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REVIEW

Phytomelatonin: An Emerging Regulator of Oxidative Imbalance Due to Abiotic Stress

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Drought, heat, cold, flood, salt, light, air pollution, and pesticide-induced oxidative damage have a detrimental impact on plant growth, reproduction, and survival. Thus, our research seeks to establish through a tryptophan-derivative plant molecule known as phytomelatonin, which may play a significant function in plant responses to various environmental stresses. Through the pieces of literature analysis, we reviewed the exogenous melatonin application and its influence on oxidative stress such as ROS and RNS generated in plant tissues under different abiotic stimuli. Our investigations also concern how phytomelatonin impacts the level of antioxidative proteins such as Superoxide dismutase (SOD), Catalase, and Glutathione Peroxidase (GPx) under these stimuli. After our deep investigation through the literature survey, we found that phytomelatonin acts as a powerful scavenging agent to detoxify ROS and RNS under abiotic threats. Additionally, it also significantly enhanced the level of oxidant proteins to minimize the negative impact of reactive species under these threats. In this way, phytomelatonin exhibits multiple crucial capabilities including root growth, leaf senescence, photosynthetic rate, and increased biomass. Moreover, we discussed in brief how phytomelatonin acts as an emerging regulator of oxidative imbalance between oxidative stress and antioxidative proteins induced by abiotic stresses, generated primarily in cell organelles, nuclei, plasma membrane, cytosol, and apoplast. Thus, it may be concluded that the phytomelatonin molecule might be improving the balance of these stressful conditions in plants for its better-surviving capacities under different threatful situations.

Key words: Abiotic stress, Antioxidative proteins, Phytomelatonin, Molecular mechanism

Plants' growth is interrupted by any sort of trade in surroundings that harms the cell, and ends the bloom of flowers is known as environmental stress. Environmental stresses are mainly biotic and abiotic types. Biotic stress is caused by weeds, bugs, bacteria, fungi, nematodes, viruses, and so on. Drought, heat, cold, flood, salinity, light, air pollutants, and pesticides are covered in abiotic stress, which hurts plant growth, reproduction, and survival. Thus, the plant hormones together with nitrogen, oxygen, sulfur species, and high levels of calcium ions have a direct impact on oxidative burdens in plants (Niu and Liao, 2016). Thus, our investigation goal whether a new and latest plant molecule referred to as phytomelatonin has a crucial function in the reaction of plants to environmental stress. In this admire, we also assess the position of its endogenous production or exogenous application and its impact on the reduction of oxidative stress in plant life through the literature survey.

Melatonin was primarily known as an animal hormone as it was first located in the bovine pineal gland of vertebrates (Lerner *et al.*, 1958). Moreover, melatonin found in higher plants, termed phytomelatonin has a pivotal position in leaf senescence, environmental stress, flowering, photosynthesis, and seed germination (Wang *et al.*, 2018). Melatonin is metamorphically preserved with multiple phenotypic expressive molecules that are present in almost all living entities (Hardeland, 2015). As it is amphiphilic or amphipathic in nature, it may let in melatonin directly via the lipid membrane to the cytoplasm or nucleoplasm, and/or in the other cell organelles (Debnath *et al.*, 2019). Further, in plants, the biosynthesis of melatonin (phytomelatonin) through four ways are well described by Mannino et al, (2021). The most important sites of phytomelatonin biosynthesis are cytoplasm, chloroplast, and mitochondria (Mannino *et al.*, 2021). In animals, melatonin regulates circadian rhythms, immunological enhancement, sexual behavior, retinal body structure, sleep, reproductive physiology, and aging therefore it is referred to as a potent biological modulator (Cipolla-Neto and Amaral, 2018). Similarly, melatonin has many crucial capabilities in plants (Arnao and Hernandez-Ruiz, 2006). Most of the literature stated that phytomelatonin may be considered as a most potent regulative molecule, to modulate the unique physiology of vegetations (Arnao, 2014). This alters the production of plant growth by increasing photosynthesis, and biomass (Sun *et al.*, 2021), but here we discuss in brief mainly how melatonin acts as a potent molecule to reduce the oxidative stress in plants under different abiotic burdens. The antioxidative nature of melatonin against different reactive species has been well described by many scientists in their earlier reports (Chitimus *et al.*, 2020). In this paper, we discussed in brief about how phytomelatonin acts as an emerging regulator of oxidative imbalance between oxidative stress (ROS/RNS) and oxidative proteins (SOD/Catalase/GPx) due to abiotic stress.

