata by inhibiting the activity of intracellular transcription targets and efflux pumps. Sherwood and Bonello¹¹⁹ suggested that lignin has potent antifungal activity against the fungi Diplodia pinea under in vitro conditions. Anttila *et al.*,⁷ suggested that the tannin extract isolated from the cone and bark of conifer plants has a toxic effect on four soft rot fungi, three white rot fungi, and eight brown rot fungi. Rashed et al., 106 observed the toxic effect of Ammivisnaga seed extract against the fungi Rhizoctonia solani was due to the presence of coumarins. In sugarcane, Marques et. al.,⁸⁵ observed the accumulation of phenolic compounds at the infected site during the early stage that might be helpful to prevent the penetration and spread of Sporisorium scitamineum fungi in other parts of the plant.

Kumar and Pandey⁶⁸ suggested that phenolic compounds suppress viral infection in plants by inhibiting viral replication through simultaneous damageof protein, and nucleic acids and inhibition of viral enzyme activities. Hu *et al.*⁵³ observed the antiviral activity of different phenolic compounds isolated from *Arundina graminifolia* against the tobacco mosaic virus. Zhao et al.,¹³⁷ suggested that the two flavonoids (fistula flavonoid B and C) isolated from the bark and stem of the plant Cassia fistula has antiviral activity against the tobacco mosaic virus. Shokoohinia et al.¹²⁰ suggested that coumarins inhibit viral replication in cells by inhibiting enzymes such as protease, integrase and reverse transcriptase. Li et al.,75 identified the phenolic compound gramniphenol which exhibited antiviral activity against the tobacco mosaic virus. Later in 2016, Liu et al. reported the antiviral potential of two coumarins isolated from leaves of Nicotiana tabacum against tobacco mosaic virus. Zakaryan et al., 135 suggested that flavonoids suppress viral infection by distracting of viral RNA translation, inhibiting viral DNA replication, inhibiting viral protein synthesis, inhibiting transcription factors responsible for viral enzymes and genome synthesis, and interfering with viral structural protein.

Role of plant phenolics in countering insects, nematodes, and herbivorous organisms :

Plants have to face various pathogenic attacks in the natural environment. To resist these pathogens plants have adjusted their physiological metabolism and developed metabolic pathways which synthesize a wide range of phenolic compounds. These phenolic compounds are used either to attract or repel different organisms as per plants' benefit. Through their toxicant effect and inhibition, they protect plants from various insects, nematodes, and herbivorous animals which feed on them¹⁹. Feeny³⁸ suggested that tannins have an inhibitory effect on the growth of Opheropthera brumata larvae. Levin⁷⁴ suggested that the phenolic quinone hypericin secreted by glands on leaves, sepals, or petals of Hypericum spp. is toxic to insects and mammals. He also suggested that the presence of gossypol in the leaves and flowers of plants can inhibit grazing by mammals and infection by tobacco budworms or bollworms. Hedin et al.,49 suggested that some flavonoids present in cotton plants are feeding inhibitors for the boll weevil, Anthonomus grandis. Luczynski et al.,⁷⁹ suggested that the concentration of catechol increases in the leaves of strawberries when infected by spotted spider mites. Byers²⁵ suggested that the bark beetle Scolytus multistriatus does not consume Carva ovata due to the presence of the phenolic compound juglone which is not palatable to them Accumulation of anthocyanins provides red, blue, or purple color to leaves, and flowers or fruits which protects the plant from the herbivorous animals and insect pathogens. These pigments developed in leaves are either not palatable for animals to eat or are not visible to animals due to a lack of red visualization receptors. Usually, insect pathogens are found to avoid red leaves and are noted to colonize mostly on green leaves. Because red leaves have better chemical defense, coupled with the worst nutritional value, which induces adverse effects in insects. Hence autumn colors of leaves is an adaptive mechanism of plants to reduce pathogen attacks^{8,44,71}. Further, Rehman et al.,¹⁰⁷ suggested that catechol, a phenolic compound binds to the digestive system of mites and inactivates digestive enzymes mites. Furstenberg-Hagg et al.⁴⁰ opined that most wheat cultivars arevery rich in phenolic content, therefore, not consumed by cereal aphids Rhopalosiphum padi.

