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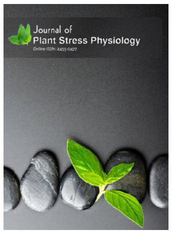

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Plant defense mechanism in combined stresses - cellular and molecular perspective

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ABSTRACT

The various abiotic stresses negatively influence the growth and development of plants. However, recent predictions of global climate change models have amplified the chances that plants will encounter new and more combinations of abiotic and biotic stresses. The plants adopt different strategies in combined stresses as compared to a single stress. This stress combination can be antagonist or synergistic depending on the interaction of stresses. Plants are sessile, to resists these stresses they activate defense mechanism which are complex cellular and molecular responses under combined stress conditions. At the cellular level, various kinds of biomolecules are produced that have positive and negative effects against stresses. The basic cellular process generates more reactive oxygen species (ROS) in stress conditions and causes extensive damage and inhibition of photosynthesis. Various plant hormones are involved in cellular activations to adapt the plants under stressful conditions. Further, to overcome the adverse effects of stress, the plant activates several molecular cascade mechanisms involving kinases, transcription factors, micro-RNAs, heat shock proteins, epigenetic changes. Besides, plants developed a robust signal perception and transduction mechanism to cope effectively with unfavorable conditions. Phytohormone plays a crucial role in signaling that is activated in response to combined stress conditions and in individual stress which are activated in response to abiotic and biotic stress combinations. Besides, ROS is also involved in signaling. They control a broad range of biological processes and have a conserved signaling network. Therefore, the crosstalk between different signaling pathways activates defense mechanisms and helps in the survival of plants from the various combined abiotic and biotic stress conditions.

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INTRODUCTION

The recent forecast by climate change models (IPPC, 2014) has augmented the chances of simultaneous incidence of two or more stresses in combination in the field. Abiotic stresses like; drought and heat, waterlogging, and salinity along with the biotic stresses prevail in most parts of the globe. In combined stress conditions, interaction of various stresses, determined the plant response and however, they are different from the response of single stress (Atkinson *et al.*, 2013; Pandey *et al.*, 2015; Ramu *et al.*, 2016). However, some responses are unique while others are common that depend on the interaction of stresses (Pandey *et al.*, 2017). The interaction between the combined stresses is not always undesirable but sometimes the two stress factors have a positive impact on each other for example under combined stress (drought x waterlogging) applied simultaneously, an increase in plant height, leaf area and stem diameter were observed (Rafique *et al.*, 2019). On the other hand, under simultaneous drought and heat stress the soil becomes drier, which further intensifies the drought and leads to higher reduction in crop yields (Rizhsky *et al.*, 2004). Similarly, a stress combination of abiotic/biotic interaction harms plants such as higher temperatures leads to bacterial diseases (Kůdela, 2009). Therefore, the range of different types of stress interactions is influenced by nature, severity and duration of stress (Pandey *et al.*, 2017). Plants adopt diverse defense mechanisms for their survival, reproduction and adapt them in adverse conditions (Pieterse *et al.*, 2009). Plant's ability to perceive stress early on time and efficient response is a critical component of plant defense. Once identified, plants inherent basal defense mechanisms activated complex signaling mechanisms of defense that vary from one stress to another stress combinations (Chinnusamy *et al.*, 2004; AbuQamar *et al.*, 2009; Andreasson & Ellis, 2010). In response to combined stresses, certain ion channels and kinase cascades are activated (Fraire-Velázquez *et al.*, 2011), reactive oxygen species (ROS) and hormones such as ethylene (ET), salicylic acid (SA), ABA, and jasmonic acid (JA) (Laloi *et al.*, 2004; Spoel & Dong, 2008) brought changes in the genetic, makeup is reprogrammed and produce adequate defense responses and enhance plant tolerance mechanism (Fujita *et al.*, 2006). Research work done to understand the plants responses to single abiotic or biotic stresses (Qin *et al.*, 2011; Todaka *et al.*, 2012; Thakur & Sohal, 2013) In present scenario, increase in greenhouse gases led to change the climatic conditions and crops are facing frequent incidence of two or more abiotic and biotic stresses at the same time. Therefore, in combined stresses plants show specific responses. However, their response is completely different from the individual stress response and unpredictable (Atkinson & Urwin, 2012).