Oxidative Stress

Oxidative burden results imbalance between the generation of reactive oxygen/nitrogen species and a low level of antioxidants toxifies the plant metabolism and their threats to survival. Ecological factors like drought, heat, cool, injury, heavy metals, and UV light may increase oxidative burden (Xie *et al.*, 2019). ROS are principally produced by two processes. The first is the electron pass to oxygen, emerging the production of superoxide anion ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2), and hydroxyl free radical ($^{\cdot}OH$). The latter is the exchange of power to atomic O_2, prompting the generation of singlet oxygen ($^1O_2$) (Li *et al.*, 2016). A few RNS have been portrayed in plants, however, the most significant species are nitric oxide ($^{\cdot}NO$), nitrogen dioxide ($^{\cdot}NO_2$), peroxynitrite ($ONOO^-$), and S-nitroso glutathione (GSNO). Other reactive species are NO^-, NO^+, NO_3, N_2O, N_2O_3, N_2O_4 and $ClNO_2$. Despite the relative multitude of previously mentioned free radicals, just a few are produced biologically, while others are produced via only chemical pathways (Del Rio, 2015). These reactive species are majorly produced in different cell organelles, nuclei, endoplasmic reticulum, lipid membrane, cytosol, and apoplast (Pandita, 2021).

Effect of oxidative damage to biomolecules

The threshold level of reactive species increases the lipid peroxidation in the plasma membrane by creating lipid-free radicals which affects normal cellular functioning by damaging peptides and nucleic acids. Ecological burdens in plants enhanced lipids deterioration which matches with the expanded creation of ROS (Das and Roychoudhury, 2014). Malondialdehyde (MDA) production is the marker of lipid peroxidation (Ayala *et al.*, 2014) which confirms the damage of lipid bilayers. The ROS assault on proteins might cause alteration of proteins directly or indirectly. The structure of proteins is altered indirectly due to interaction with increased MDA levels from unsaturated fat peroxidation while, direct change includes tempering of peptide chains (Kalinina and Novichkova, 2021). As an outcome of exorbitant ROS creation, results of peptide sequence change, deletion of amino acids from the protein chain, modified cations/ anions, and expanded sensitivity of peptides to its degradation. In plants, cells are harmed by reactive species resulting in the carbonylation of proteins, and continuous changes in peptides under different burdens (Baraibar *et al.*, 2013). Moreover, several reports suggested that the protein sequence may vary after interaction with ROS, as it is a very sensitive locale for assault by ROS (Anjum *et al.*, 2015).

ROS is a significant source of oxidative harm to nucleic acids that can make changes in encoded proteins and may prompt defective proteins (Juan *et al.*, 2021). ROS assaults DNA through oxidizing its sugar molecule, DNA break up, evacuation and modification of nitrogenous bases, DNA-protein interactions, and mismatches with the nucleotide's results mutations (Weber, 2014). Plants exposed to natural burdens such as excess concentration of salt and metals deteriorated their DNA concentration (Dutta *et al.*, 2018). Oxidative assault on DNA bases includes •OH expansion, while hydrogen deliberation from deoxyribose harms predominantly sugar molecules. This free radical expansion might be responded to with all nitrogenous bases of DNA and, additionally affects the nucleotide backbone (Cadet and Wagner, 2013). Thus, increased reactive species levels are greatly active and badly affect different cellular, physiological, and biochemical activities together with rupture of lipid bilayer via reduction of sugar molecules, free radicals attack on polyunsaturated fatty acids, peptide degradation, and the deterioration of nucleic acids, oxidants, and colored pigments. Further ROS might impact photoprotection and resistance in plants (Sharma *et al.*, 2012). However, ROS oxidizes and changes a cell by causing irreversible harm to DNA and hindering its unique capabilities. This implies the double nature of ROS, as it might be destructive or defensive relying upon the balance between ROS generation and scavenging nature at appropriate timing. Also, in chloroplasts, the creation of ROS may be because of the spillage of electrons in the ETC (Huang *et al.*, 2019).