Plants constantly interact with the environment, and climate change has already impacted their diversity, growth, and survival. In order to minimize the impact of various climate change-related stresses, plants produce diverse defense secondary metabolites, mainly phenolic compounds. Phenolic compounds regulate crucial steps in plant metabolism to provide resistance against various biotic and abiotic stresses. To protect against UV radiation plants synthesize phenolic acids and flavonoids to scavenge the reactive oxygen species (ROS) generated. During temperature stress activity of the phenylalanine ammonialvase(PAL) enzyme increases which results in the accumulation of phenols in plant tissues. The accumulation of phenols during drought stress is regulated by the activity of either phenylalanine ammonia-lyase (PAL) or chalcone synthase (CS). Phenylalanine ammonia-lyase (PAL) acts as a precursor for the biosynthesis of various phenolic compounds. Chalcone (CS) synthase helps to accumulate numerous flavonoid compounds in plants during water deficiency. During salinity stress plants accumulate polyphenols, flavonoids, anthocyanins, phenolic acids, and terpenes to resist oxidative stress. Plants also accumulate salicylic acid during salinity stress to decrease the level of H₂O₂ and reduce oxidative damage. Plants synthesize phenols and flavonoids to scavenge the reactive oxygen species (ROS) produced during heavy metal stress. Plants accumulate phenolic compounds at the infection site to inhibitthe growth and penetration of microbial pathogens in other tissues and organs. It recognizes microbial pathogens and induces a defense response at the genetic level to biosynthesize defense metabolites. Plants also accumulate salicylic

acid and H_2O_2 at the infection site to regulate systemic acquired resistance (SAR). Phenolic compounds also play a vital role as inhibitors or toxicants for nematodes, insects, and herbivores.

Future prospective :

The biosynthesis of phenolic compounds in plants during abiotic and biotic stress increases the adaptation of plants in extreme environmental conditions. Therefore, it is necessary to understand the molecular mechanism regulating biosynthesis and accumulation of specific phenolic compounds during particular stress conditions. There should be molecular and genetic level studies on the regulation of transcription factors responsible for the biosynthesis of specific phenolic compounds during each type of stress. A line of progressive study on interactive biology between phenolic compounds and salicylic acid is possible to understand the crosstalk between them while respondingto salinity stress, oxidative damage, and microbial pathogen attack. This will help to develop effective strategies to develop crop varieties that could overcome stress conditions.

Reference :

- 1. Akula, R. and G. A. Ravishankar, (2011). *Plant Signaling and Behavior* 6(11): 1720-1731.
- Al-Amiery, A. A., A. A. Kadhum, and A. B. Mohamad, (2012). *Molecules*. *17*(5): 5713-5723.
- 3. Al-Barwani, F. M. and E. A. Eltayeb, (2004). *Biochemical Systematics and Ecology*. 32: 1097-1108.
- 4. Ali, M. B., N. Singh, A.M. Shohael, E. J.

Hahn, and K. Y. Paek, (2006). *Plant Science* 171(1): 147-154.