Field grown crops are different from plants grown in controlled conditions. The influence of one stress on defense response is more compared to other stress. Moreover, plants differential sensitivity relies on the plants developmental stage (Mittler & Blumwald, 2010). Besides, other factors that can effect are interaction of stresses on plant species, it may base on the specific stress combination and on the degree of simultaneous occurrence (Rasmussen *et al.*, 2013; Ramegowda *et al.*, 2013). The nature of interaction of combined stresses (abiotic/abiotic or abiotic/biotic) is not always negative but sometimes the two stress factors have positive impact on each other for examples under combined stress (drought x waterlogging) applied simultaneously, had increased plant height, leaf area and stem diameter (Rafique *et al.*, 2019). However, in drought and heat stress simultaneously may evaporate water from the soil this may intensify the drought and crop yield potentials decline more and led to huge loss (Rizhsky *et al.*, 2004). A powerful regulatory system in plants acclimatizes them to the changing environments. Plants defending themselves in multiple stress conditions shows more resistance towards one stress remarkably (Bowler & Fluhr, 2000), perhaps showing cross tolerance (Capiati *et al.*, 2006; Suzuki *et al.*, 2012). An r example, of cross tolerance was seen in tomato plants after receiving wound salt tolerance increases also, tomato plants infected by *Pseudomonas syringae* pv. tomato (Pst) induces systemic resistance to the herbivore insect *Helicoverpa zea* (Stout *et al.*, 1999; Capiati *et al.*, 2006). Climate change impact on plant-pest interactions has been the subject of numerous recent studies and reviews (Chakarbaty, 2005; Gregory *et al.*, 2009; Luck *et al.*, 2011; Newton *et al.*, 2011). Abiotic stresses affect the severity of pathogen infection on plants. These stresses influence both positive and negative ways, for example, salinity increased tomato susceptibility to *Phytophthora infestans* and *Pseudomonas syringae* (Thaler & Bostock, 2004). This may suggest that between abiotic-biotic stress combinations, pathogen infection accelerated by abiotic stresses (Luo *et al.*, 2005; Király *et al.*, 2008). Therefore, pathogen susceptibility increases under abiotic stress may be due to change brought in hormonal balance, defense capability reduces, and down-regulation of primary metabolism stress (Mohr & Cahill, 2003; Prasch & Sonnewald, 2013). Similar reports by Prasch and Sonnewald (2013) shows that combination of drought and heat stress increased the susceptibility of *Arabidopsis* plants to Turnip mosaic virus infections. This may be due to suppression of defense responses to the biotic stress. Whereas, fungal pathogen (*Sclerotinia sclerotiorum*) infects the drought acclimated *N. benthamiana* it shows fewer symptoms (Ramegowda *et al.*, 2013) this may be due to higher endogenous ABA and ROS levels which suppress and minimize the effect of pathogen infection (Fujita *et al.*, 2006; Mauch-Mani & Mauch, 2005). Another study shows that, salinity enhanced resistance against *Botrytis cinerea* (Achuo *et al.*, 2006). In contrast, abiotic and biotic stresses manifested negative interactions also drought stress increased the antagonism of the fungus *M. oryzae*. However, both cold and heat stresses are found to lower the resistance of plants to biotic stresses showing the negative impact between abiotic/biotic stresses (Atkinson & Urwin, 2012). According to Rasmussen *et al.* (2013), the severity and complexity of combined stress conditions determine the number of differentially expressed genes. In triple stress, the transcriptomic responses are much more severe, where, *Arabidopsis* plants are subjected to virus infection in combination with drought and/or heat, (Prasch & Sonnewald 2013). Another study, demonstrates the molecular multiple stresses response interaction (drought, heat, and salinity), down-regulates the highly transcribed genes and cell cycle genes but increases protein degradation. It has been concluded that in hostile environments, *Arabidopsis* moves to a reserve state in which growth was arrested but enhanced molecular mechanisms for survival (Sewelam *et al.*, 2020). As plants are exposed to abiotic stressors, they emit certain chemicals called phytohormones. These chemicals, which include ethylene (ET), jasmonic acid (JA), and abscisic acid (ABA), build up and trigger signaling cascades that control transcriptional responses downstream (Acevedo *et al.*, 2015). According to Verma *et al.* (2019), additional key actors in signaling include ABA, ROS, MAPK, and Ca^{2+}. These players also trigger different signaling cascades that cause cross-tolerance to a variety of abiotic factors. Similarly, drought in rice triggers a signaling cascade that results in the expression of early responsive and late responsive genes. The primary class of genes codes for substances that give plants protection and osmo-tolerance, while the second type modifies the target genes involved in signal transduction (Dash *et al.*, 2018). On the other hand, complex multicomponent signaling networks in plants enable tolerance to coupled abiotic stress conditions like drought and salinity, which restores cellular homeostasis and increases survival (Golldack *et al.*, 2014). This review has covered the defense mechanism at the cellular and molecular level in the context of combined abiotic and biotic stresses, as well as detailed discussion on the significance of the signaling cascade in response to defense mechanisms.