Scavengers of ROS and RNS in plants

Reactive species are generated in almost all life forms including from bacteria to higher plants that are threatened under oxidative stress. They are mainly of two types *i.e.*, oxygen-/nitrogen-containing reactive species (ROS/RNS), despite these other non-radical and radical species are listed (Ferreira *et al.*, 2018). ROS can be killed by enzymatic reactions with anti-oxidative proteins *i.e.*, superoxide dismutase (SOD), catalases, and peroxidases (GPx) that catabolized $O_2^{\cdot -}$ and H_2O_2. These anti-oxidative proteins have a well-known defense mechanism in biological systems, thus considered as the first line of protection to maintain ROS homeostasis within the cells. Further, SOD can facilitate the first line of defense against ROS by converting free radical superoxide ions ($O_2^{\cdot -}$) to dioxygen (O_2) and then to dihydrogen dioxide (H_2O_2). Further, this H_2O_2 is known for a non-radical ROS and acts as a substrate for catalase. This enzyme neutralizes the adverse effect of H_2O_2 by converting it into H_2O and O_2, maintaining as most favourable environment within the cell. While GPx is also a well-known catalytic protein that may reduce H_2O_2 into H_2O and O_2. Additionally, it also reduces the non-radical H_2O_2 into alcohols and oxygen with the help of catalytic reactions (Kellner *et al.*, 2017), and maintains ROS homeostasis. Moreover, the RNS can be scavenged by a very diverse set of antioxidant compounds (non-enzymatic such as flavonoid, phenolic acids, tryptophan, tocopherol, etc.) that react with RNS by several complex mechanisms resulting in the neutralization of these reactive species (Kellner *et al.*, 2017). Despite this melatonin also has been reported as a potent scavenger molecule for RNS and ROS.

Melatonin as a Stress Reducer

Plant development is additionally improved by melatonin content which assists in minimising oxidative burdens (Sun *et al.*, 2021). Phytomelatonin levels might have been provoked by quick changes in temperature, light, and other natural circumstances in plants. Further, melatonin levels may vary under different stressed plants (Mannino *et al.*, 2021). Reiter's (1993), first showed that melatonin acts with predatory capability against free hydroxyl radical, and explained that melatonin is a great treatment against certain herbicides and harmful mixtures. Melatonin acts like anti-reactive radicals in two significant ways by moving either electrons or hydrogen (Reiter *et al.*, 1993). Since ROS/RNS and other destructive drug species are neutralized by melatonin in both plants and animals. Thus, melatonin shows its most potent neutralizing and predatory capability against reactive nitrogen radicals and non-radicals (Di Meo, 2016). Melatonin limits the poisonous and unsafe impacts of a few toxins, medications, and herbicides in animal and plant cells. Though melatonin is amphiphilic, in this way, it shows two activities, (i) a direct action of melatonin as it directly enters into the cell and scavenging the reactive radicals produced due to the presence of unfamiliar material, and (ii) an indirect activity through its membrane receptor and increased the level of Ca^{2+} which may further induce the various genes to get turned on, and enhance the production of antioxidant proteins, ascorbate-/glutathione-/halo-peroxidases, glutathione-reductases/synthases, glutathione S-transferases, ascorbate oxidases, monodehydro- / dehydroascorbate-reductases, peroxi-/thio-redoxins, and so on. They all limit the harmful activity of the reactive species (Pardo-Hernandez *et al.*, 2020). The detoxifying activity of the unfamiliar substance intervened by melatonin might make sense of the ideal outcomes in melatonin-applied herbs under heavy metal stress (Tordjman *et al.*, 2017). Thus, melatonin has been believed to act in plants and likewise in animals (Agathokleous *et al.*, 2019).