- Amarowicz, R., S. Weidner, I. Wójtowicz, M. Karmac, A. Kosinska and A. Rybarczyk (2010). *Functional Plant Science and Biotechnology 4*: 90-96.
- Ansari, M. A., Z. Fatima and S. Hameed, (2014). *Journal of Pathogens 24:* 895193.
- Anttila, A-K., A.M. Pirttila, H. Häggman, A. Harju, M. Venalainen, A. Haapala, *et al.* (2013). *Holzforschung.* 67(7): 825-832.
- Archetti, M., T. F. Doring, S. B. Hagen, N. M. Hughes, S. R. Leather and D. W. Lee, (2009). *Trends in Ecology and Evolution 24*: 166-173.
- 9. Ardebili, N.O., S. Saadatmand, V. Niknam and R. A. Khavari-Nejad, (2014). *Acta Physiologiae Plantarum 36(12):* 3199-3205.
- 10. Asada, K. (2006). *Plant Physiology* 141(2): 391-396.
- 11. Asensi-Fabado, M. and S. Munne-Bosch (2011). *Journal of Plant Growth Regulation 30*: 456-466.
- Ashraf, M. A., M. Riaz, M. S. Arif, R. Rasheed, M. Iqbal, I. Hussain and M. S. Mubarik (2019). The role of non-enzymatic antioxidants in improving abiotic stress tolerance in plants. In: *Plant Tolerance to Environmental Stress*: Role of Phytoprotectants. Boca Raton: CRC Press; 2019. pp. 129-144.
- 13. Ashraf, M., N. A. Akram, R. N. Arteca, and M.R. Foolad (2010). *Critical Reviews in Plant Sciences 29:* 162-190.
- Badere, R. S., D. K. Koche, S. E. Powar, and A.D. Choudhary, (2007). *Journal of Plant Biology 34*: 139-145.
- 15. Bais, H.P., T.S. Walker, F.R. Stermitz,

R.A. Hufbauer, and J.M. Vivanco (2002). *Plant Physiology 128*(4): 1173-1179.

- Balasundram, N., K. Sundram, and S. Samman, (2006). Food Chemistry 99(1): 191-203.
- Balla, K., S. Bencze, T. Janda, and O. Veisz (2009). *Acta Agronomica Hungarica* 57(4): 437-444.
- Belofsky, G, M. Kolaczkowski, E. Adams, J. Schreiber, V. Eisenberg, and C.M. Coleman, *et al.* (2013). *Journal of Natural Products* 76(5): 915-925.
- Bhattacharya, A., P. Sood and V. Citovsky (2010). *Molecular Plant Pathology 11:* 705-719.
- 20. Bittel, P. and S. Robatzek (2007). *Current* Opinion in Plant Biology 10: 335-341.
- 21. Borgognone, D., M. Cardarelli, E. Rea, L. Lucini, and G. Colla, (2014). *Journal* of the Science of Food and Agriculture 94: 1231-1237.
- 22. Boudet, A. (2007). *Phytochemistry* 68(22-24): 2722-2735.
- 23. Broun, P. (2005). Current Opinion in Plant Biology 8(3): 272-279.
- Brunetti, C., F. Loreto, F. Ferrini, A. Gori, L. Guidi, D. Remorini, M. Centritto, A. Fini and M. Tattini (2018). *Tree Physiology* 38(11): 1640-1165.
- 25. Byers, J. A. (1995). Chemical Ecology of Insects. 2: 154-213.
- Cao, Y., Z. W. Zhang, L. W. Xue, J. B. Du, J. Shang, F. Xu, S. Yuan and H.H. Lin (2009). *Zeitschrift für Naturforschung*. *C64*: 231-238.
- 27. Caputi, L., M. Malnoy, V. Goremykin, S. Nikiforova, and S. Martens, (2012). *The Plant Journal 69*(6): 1030-1042.
- Chalker-Scott, L. and L. H. Fuchigami, (2018). The role of phenolic compounds in plant stress responses. In: Low-

Temperature Stress Physiology in Crops. Boca Raton: CRC Press; pp. 67-80.