DEFENSE MECHANISM UNDER CELLULAR PERSPECTIVE IN COMBINED STRESSES

Relevance of Biomolecules

Biomolecules comprising sugars, amino acids, Osmoprotectants (proline, glycine, betaine), hormones, redox-active molecules such as ascorbate, glutathione (GSH), NADP(H), small proteins (thioredoxin, glutaredoxins), and a variety of different metabolites like; phenolics, amino acids, carotenoids, and tocopherol are among the various biomolecules. Thus, sucrose replaced proline as the primary osmoprotectant in the event of heat stress and drought. According to Rizhsky *et al.* (2004), several plant species that experience heat stress, drought, or both exhibit changes in their metabolite profiles, which include intermediates of the Krebs cycle, carbohydrates, polyols, amino acids, and osmoprotectants (Suzuki *et al.*, 2014). Saline and heat conditions together promote the buildup of osmoprotectants in tomato plants, similarly glycine betaine and trehalose, protect plants from this particular combined stress (Rivero *et al.*, 2014). The type of stress imposed determines which suitable solutes are produced, according to metabolite profile analysis of combined stresses. Additionally, the plants changed their metabolism to a survival state with reduced productivity when exposed to combined stress conditions (Sewelam *et al.*, 2020). Secondary plant metabolites from grasses called benzoxazinoids (BXs) have a strong potential to function as a chemical defense against biotic stressors from a variety of kingdoms. A comprehensive overview of the production, metabolism, and biological functions of BXs is given by Niculaes *et al.* (2018). They discuss the wide range of biological activities of BXs, such as their toxic and health-promoting effects on insects. Studies provide additional proof of the crosstalk between biotic and abiotic stress resistance. Consequences of exogenous chemical application that, through a process known as priming, increase plant defense responses (Goellner & Conrath, 2008). For instance, applying the non-protein amino acid β-aminobutyric acid (β-ABA) to *Arabidopsis* thaliana increases the plant's resistance to a variety of stresses, such as heat, drought, and salinity stress, as well as to fungi that are both biotrophic and necrotrophic (Ton *et al.*, 2005). According to Benešová *et al.* (2012) and Balchin *et al.* (2016), stress-responsive biomolecules like heat shock proteins function as molecular chaperones in the correct folding, unfolding, and transport of proteins as well as the breakdown of non-native proteins. HSPs are important in several stress scenarios. For instance, HSP70 expression increased in tobacco when exposed to heat stress, but it increased significantly when subjected to both heat and drought stress (Rizhsky *et al.*, 2002). The accumulation and reduction-oxidation states of a number of redox-active substances affect the redox state of cells. Ascorbate, glutathione (GSH), NADP(H), tiny proteins that function as antioxidants like glutaredoxins and thioredoxins, as well as a variety of other metabolites such phenolics, amino acids, carotenoids, and tocopherols, are their primary constituents. They serve to preserve cellular homeostasis by acting as a buffer and sensor in response to environmental disturbances. According to Potters *et al.* (2010), they serve as a major integrator of ROS, energy, and metabolic regulation both under stress and in ideal conditions.