Phytomelatonin vs Abiotic Stress

Function of melatonin in drought stress

Drought implies low precipitation all through a significant period. Drought as an abiotic stress causes immense difficulty in normal plant development (Tiwari *et al.*, 2020). Drought-induced oxidative burden in plants results in the imbalance between ROS creation and antioxidants. The impact of UV radiation on plants brings about unusual development and even prompts negative effects to survive the plant. In this way, to adapt to these adverse and malicious impacts of radicals in plants, the application of melatonin might be assumed to work as a strong shield (Hollosy, 2002). Similarly, phytomelatonin acts as a defensive molecule against the adverse effects of ultraviolet and drought stress. Melatonin treatment significantly reduces drought-initiated harm because of photosynthetic inhibition, injury of the plasma membrane, and enhanced performance of stomata. Further, the roots triggered by melatonin improved the electrolyte spillage, chloroplast activity, water availability, provoked rate of photosynthesis proficiency, and function of stomata (Dai *et al.*, 2020). Additionally, melatonin application showed significantly decreased levels of reactive radicals and abscisic acid in drought-stressed plants, which improved the function of stomata (Silalert and Pattanagul, 2021). Moreover, the application of melatonin significantly induced the production of defensive enzymes SOD, catalase, and GPx, subsequently adjusting the physiology and development in alfalfa, maize, wheat, and apple, etc. and in this way adapting to these burdens (Nawaz, 2021).

Function of melatonin in cold stress

Cold stress mediates specific changes in plant antioxidant functions and lightens the unfavorable effects of ROS. The expansion in the amount of antioxidant proteins alleviates the unfavorable effects of cold stress. Melatonin treatment further enhanced the level of antioxidant genes and further developed the ability to tolerate cool distress. Similarly, melatonin sprinkled on seeds and herbs impressively expanded the impression of antioxidant defense enzymes which thus further develops the overall growth of plants in terms of tolerance to cold stress (Ahmad *et al.*, 2021). Moreover, melatonin also expanded the level of IAA and jasmonic acids, while ABA levels diminished in cold-stressed plants (Ding *et al.*, 2022). This suggested that melatonin acts cooperatively with auxin and jasmonic acids and adversely with abscisic acid to control the effect of cool distress. Cool distress additionally expands the level of unsaturated fat desaturase (FAD2), while melatonin treatment brings down the FAD2 genes and subsequently decreases lipid peroxidation under cold stress (Qari *et al.*, 2022). Besides, melatonin also regulates the production of ABA synthesis and catabolism genes to negotiate cool distress in plants (Zhao *et al.*, 2017). The utilization of melatonin additionally enhances the Ca^{2+} level that conveys messages for antioxidant functions to tolerate cold stress by upregulating the SOD, catalase, and GPx (Yujin *et al.*, 2021).