- 29. Cheynier, V., G. Comte, K. M. Davies, V. Lattanzio, and S. Martens, (2013). *Plant Physiology and Biochemistry* 72: 1-20.
- Cho, M. and S. Lee (2015). International Journal of Molecular Sciences 16(12): 29120-29133.
- 31. Ciriakova, A. (2009). *Oecologia Montana 18*(1-2): 23-26.
- 32. Commisso, M., K. Toffali, P. Strazzer, M. Stocchero, S. Ceoldo, B. Baldan, M. Levi, and F. Guzzo, (2016). *Frontiers in Plant Science 7:* 1439.
- Conejero, G., M. Noirot, P. Talamond, and J. L. Verdeil, (2014). *Frontiers in Plant Science*. 5: 39.
- Csepregi, K., A. Coffey, N. Cunningham, E. Prinsen, E. Hideg, and M. A. Jansen, (2017). *Environmental and Experimental Botany 140:* 19-25.
- 35. Do Nascimento, N. C. and A. G. Fett-Neto (2010). Plant secondary metabolism and challenges in modifying its operation: An overview. In: Fett-Neto A, editor. *Plant Secondary Metabolism Engineering. Methods in Molecular Biology* (Methods and Protocols). Vol. 643: Totowa, NJ: Humana Press; 2010. pp. 1-13.
- Esmaeili, S., M. Sharifi, F. Ghanati, B.M. Soltani, E. Samari, and M. Saghariyan, (2023). *Scientific Reports* 13: 4158. https://doi.org/10.1038/s41598-023-30954-9.
- Falcone Ferreyra, M. L., S. Rius, J. Emiliani, L. Pourcel, A. Feller, K. Morohashi, P. Casati, and E. Grotewold, (2010). *The Plant Journal 62*(1): 77-91.
- 38. Feeny, P. (1970). Ecology 51: 565-581.

DOI: 10.2307/1934037.

- Fernandes, K.R.P., P.S. Bittercourt, A.D.L. Souza, A. Q. L. Souza, F.M.A. Silva and E. S. Lima, (2019). *Acta Amaz.* 49(1): 48-53.
- Fürstenberg-Hagg, J., M. Zagrobelny and S. Bak, (2013). *International Journal* of Molecular Sciences. 14: 10242-10297. DOI: 10.3390/ijms140510242
- Gallego-Giraldo, L., Y. Jikumaru, Y. Kamiya, Y. Tang, and R. A. Dixon, (2011). *The New Phytologist 190:* 627-639.
- 42. Gharibi, S., B. E. S. Tabatabaei, G. Saeidi, and S. A. H. Goli. (2016). *Applied Biochemistry and Biotechnology 178*(4): 796-809.
- 43. Ghasemzadeh, A., H. Z. Jaafar, and A. Rahmat, (2010). *Molecules* 15(6): 4324-4333.
- 44. Gould, K. S. (2004). Journal of Biomedicine and Biotechnology 5: 314-320.
- 45. Hanen, F., R. Ksouri, W. Megdiche, N. Trabelsi, M. Boulaaba, and C. Abdelly, (2008). Effect of salinity on growth, leaf phenolic content and antioxidant scavenging activity in Cynara cardunculus L. In: Abdelli C, Öztürk M, Ashraf M, Grignon YC, editors. 2008 Biosaline Agriculture and High Salinity Tolerance. Basel: Birkhauser Verlag; pp. 335-343.
- 46. Hanifah, N. and Y. A. Purwestri, (2021). The effect of NaCl salinity stress to phenolic compound, total flavonoid and antioxidant activity of Pegagan (*Centella* asiatica (L.) Urban) Leaves. BIO Web of Conferences 41, 06004. https://doi.org/ 10.1051/bioconf/20214106004.
- Hao, L., Y. Zhao, D. Jin, L. Zhang, X. Bi, H. Chen, Q. Xu, C. Ma, and G. Li, (2012). *Plant and Soil 354*: 81-95.
- 48. Hasanuzzaman, M., K. Nahar, M. Alam,