Role of Osmo-protectants in Defense Mechanism

The stress combination that could have a major effect on agriculture is summarized in Mittler's "stress matrix," which highlights the stress combination as a novel state of abiotic stress in plants (Miller & Mittler, 2006). Much work has been done on Drought and heat compared to other combinations. Drought and heat stress combination have a greater detrimental effect on plant growth and development than either stress alone causes (Rizhsky *et al.*, 2004; Chen *et al.*, 2012). This includes tobacco, *Arabidopsis*, sorghum, maize, barley, and other grasses. When plants experience both the heat and drought stress, the effects are more severe; under heat stress, photosynthetic rate and stomatal conductance decreases, and higher leaf temperature was observed. However, compared to drought-tolerant cultivars, drought-sensitive cultivars displayed more changes in these parameters (Rollins *et al.*, 2013). Furthermore, the combined effects of heat and drought stress increased the buildup of proline and malondialdehyde. Heat stress decreases leaf relative water content, photosynthesis, and reduced chlorophyll content. Furthermore, metabolic profiling showed that plants gained proline and other carbohydrates including maltose and glucose when exposed to combined drought and heat stress. According to Rizhsky *et al.* (2004), sucrose thus took the position of proline as the main osmo-protectant during a combined heat and drought stress. The metabolic profile of different plant species changes in response to drought, heat stress and their combination, including, osmoprotectants, carbohydrates, polyols, amino acids, and Krebs cycle intermediates (Suzuki *et al.*, 2014). A combination of salinity and heat stress enhances the accumulation of osmoprotectants such as glycine betaine and trehalose in tomato plants, thus play an important role in protecting plants against this stress combination (Rivero *et al.*, 2014). Analysis of metabolite profile in combined stresses indicated that metabolic profile revealed that production of specific compatible solutes depends on the nature of the stress applied under combined stresses. Moreover, plants metabolism shifted to a survival state characterized by low productivity (Sewelam *et al.*, 2020).

Antioxidant Defense Mechanism Under Combined Stresses

In conditions of drought, heat, and their combination, antioxidant defense mechanisms are crucial. According to Koussevitzky *et al.* (2008), cytosolic ascorbate peroxidase1 (APX1) protein accumulated, and plants deficient in APX1 were more susceptible to this combination of stresses than plants of the wild type. Two genotypes of barley Different responses were seen in Tibetan wild barley (XZ5-tolerant to drought, XZ16-tolerant to salinity and Al), and cultivated barley (Salinity tolerant cv CM72) to combined stress conditions of salinity and drought. In XZ5 and XZ16, callose content and chitinase activity, Sucrose synthase (SuSy) SPS, and acid invertase were higher. But in combined stress (D+S), phenylalanine ammonia- lyase (PAL) and cinnamyl alcohol dehydrogenase (CAD) activity rise in XZ5, except all other enzymes (Ahmed *et al.*, 2015). Transgenic tobacco plants expressed the cysteine protease inhibitor oryzacystatin I (OC-I), decreased H2O2 accumulation, and increased glutathione peroxidase activity (GPX) when grown in drought, heat, and high light conditions. Demirevska *et al.* (2010) concluded that the expression of OC-I in tobacco leads to the protection of the antioxidant enzyme GPX under combined stresses. Moreover, salt and drought stress in rice improves by overexpressing OsHsp17.0 and OsHsp23.7 (Zou *et al.*, 2012). With small HSPs to multiple stresses, a similar pattern was noted (Wang *et al.*, 2015). Additionally, Sun *et al.* (2001) observed that in *Arabidopsis* overexpression of HSP17.6 had improved tolerance to salinity and dry conditions. Additionally, according to certain research, the protective enzyme activities are positively regulated by HSP gene expression. According to Driedonks *et al.* (2015), in

Arabidopsis increased SOD activity was found by overexpressing HSP17.8, while, HSP16.9 overexpression in tobacco increased POD, CAT, and SOD enzyme activities.

Importance of Nutrients in Defense Mechanism

The nutrient is crucial for detecting and communicating events. Plants' morphological and physiological reactions are changed by nutrient deficiencies (Hodge, 2004). When roots are deprived of nitrogen, phosphorus, and potassium, they frequently produce reactive oxygen species (ROS) (Shin *et al.*, 2005). Furthermore, Shin and Schachtman (2004) demonstrated that ROS may be a part of a signal cascade in the roots of plants that have experienced a potassium shortage and that the production of ROS by a single NADPH oxidase is crucial in the reaction of plants to potassium deprivation. When a pathogen is present or nutrients are lacking, roots or tubers can also experience an oxidative burst (Torres & Dangl, 2005; Shin *et al.*, 2005).