Function of melatonin in heat stress

Heat stress harms the action of proteins and the injury of membrane lipids, subsequently influencing the action of chloroplast- and mitochondria-based enzymes and plasma membrane integrity which brings altered development of plants and in this way loss of yield (Hu *et al.*, 2020). Extensive heat intensity for an ample duration causes cell harm and cell demise, even though intensity plays a pivotal role in crop production in tropical locales (Mazdiyasni *et al.*, 2019). In plants under heat and distressing circumstances, the melatonin biosynthesis genes are mainly induced and result from more elevated levels of melatonin. For example, under high-temperature conditions, the degree of melatonin is expanded in rice (Fan *et al.*, 2022) proposing the function of melatonin in protection against heat stress. In *Ulva* sp. climbing in temperature might increment melatonin levels, affirming its capacity to further develop heat tolerance (Hardeland, 2012). Likewise, a new report detailed that the use of melatonin turns on stress-responsive genes (C-repeat Binding Factors; CBF /Dehydration Responsive Element Binding; DREB) to beat heat stress in Bermuda grass (Tiwari *et al.*, 2020). Thus, it suggested that melatonin has a high potential to further develop heat tolerance. Moreover, another report explains whether the lack of endogenous melatonin provokes high heat-prompted oxidative burden as manifested by expanded electrolyte spillage rate, malondialdehyde level, and oxidized and insoluble protein aggregation in tomato leaves. Conversely, exogenous melatonin is added to the endogenous melatonin level to cope with temperature-induced oxidative burden and further developed heat resistance (Ahammed *et al.*, 2019).

Function of melatonin in salt stress

Salt stress means collection of salt in the soil influences plants in different ways like osmotic burden, ionic stress, oxidative stress, and hormonal variance. The osmotic stress is brought by the overabundance of Na^+ and Cl^- ions in the soil that decline the osmotic potential and hampers the water take-up and supplements. Accordingly, soil salinity is capable of ROS generation in rice greatly impacts the efficiency by limiting the function of enzymatic and non-enzymatic cell defense proteins (Tavakkoli *et al.*, 2011). Melatonin has long been perceived as a positive hormone that can mitigate the harm caused because of salt by diminishing relative electrolyte spillage and better K^+/Na^+ homeostasis. Additionally, melatonin induced the action of nitric oxide synthase (NOS), polyamine content, and the use of arginine, in this manner NO level is expanded in salt-stressed rice seedlings (Yan *et al.*, 2020). Moreover, melatonin with NO regulated the formation of Cu/Zn/Mn-SOD proteins in sunflowers (Arora and Bhatla, 2017). Further, exogenous melatonin lightens oxidative harm instigated due to salt stress by enhancing the expression of ABA and GA biosynthesis (Zhang *et al.*, 2014). Melatonin pre-treatment additionally reduces the growth hindrance and oxidative harm of *Malus hupehensis* by directly scavenging H_2O_2 and increasing the expression of the antioxidant defense-related gene, and by controlling the ion-channel proteins to keep up with homeostasis (Gong *et al.*, 2017).

Effect of melatonin under heavy metal stress

Day by day the quantity of manufacturing plants is sullying the soil and farming area with heavy metals transmitted from industries, harming and diminishing the growth of crop yields gradually. Since, heavy metals like Fe, Mn, Zn, Cu, Mo, Ni, and Co are required by plants at a specific concentration, whereas excessive concentrations of these become harmful to plants

(Chibuike and Obiora, 2014). Conversely, Pb, Cd, Hg, and As are not needed by plants, and these are greatly hurtful to plants (Liping *et al.*, 2017). Accordingly, the accumulation of these heavy metals triggers the ROS production in the chloroplast, mitochondria, and peroxisomes resulting in stomatal closure, increased rate of photorespiration, photosynthesis, and nitrogen metabolism, interrupts the antioxidant system impedes the electron transport chain and lipid peroxidation deteriorates the cell membrane integrity (Sachdev *et al.*, 2021), and thus slow down the growth rate. Further, it was demonstrated that the application of exogenous melatonin as a potent plant growth regulator can alleviate the heavy metals-induced damage due to ROS accumulation, and improve tolerance in plants through the activation of antioxidative defense systems that improve the overall growth and productivity of plants under this stress. Additionally, the exogenous melatonin could be transmitted across plant organs, and expanded concentrations of endogenous melatonin in plants suggest melatonin's contribution to regulating stress tolerance in plants under heavy metal stress (Hoque *et al.*, 2021).