R. Roychowdhury, and M. Fujita, (2013). International Journal of Molecular Sciences 14(5): 9643-9684.

- 49. Hedin P A, J N Jenkins, A C Thompson, J C McCarty, D H Smith, W L Parrott, et al. (1988). Journal of Agricultural and Food Chemistry. 36: 1055-1061.
- 50. Heil, M. (2008). *The New Phytologist* 178: 41-61.
- 51. Heleno, S. A., A. Martins, M. J. Queiroz, and I.C. Ferreira (2015). *Food Chemistry* 173: 501-513.
- 52. Hoque T S, A A M Sohag, D J. Burritt and M A. Hossain (2020). Salicylic acidmediated salt stress tolerance in plants. In *Plant Phenolics in Sustainable Agriculture*. Singapore: Springer; 2020. pp. 1-38.
- 53. Hu, Q-F., B. Zhou, J-M. Huang, X-M. Gao, L-D. Shu, and G-Y. Yang, (2013). *Journal of Natural Products* 76(2): 292-296.
- 54. Hura, T., K. Hura and S. Grzesiak (2008). Journal of Agronomy and Crop Science 194(2): 104-112.
- Isshiki, R., I. Galis, and S. Tanakamaru, (2014). Journal of Integrative Plant Biology 56(2): 181-188.
- Janczak-Pieniązek, M., J. Cichonski, P. Michalik, and G. Chrzanowski, (2023). *Molecules 28*(1): 241. doi: 10.3390/ molecules28010241.
- 57. Jayakannan, M., J. Bose, O. Babourina, Z. Rengel and S. Shabala (2013). *Journal* of *Experimental Botany* 64(8): 2255-2268.
- 58. Jini, D. and B. Joseph, (2017). *Rice Science* 24: 97-108.
- 59. Kamle, M., R. Borah, H. Bora, A. K. Jaiswal, R.K. Singh and P. Kumar (2020). Systemic Acquired Resistance (SAR)

and Induced Systemic Resistance (ISR): Role and mechanisms of action against phytopathogens. In : Hesham A L, Upadhyay R, Sharma G, Manoharachary C. and Gupta V. (Eds) Fungal Biotechnology and Bioengineering. Fungal Biology, Springer, doi.org/10.1007/978-3-030-41870-0 20.

- Kasuga, J., Y. Hashidoko, A. Nishioka, M. Yoshiba, K. Arakawa and S. Fujikawa (2008). *Plant, Cell and Environment.* 31(9): 1335-1348.
- 61. Khan, M.I.R., M. Asgher, and N. A. Khan (2014). *Plant Physiology and Biochemistry* 80: 67-74.
- 62. Khan, M.I.R., M. Fatma, T.S. Per, N. A. Anjum and N.A. Khan, (2015). *Frontiers in Plant Science 6:* 462.
- 63. K1sa, D., M. Elmastaş, L. Oztürk and O. Kayır, (2016). *Applied Biological Chemistry 59*(6): 813-820.
- Kisa, D., O. Kayir, N. Saglam, S. Sahin, L. Ozturk, and M. Elmastas, (2019). Bartin University International Journal of Natural and Applied Sciences 2(1): 35-43.
- Kovacik, J., B. Klejdus, M. Backor, and M. Repcak (2007). *Plant Science 172*(2): 393-399.
- 66. Ksouri, R., W. Megdiche, and A. Debez, (2007). *Plant Physiology and Biochemistry* 45: 244-249.
- Kumar, S., M. M. Abedin, A. K. Singh, and S. Das, (2020). Role of phenolic compounds in plant-defensive mechanisms. In: Plant Phenolics in Sustainable Agriculture. Singapore: Springer; 2020. pp. 517-532. DOI: 10.1007/978-981-15-4890-1_22.
- 68. Kumar, S. and A. K. Pandey, (2013). Scientific World Journal 16: 2750.