MOLECULAR PERSPECTIVE

Transcriptomic Studies on Defense Response Under Combined Stresses

Abiotic or biotic stresses change the expression of genes (Chinnusamy *et al.*, 2007; Shinozaki & Yamaguchi-Shinozaki, 2007); however, when a plant is under multiple stressors, its molecular response frequently exhibits an overlapping pattern. These stress-inducible genes translate important regulatory proteins like transcription factors, protein kinases, and phosphatases, as well as those involved in direct stress protection, synthesising osmoprotectants, detoxifying enzymes, and transporter proteins. Swindell (2006) analyzed the transcriptome response in *Arabidopsis* to nine different abiotic stresses such as cold, osmotic, salt, drought, genotoxic stress, UV light, oxidative stress, wounding, and heat. Each stress regulates 67 common genes, suggesting that there was a universal component of the response to each condition. While; exposure of *Arabidopsis* and tobacco to simultaneous heat and drought stress combinations led to a new pattern of gene expression (Rizhsky *et al.*, 2002, 2004). Similarly, in a microarray profiling experiment nitrogen and water limitation suggest that several genes differentially expressed under low nitrogen were very low, whereas the various water stress treatments affect a wide number of genes. Chronic nitrogen and transient drought also influence expression of some genes. The interaction between nitrogen and water dynamically influences gene expression (Humbert *et al.*, 2013). Also, Sewelam *et al.* (2020) investigated single, double, and triple combinations of salt, osmotic, and heat stresses on *Arabidopsis*. The major effect of heat was on global gene expression and metabolite level in combination with other stresses. The combination of heat stress causes a strong reduction in the transcription of genes coding for abundant photosynthetic proteins and cell life cycle proteins, while, genes for protein degradation are up-regulated. Koussevitzky *et al.* (2008) found that tolerance of *Arabidopsis* plants under combined drought and heat stress depends on the Apx1 gene. However, APX1-deficient mutant (apx1) was significantly more sensitive to the stress combination than the wild type, it might be suggested that cytosolic APX1 has a role in acclimatization of plants to a combined drought and heat stress. The genes specifically regulated by two stresses in *Arabidopsis* encodes for heat shock proteins (HSPs), proteases, lipid biosynthesis enzymes, and starch degrading enzymes, also MYB TFs, protein kinases, and defense proteins involved in protection against oxidative stress (Rizhsky *et al.*, 2004). A noticeable difference was found in the gene expression profile of fungal hyphae under drought and control (well-watered) conditions (Bidzinski *et al.*, 2016). The relationships between pathogens and drought were addressed in many studies (Ramegowda & Senthil-Kumar, 2015; Choudhury *et al.*, 2017). A combination of water deficit and nematode stress activates a unique program of gene expression among them, 50 genes specifically multiple-stress-regulated. Besides, the major role played by three genes AtRALFL 8, AtMGI, AZI1 these genes were involved in cell wall remodeling, methionine metabolism, and systemic plant immunity (Atkinson *et al.*, 2014) Thus, the study highlighted the complex nature of multiple stress responses.

Role of Plant Immune Response Under Combined Stresses

Plants are sessile organisms, which evolved specialized mechanisms, such as intricate immune response pathways, to withstand various stress (Nejat & Mantri, 2017). Plant's vulnerability and adaptive capacity are presented as two sides of the same coin. Effective identification of molecular nonspecific microbe-associated patterns and host-derived (endogenous) damage-associated patterns is essential for quantitative broad-spectrum immunity against microbial pathogens. Although, the cell-surface pattern recognition receptors (PRRs) detect these molecules sensitively (Ranf, 2018). The general and non-specific defense response is Pathogen/microbe-associated molecular patterns (PAMP/MAPM) triggered immunity (PTI) which provides immunity not only against the range of biotic stresses but also against abiotic stresses. For example, the basal defense response in plants is activated by mild drought stress, which allows plants to defend against pathogen infection. On the contrary, severe drought stress causes leakage of cellular nutrients into the apoplast which effectively leads to pathogen infection (Ramegowda & Senthil-Kumar, 2015). Effector-triggered immunity (ETI) is a pathogen-specific plant immune response that is triggered by resistance R-genes when pathogen virulence factors, or effectors, are released into plant cells (Cui *et al.*, 2015). This is also referred to as the hypersensitive response (HR) (Thomma *et al.*, 2011). Plant defense response is mediated through R-genes. In addition, basal defense response R-genes also mediated defense response during combined abiotic/biotic interaction. High temperatures decreased the defence response of both the resistance R-gene and the basal in *Arabidopsis* and *N. benthamiana* against *Pseudomonas syringae*. Plants exposed to high temperatures also had a delay in the hypersensitive response (HR) mediated by R-genes against Potato virus X (PVX) and TMV (Wang *et al.*, 2009). These results show that when high temperatures and pathogen infection coexist, both basal and R-gene-mediated defence responses are inhibited.