CONCLUSION

Ecological factors like drought, heat, cold, injury, heavy metals, and UV light may increase oxidative burden by generating reactive oxygen/nitrogen species (ROS/RNS) in different cell organelles, nuclei, endoplasmic reticulum, lipid membrane, cytosol, and apoplast. The threshold level of reactive species increases the lipid peroxidation in the plasma membrane, damaging peptides through the carbonylation of proteins, and continuous changes in peptides affect normal cellular functioning. ROS/RNS is a significant source of oxidative harm to nucleic acids through oxidizing its sugar molecule, DNA breaks up, evacuation and modification of nitrogenous bases, DNA-protein interactions, and mismatches with the nucleotide’s resulting defective proteins. Excess concentration of salt and metals deteriorated their DNA concentration through the generation of $^{\bullet}OH$ might harm sugar molecules of nucleotides. Thus, increased reactive species badly affect different cellular, physiological, and biochemical activities and colored pigments. Further, ROS can be killed by enzymatic reactions with anti-oxidative proteins i.e., superoxide dismutase (SOD), catalases, and peroxidases (GPx) considered as the first line of protection (Jena *et al.*, 2023). Additionally, the RNS can be scavenged by a non-enzymatic molecule such as flavonoid, phenolic acids, tryptophan, tocopherol, etc via several complex mechanisms to neutralize the reactive species (Aranda-Rivera *et al.*, 2022).

Despite this, tryptophan-derived melatonin has also been reported as a potent scavenger molecule for RNS and ROS. Melatonin is greatly treated against a few toxins, drugs, and herbicides in animal and plant cells. Though amphiphilic melatonin acts either by directly scavenging ROS produced in cells due to abiotic stress or through its membrane receptor-mediated pathway, an increased Ca^{2+} concentration might further induce the different antioxidant genes to get turned on. Thus, the production of antioxidative proteins such as ascorbate-/glutathione-/halo-peroxidases, glutathione-reductases/synthases, glutathione S-transferases, ascorbate oxidases, monodehydro-/dehydro-ascorbate reductases, peroxi-/thio-redoxins, etc limit the harmful activity of the reactive species in animals and likewise in plants. Similarly, phytomelatonin acts as a defensive molecule against the adverse effects of ultraviolet and drought. Additionally, melatonin application might improve electrolyte spillage, chloroplast activity, water availability, provoked rate of photosynthesis proficiency, and function of stomata under drought stress (Ahmad *et al.*, 2022). Further, melatonin acts cooperatively with auxin and jasmonic acids and adversely with abscisic acid to control the effect of cold stress. The expanded concentration of FAD2 genes under cold stress subsequently enhanced the lipid peroxidation while melatonin treatment brought down the FAD2 genes and lowered the level of lipid peroxidation. Under high-temperature conditions, the degree of melatonin is expanded due to the induction of melatonin biosynthesis which turns on stress-responsive genes (CBF/ DREB) to develop heat tolerance.

The osmotic stress due to the abundance of Na^+ and Cl^- ions in the soil declines the osmotic potential of a cell and hampers the water take-up and supplements. While application of melatonin lowered the relative electrolyte spillage, better K^+/Na^+ homeostasis, increased expression of ABA and GA biosynthesis, and controlled the ion-channel proteins to maintain homeostasis. Further, the accumulation of heavy metals triggers the ROS generation in the cell organelles, interrupts the antioxidants, impedes the electron transport chain and lipid peroxidation deteriorates the cell membrane integrity, and thus slows down the growth rate. While application of exogenous melatonin acts as a potent plant growth regulator might alleviate the heavy metals-induced damage. Finally, we may conclude that exogenous melatonin application may add the level of endogenous phytomelatonin which further might maintain homeostasis by reducing the level of ROS and increasing the expression of antioxidative proteins, growth hormones, and improved photosynthetic proficiency. To this extent, melatonin regulates the imbalance of stressful conditions in plants for its better survival strategies under abiotic threats.

CONFLICTS OF INTEREST

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

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