- 69. Laddomada, B., A. Blanco, G. Mita, L. D'Amico, R.P. Singh, K. Ammar, J. Crossa and C. Guzmán, (2021). *Foods* 10: 2142. https://doi.org/10.3390/ foods10092142.
- Lanoue, A., V. Burlat, U. Schurr and U.S. Röse, (2010). *Plant Signaling and Behavior 5*(8): 1037-1038.
- 71. Lee, D. W., and K. S. Gould, (2002). *American Scientist 90:* 524-531.
- Lee, N. Y., M. J. Lee, Y. K. Kim, J. Park, H. K. Park, J. S. Choi, J-N. Hyun, K. J. Kim, K. H. Park, J. K. Ko, and J. G. Kim (2010). Journal of Korean Society for Applied Biological Chemistry 53: 685-690.
- Leon-Chan, R.G., M. Lopez-Meyer, T. Osuna-Enciso, J. A. Sanudo-Barajas, J.B. Heredia and J. Leon-Felix (2017). *Environmental and Experimental Botany*. 139: 143-151.
- Levin, D. A. (1971). Plant phenolics: An ecological perspective. The American Naturalist. *105*(942): 157-181.
- Li, L., W-X. Xu, C-B. Liu, C-M. Zhang, W. Zhao, S-Z Shang, *et al.* (2015). *Asian Journal of Chemistry* 27: 3525-3526.
- Lim, J. H., K. J. Park, B. K. Kim, J. W. Jeong, and H. J. Kim, (2012). Food Chemistry 135: 1065-1070.
- Lin, D., M. Xiao, J. Zhao, Z. Li, B. Xing, X. Li, M. King, L. Li, Q. Zhang, Y. Liu, H. Chen, W. Qin, H. Wu, and S. Chen, (2016). *Molecules.*, *21*: 1374-1393.
- Lobiuc, A., V. Vasilache, O Pintilie, T. Stoleru, M. Burducea, M. Oroian and M.M. L. Microgreens. Molecules 22(12): 2111.
- 79. Luczynski A, MB. Isman and DA. Raworth (1990). *Journal of Economic Entomology* 83: 557-563. DOI: 10.1093/ jee/83.2.557.

- Ma P, J Liu, C. Zhang and Z. Liang (2013). Applied Biochemistry and Biotechnology 170(6): 1253-1262.
- Malcovska, S. M., Z. Ducaiova, I. Maslanakova, and M. Backor, (2014). *Water, Air, and Soil Pollution 225*(8): 2056
- Mandal, S. M., D. Chakraborty, and S. Dey, (2010). *Plant Signaling and Behavior 5*(4): 359-368.
- 83. Manukyan, A. (2013). *Photochemistry* and *Photobiology* 89(2): 406-414.
- Marquez-Garcia, B., M. Fernandez-Recamales, and F. Cordoba, (2012). *Environmental and Experimental Botany* 75(1): 159-166.
- 85. Marques, J.P. R., J.W. Hoy, B. Appezzatoda-Gloria, A. F. G Viveros, M. L. C. Vieira, and N. Baisakh, (2018). *Frontiers in Plant Science 9:* 698.
- 86. Michalak, A. (2006). Polish Journal of Environmental Studies 15(4): 523-530.
- Mierziak, J., K. Kostyn and A. Kulma (2014). *Molecules* 19(10): 16240-16265.
- Mikulic-Petkovsek, M., A. Slatnar, R. Veberic, F. Stampar, and A. Solar, (2011). *Physiological and Molecular Plant Pathology 76*(3-4): 159-165.
- Miura, K., A. Sato, M. Ohta and J. Furukawa (2011). *Planta 234*:1191-1199.
- Moayedinezhad A, B Mohammadparast, G H Salekdeh, E. Mohseni fard and MA. Nejatian (2020). *Journal of Plant Process* and Function 8(34): 19-26.
- Nadeem, M., B. H. Abbasi, M. Younas, WAhmad, A. Zahir and C. Hano, (2019). Journal of Photochemistry and Photobiology B: Biology. 190: 172-178.
- Nakabayashi, R., K. Yonekura Sakakibara, K. Urano, M Suzuki, Y Yamada, T Nishizawa, F Matsuda, M Kojima, H

Sakakibara, K Shinozaki, A J Michael, T Tohge M. Yamazaki and K. Saito (2014). *The Plant Journal* 77(3): 367-379.