Role of Hormones, TFs and mi-RNAs Under Combined Stresses

Plant hormones have a major role in the synchronisation of growth under both favourable and adverse conditions, as well as in the regulation of defence responses in the aftermath of pathogen invasion. In a combined abiotic and biotic stress combination, hormones are important because they influence the interaction and antagonistic relationship between the signalling pathways of the two stresses (Anderson *et al.*, 2004; Asselbergh *et al.*, 2008b; Atkinson & Urwin, 2012). It is also recognised that Abscisic Acid (ABA), the main regulator of the drought stress response, can change plants' defences against pathogens. Accumulation of ABA in drought stress closes stomata and inhibits bacterial invasion through stomata (Melotto *et al.*, 2017). On the other hand, ABA inhibits the development of defence chemicals such as lignins and phenylpropanoids and suppresses systemic acquired resistance to infections (Mohr & Cahill, 2007; Kusajima *et al.* 2010). Consequently, ABA can affect a plant's response to a pathogen infection in both good and negative ways. Additionally, Cao *et al.* (2011) investigated the effects of ABA's antagonistic or synergistic interactions with other hormones, including SA, JA, and ET, on biotic stress. Anderson *et al.* (2004) found that high ABA levels inhibit ethylene, JA, or SA-mediated signaling, which in turn suppresses the expression of defence genes in plants. The hormones SA, JA, and ethylene play a significant role in the later phases of pathogen infection, even though ABA suppresses a variety of defensive chemicals (Asselbergh *et al.*, 2008a; Ton *et al.*, 2009). Additionally, hormones and temperatures have an impact on the genes that control the defense response during biotic stress reactions. SA mediates the defense responses in *Arabidopsis* and *Pseudomonas syringe* interact at high (28 °C) and extreme (37 °C and 42 °C) temperatures (Wang *et al.*, 2009; Janda *et al.*, 2019). The exogenous administration of ABA increased the resistance of *Arabidopsis* plants to fungal diseases, including *Alternaria brassicicola*, which produces dark leaf spot, and *Pythium irregulare*, which causes damping-off (Adie *et al.*, 2007).

Role of Transcription Factors

TFs have multiple roles in the development and growth of plants and respond to various abiotic stressors). Under stressful conditions, transcription factors (TFs) play a critical function in the gene regulatory network by controlling the transcription rate through the activation or repression of gene expression (Tsuda & Somssich, 2015). Many of the stress combination-specific genes here encode transcription factors and other regulatory genes. Reports have shown how WRKY transcription factors support the biotic and abiotic stress response of plants using ethylene signalling, salicylic acid (SA), and jasmonic acid (JA). According to Besseau *et al.* (2012), pathogen- and oxidative stress-induced salinity and oxidative stress conditions improved *Arabidopsis* seed germination when AtWRKY30 was overexpressed. Prasch and Sonnewald's (2013) transcriptome analysis of *Arabidopsis* plants exposed to the triple stress combination (heat, drought, and virus infection) reveals that 23 transcripts were up-regulated when all three stresses were present. Two zinc finger proteins and DREB2A are the primary transcripts. Furthermore, in all three stress combinations, the R-mediated disease response was also inhibited. Therefore, the findings imply that the pathogen-related signaling network is dependent on abiotic stressors that cause the defense response to be deactivated and increase plant susceptibility. As a positive regulator, the NAC family of transcription factors participates in the defensive response to biotic and abiotic stresses (Nakashima *et al.*, 2007). Ohnishi *et al.* (2005), Nakashima *et al.* (2007) and Takasaki *et al.* (2010), wounding was among the factors that induced the OsNAC6 gene, (member of the NAC family) in rice. Transgenic rice plants that overexpressed OsNAC6 demonstrated enhanced tolerance to drought and high salinity, as well as some resistance to the hemibiotrophic fungal disease *Magnaporthe oryzae*, according to Nakashima *et al.* (2007). Recently, Atkinson *et al.* (2013) in transcriptional analysis on *Arabidopsis* plants exposed to drought, nematode infection, or both. The co-occurrence of nematode infection and drought resulted in modifications to a distinct collection of transcripts. Among them are Azealic Acid induced 1 (AZI1), Methionine Gamma Lyase (AtMGL), and Rapid Alkalization Factor -LIKE8 (AtRALFL8). Joshi *et al.* (2010) claim that signal peptides generated by AtRALFL8, which was induced in roots, may cause cell wall remodeling. The expression of the methionine homeostasis gene AtMGL was upregulated in leaves under the combined stress conditions. It may regulate methionine metabolism, which is critical for signaling in a range of stressful circumstances and the synthesis of osmolytes (Pearce *et al.*, 2001). Additionally, as part of the ABA-induced regulation of pathogen response genes, AZI1, which is involved in systemic acquired resistance was down-regulated in leaves (Yasuda *et al.*, 2008; Jung *et al.*, 2009). Nevertheless, additional vital defence molecules that regulate the synthesis, folding, assembly, translocation, and degradation of proteins are protein chaperones, also referred to as molecular chaperones (Wang *et al.*, 2004). The primary transcriptional regulators of HSPs are heat shock transcription factors (HSFs), which bind to highly conserved motifs of the promoter regions of HSP genes known as heat stress-elements (HSEs; 5′ -AGAAnnTTCT-3′). Increased resistance to biotic and abiotic stressors is the consequence of this (Hu *et al.*, 2015; Virdi *et al.*, 2015). The HSPs control both biotic and abiotic defence genes. For example, *Arabidopsis* developed HSPs due to necrotrophic fungal infection, cold, dehydration, and oxidative stress (Sham *et al.*, 2014). However, Li *et al.* (2013) observed that HsfA3 was upregulated in response to drought and salt stress.