- 93. Negritto, M. C., C. Valdez, J Sharma, C. Rosenberg and C R. Selassie (2017). *ACS Omega 2*(12): 8568-8579.
- 94. Nicaise, V., M. Roux and C. Zipfel (2009). *Plant Physiology 150:* 1638-1647.
- 95. Nicholson, R. L. and R. Hammerschmidt, (1992). *Annual Review of Phytopathology 30*: 369-389.
- Oh, M.M., E.E. Carey and C.B. Rajashekar (2009). *Plant Physiology and Biochemistry* 47(7): 578-583.
- 97. Palma F, M López-Gómez, N A. Tejera and C. Lluch (2013). *Plant Science 208:* 75-82.
- Parida, A. K., A. B. Das, Y. Sanada, and P. Mohanty (2004). *Aegiceras corniculatum. Aquatic Botany* 80 : 77-87.
- Park, Y. J., D.Y. Kwon, S.Y. Koo, T. Q. Truong, S-C. Hong, J. Choi, J. Moon, and S.M. Kim, (2023). *Frontiers in Plant Science 14*: 1140509. doi: 10.3389/fpls. 2023.1140509.
- 100. Petridis, A., I. Therios, G. Samouris, and C. Tananaki, (2012). *Environmental and Experimental Botany* 79: 37-43.
- 101. Phimchan, P., S. Chanthai, P. W. Bosland, and S. Techawongstien, (2014). *Journal* of Agricultural and Food Chemistry 62(29): 7057-7062.
- 102. Postel, S. and B. Kemmerling (2009). Seminars in Cell and Developmental Biology, 20(9): 1025-1031.
- 103. Radyukina, N. L., V.I. Toaima, and N.R. Zaripova, (2012). *Russian Journal of Plant Physiology* 59(1): 71-78.
- Rajeshwari, V. and V. Bhuvaneshwari, (2017). International Journal of Plant Biology and Research 5:1067.

- 105. Rana, S. and S. Bhushan (2016). *Journal* of Food Science and Technology. 53(4): 1727-1738.
- 106. Rashed, Y. M., D. G. Aseel, and E. E. Hafez (2018). *Phytopathologia Mediterranea*. *57*(1): 73-88.
- 107. Rehman, F., F. A. Khan, and S M A. Badruddin (2012). Role of phenolics in plant defense against insect herbivory. In: Chemistry of Phytopotentials: Health, Energy and Environmental Perspectives. Berlin/Heidelberg: Springer; 2012. pp. 309-313
- 108. Rivero, R. M., Ruiz, J M, P C Garcia, L R Lopez-Lefebre, E. Sánchez and L. Romero (2001). *Plant Science* 160(2): 315-321.
- Rodríguez-Calzada, T., M. Qian, A. Strid, S. Neugart, M. Schreiner, I. Torres-Pacheco and R. Guevara-Gonzalez (2019). *Plant Physiology and Biochemistry 134:* 94-102. DOI: 10.1016/j. plaphy.2018.06.025.
- 110. Sakamoto, A. and N. Murata (2000). Journal of Experimental Botany 51(342): 81-88.
- 111. Sakihama, Y. and H. Yamasaki, (2002). *Biologia Plantarum* 45(2): 249-254.
- 112. Sarker, U. and S. Oba (2018). *BMC Plant Biology 18*(1): 258.
- 113. Sarker, U. and S. Oba, (2020). Frontiers in Plant Science 11: 559876.
- 114. Schulz, E., T. Tohge, E Zuther, A R Fernie, and D. K. Hincha (2016). *Scientific Reports* 6(1): 1. DOI: 10.1038/srep34027.
- 115. Schutzendubel, A. and A. Polle, (2002). Journal of Experimental Botany 53: 1351-1365.
- 116. Serpa, R., E. J. Franca, L. Furlaneto-Maia, C.G Andrade, A. Diniz and M. C. Furlaneto (2012). *Journal of Medical Microbiology 61:* 1704-1708.

- 117. Shao, H.B., L.Y. Chu, Z. H. Lu and C.M. Kang (2008). *International Journal of Biological Sciences* 4(1): 8.
- 118. Shemet, S. A. and V.S. Fedenko, (2005). Fiziologiia i biokhimiia kul'turnykh rastenii 37(6): 505.
- 119. Sherwood, P. and P. Bonello, (2013). *Tree Physiology 33*(8): 845-854.
- 120. Shokoohinia, Y., S.E. Sajjadi, S. Gholamzadeh, A. Fattahi and M. Behbahani (2014). *Pharmaceutical Biology 52*(12): 1543-1549.
- 121. Siracusa, L., F. Gresta, E. Sperlinga, and G. Ruberto, (2017). Journal of Food Composition and Analysis 62: 1-7.
- 122. Stagnari, F., C Di, Mattia, A. Galieni, V. Santarelli, D'Egidio, G. Pagnani and M. Pisante, (2018). *Industrial Crops and Products 122:* 277-289.
- 123. Sytar, O., A. Kumar, D. Latowski, P. Kuczynska, K. Strzałka and M.N.V. Prasad (2013). Acta Physiologiae Plantarum 35(4): 985-999.
- 124. Szymanska, R., I. Slesak, A. Orzechowska and J. Kruk, (2017). *Environmental and Experimental Botany*, 139: 165-177.
- Taulavuori, K., A. Pyysalo, E. Taulavuori, and R. Julkunen-Tiitto, (2018). *Environmental and Experimental Botany*. 150: 183-187. DOI: 10.1016/j.envexpbot.2018. 03.016.
- 126. Teerarat, Duangsodsri (2021). Phenolic compounds in the response of Coffea arabica L. to abiotic stresses. Agricultural sciences. Université Montpellier, 2020.
- 127. Tuladhar, P., S. Sasidharan and P. Saudagar (2021). Role of phenols and polyphenols in defense response to biotic and abiotic stresses. Biocontrol Agents and Secondary Metabolites, 419-441.
- 128. Upadhyay, A., S. Mooyottu, H. Yin, M. Nair,

V. Bhattaram, and K. Venkitanarayanan, (2015). *Medicine 2:* 186-211.

- 129. Wang, L., R. Sun, Q. Zhang, Q. Luo, S. Zeng, and X. Li, (2018). An update on polyphenol disposition via coupled metabolic pathways. In: Expert Opinion on Drug Metabolism and Toxicology. London: Ashley Publications; 2018. pp. 1-15.
- 130. Weidner, S., M. Karolak, M. Karamac, A. Kosinska, and R. Amarowicz, (2009). Acta Societatis Botanicorum Poloniae 78(2): 97-103.
- 131. Widodo, G. P., E. Y. Sukandar, and I. K. Adynyana (2012). *ITB Journal of Science* 44A: 145-151.
- 132. Wink, M. (1999). Biochemistry of Plant Secondary Metabolism. UK/Sheffield, Boca Raton: Sheffield Academic Press/ CRC Press.
- 133. Wurst, S., R. Wagenaar, A. Biere, and

W. H. Van der Putten, (2010). *Plant and Soil*. *329*(1) : 117-126.

- 134. Yang, L., K. Wen, X Ruan, Y. Zhao, F. Wei and Q. Wang (2018). *Molecules 23*: 276.
- 135. Zakaryan, H., E. Arabyan, A. Oo, and K. Zandi (2017). *Archives of Virology* 162(9): 2539-2551.
- 136. Zhang, J. and M. B. Kirkham, (1994). *Plant and Cell Physiology* 35(5): 785-791.
- 137. Zhao, W., X.Y. Zeng, T Zhang, L. Wang,G. Y. Yang, and Y. K. Chen, (2013). *Phytochemistry Letters*. 6: 179-182.
- 138. Zipfel, C. (2008). Current Opinion in Immunology 20: 10-16.
- Zuzarte, M., L. Vale-Silva, M.J. Goncalves, C. Cavaleiro, S. Vaz and J. Canhoto (2012). European Journal of Clinical Microbiologyand Infectious Diseases. 31(7): 1359-1366.