Role of Micro RNAs

Non-coding RNAs known as microRNAs are involved in the majority of biological processes in both plants and animals. The control of numerous biological processes depends on them (Bartel & Bartel, 2003; Stefani & Slack, 2008). Currently, research on the functions of miRNAs in the control of biological stressors has primarily focused on rice and *Arabidopsis*. When rice plants are infected with the stripe virus (RSV), a large number of miRNAs accumulate. The miR160, miR166, and miR396 families of miRNAs are among these (Seo *et al.*, 2013). Furthermore, Kulcheski *et al.* (2011) examined the pattern of miRNA expression in soybean cultivars susceptible and resistant to the Asian soybean rust, *Phakopsora pachyrhizi*, under conditions of drought stress. Numerous miRNAs are implicated in the response to both biotic and abiotic challenges, even though their expression levels in response to rust infection and drought stress were drastically different and contrasting. When wheat plants (*Erysiphe graminis* f. sp. tritici (Egt)) were subjected to both circumstances, it was discovered that nine miRNAs were co-regulated by heat stress and powdery mildew infection (Xin *et al.*, 2010).

SIGNALING AND CROSSTALK IN COMBINED ABIOTIC STRESSES AND COMBINED BIOTIC/ ABIOTIC STRESSES

Plants are sessile organisms, on sensing the abiotic and biotic stresses they initiate complex signaling pathways on sensing combined (abiotic and biotic) stresses. In the first step of signaling intercellular Ca^{2+} concentration changes, later, elevated Ca^{2+} levels activate calcium-dependent protein kinases (CDPKs), calcium/calmodulin-dependent protein kinases (CCaMKs), or phosphatases. Stress-responsive gene expression is regulated by the phosphorylation/dephosphorylation of specific transcription factors (Reddy *et al.*, 2011). Signaling pathways in response to combined stresses are primarily under the control of hormones. ABA is the key hormone produced in response to abiotic stresses, and it induces a range of downstream processes for tolerance to stress. Whereas, the biotic stresses response is produced by antagonism of hormones jasmonic acid, salicylic acid, and ethylene. Thus, the signaling pathways interact and antagonize each other (Anderson *et al.*, 2004; Asselbergh *et al.*, 2008b; Atkinson & Urwin, 2012). Combined abiotic stresses in plants trigger the overproduction of ROS and can pose a hazard to plant cells. However, ROS in low or moderate concentrations acts as second messengers in ABA intracellular signaling cascades. The main ROS molecule i.e. H_2O_2 is a non-ionic, relatively stable that involves signaling (Sewelam *et al.*, 2016; Kumar *et al.*, 2017). ROS regulates abiotic stress response and activates signaling in a highly harmonized way. ROS activates antioxidants, kinases, defense genes, and an influx of Ca^{2+} ions. Also, phospho-proteins increased the synthesis of plant hormones like SA, JA and ethylene. Whereas, in biotic stresses, early defense responses are activated such as the synthesis of phytoalexins and pathogenesis-related proteins, as well as cell wall strengthening/PCD promotion, restricting invasion/multiplication/spread of pathogens in plant cells (Camejo *et al.*, 2016; Kumar *et al.*, 2017; Andersen *et al.*, 2018; Shah *et al.*, 2019). However, some reports show that antioxidant system in combined abiotic/biotic stresses. manage ROS responses The ascorbate-glutathione (AA-GSH) cycle is the major ROS regulating process that protects against ROS in abiotic and biotic stress factors (Kuźniak, 2010; Foyer & Noctor, 2011; Shigeoka & Maruta, 2014). For example, in biotic stress ascorbate peroxidase (APX) (Satapathy *et al.*, 2012; Nenova & Bogoeva, 2014) or APX and glutathione reductase activities under salt stress and fungal infection (Nostar *et al.*, 2013). Atkinson and Urwin (2012) showed that, in multiple stress conditions heat shock factors (HSFs) act as master regulators. The heat shock TFs act as molecular sensors, they sense cellular changes in ROS and induce the expression of heat shock proteins (Miller & Mittler, 2006). As a result of varied stresses, distinct combinations of HSPs are generated, which may aid in stress adjustment (Rizhsky *et al.*, 2004; von Koskull-Döring *et al.*, 2007; Yoshida *et al.*, 2011). The complex process of signalling involves mitogen-activated protein kinase cascades, cross-talk between various transcription factors, reactive oxygen intermediates (ROI), calcium, calmodulins, and the sense of stress (Bowler & Fluhr, 2000; Knight & Knight, 2001; Kovtun *et al.*, 2000; Chen *et al.*, 2002). Remarkably drought and cold activates common stress responses and pathways (Seki *et al.*, 2001; Chen *et al.*, 2002). According to Bowler and Fluhr (2000), Different stresses showed a high degree of overlapping between gene clusters. This overlapping may explain the cross-tolerance phenomenon," where one particular stress can induce resistance in plants to subsequent stress that is different from the initial one. Further, several workers reported that specific abiotic stress responsible for enhancing the resistance of plants to biotic stress (Sandermann, 2004; Carter *et al.*, 2009). However, plants exposed to prolonged duration of abiotic stresses, such as drought, extreme temperature, nutrient stress, or salinity, cause weakening of plant defenses and enhanced susceptibility to biotic stresses (Szittya *et al.*, 2003; Xiong & Yang, 2003; Grodzki *et al.*, 2004; Amtmann *et al.*, 2008; Mittler & Blumwald, 2010; Zhu *et al.*, 2010)

CONCLUSIONS AND FUTURE PROSPECTS

In response to the combination of stresses, whether abiotic/ abiotic or abiotic/biotic plants activate defense mechanisms for growth, development, and acclimation at a cellular and molecular level. These abiotic/abiotic stress combinations interact synergistically or antagonize each other, however, in response, the abiotic/biotic stress combination plays a significant role in the plant's immune response in defense against the pathogen infection. However, long-term abiotic stresses weaken the defense process and enhance the susceptibility of plants to pathogen attack. Thus, under such conditions, plants must be exposed to varied stress treatments and select and test the traits responsible for resistance. The combination of two or more different stresses shows unique and overlapping transcriptomics responses compared to individual stresses. The regulation of transcription factors, hormones, miRNAs, and Heat shock factors have an importance in combined abiotic and biotic response and defense mechanisms. Several combined abiotic and biotic stresses significantly affect plant growth and development. To survive unfavorable environmental conditions plants, allocate their resources mainly in the growth, reproduction, and defense of the plants. The fine-tuning of complex signal transduction pathways integrates and allocates nutrients and energy between growth/reproduction and defense-associated processes. Whereas, signals are mediated through calcium, ROS, and cross-talk between different hormones, kinases, receptors as well as transcription factors enables the plants to adapt to adverse environmental conditions. In the future research work, characterization of different stress conditions is important to understand the intensity of the different stresses. Prasch and Sonnewald (2015) described the comparative study of multifactorial stress experiments to identify the stress-specific and common signaling network and also explained plants' response to stress conditions and activation or deactivation of various gene expression programs. These data can be utilised to investigate the function of discovered transcription factors, kinases, and receptors to gain a better understanding of the key gene networks that confer stress tolerance in real-world settings. Therefore, developing crops and plants that are stress-resistant requires an understanding of the molecular mechanisms underlying coupled abiotic and biotic stressors.

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