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Review

Melatonin As a Protective Agent Against Environmental Stresses: A Review into Its Molecular Regulation in Plants

Buti Obaid Saeed Alfalahi [1], Imane Lamdjad [2], Mustafa Alnujaifi [3], Noaman Atallah Alheety [3], Abdul Qayyum [4, *]

1. Emirate Academic, Faculty of Science, United Arab Emirates, AbuDhabi, United Arab Emirates; E-Mail: buttaya86@gmail.com
2. University M'sila, Faculty of Science and Earth, M'sila, Algeria; E-Mail: imane.lamdjad@univ-msila.dz
3. College of Sharia and Law, University of Khorfakkan, Khorfakkan, Sharjah, United Arab Emirates; E-Mail: Mustafa.salim@ukf.ac.ae; Noaman.Mahmood@ukf.ac.ae
4. University of Haripur Pakistan, Department of Agronomy, Khyber, Pakistan; E-Mail: qayyum2811@gmail.com

* **Correspondence:** Abdul Qayyum; E-Mail: qayyum2811@gmail.com

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Abstract

Understanding the impact of melatonin (N-acetyl-5-methoxytryptamine) on plant gene expression is crucial for unlocking its full potential as a tool for crop improvement and stress tolerance. Melatonin has emerged to have several influences on the transcriptional activity of numerous genes, helping to orchestrate plant responses to environmental cues. Furthermore, it has been shown that melatonin signaling pathways control downstream gene expression to ensure proper plant growth and development. Therefore, clearing out the complex interaction between melatonin and plant gene expression has enormous potential to further our knowledge of plant biology and develop novel farming techniques.

In this review, we have gathered the recent studies that elucidate the role of applied melatonin in regulating stress-responsive genes under various abiotic stresses.

Keywords
Melatonin; abiotic stress; gene expression and transcription factors

1. Introduction

Melatonin, commonly known as the "sleep hormone," is an endogenous hormone that regulates the sleep-wake cycle in animals and humans and is produced by the pineal gland [1]. However, it has been found that melatonin is also vital in plants, specifically in gene expression that regulates various plant metabolic, growth, and developmental processes [2-4]. Melatonin can be a signaling molecule regulating plant growth and stress responses [5]. For example, melatonin can upregulate gene expression involved in cell division, ethylene, and isoflavones biosynthesis in *Glycine max* [6]. Furthermore, melatonin has been discovered to promote the production of stress-responsive genes, which helps plants cope with diverse environmental challenges such as drought, salinity, and temperature extremes [7-10].

On the other hand, melatonin has been found to interact with other plant hormones, i.e., auxin [11], ABA [12], polyamines [7], and cytokinin [13]. In addition, multiple lines of evidence suggest that melatonin can affect the expression of genes involved in ROS detoxification and antioxidant defense systems, leading to plant survival under several stressful conditions [3, 14-16]. Furthermore, melatonin is vital in controlling plant gene expression by acting as a transcriptional regulator, affecting various physiological processes [17]. For example, melatonin has been shown to enhance the expression of genes involved in stress tolerance, photosynthesis, and root development while suppressing the expression of genes involved in senescence and cell death [18-20].

It is also involved in epigenetic regulation, which refers to heritable changes in gene expression without any changes in the DNA sequence itself [21]. In this respect, Ahmad *et al.* [21] found that melatonin can influence DNA methylation and histone modifications, which are essential in the epigenetic mechanisms regulating gene expression. Through this modulation of epigenetic marks, melatonin can alter the accessibility of genes to transcription factors, resulting in modifications to gene expression patterns [16]. This review endeavors to understand the molecular mechanisms by which melatonin helps plants cope with various environmental challenges, emphasizing its potential as a protective agent (Figure 1).

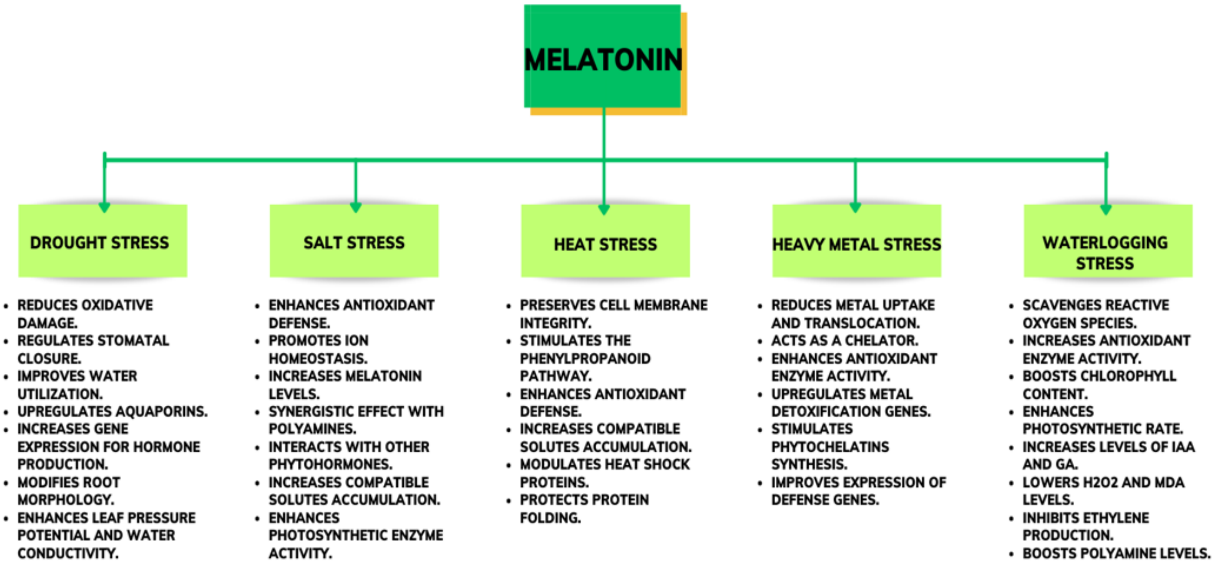

Figure 1 Melatonin acts as a protective agent against various environmental stresses.

2. Melatonin and Delaying of Leaf Senescence

Leaf senescence, or the final stage of leaf development, substantially impacts plant productivity and survival. Melatonin has been shown to slow this process, extending the functional lifespan of leaves. Melatonin has been known as a promoter of the synthesis of photosynthetic pigments in plants. Studies have shown that melatonin can enhance chlorophyll and carotenoid levels in leaves, promoting photosynthetic activity and improving plant growth and development [12, 22, 23]. Melatonin can reduce the produced free radicals by scavenging various cascade reactions and inducing several antioxidative defense systems [10, 12, 24]. It has been found that melatonin can prevent photoinhibition in chloroplast by accelerating the non-photochemical quenching, which protects the structure of photosynthetic proteins and lipids and promotes the xanthophyll cycle [25]. Research suggests that melatonin inhibits the breakdown of chlorophyll by reducing the expression of genes associated with chlorophyll degradation, including pheophorbide an oxygenase (PAO), pheophytinase (*PPH*), red chlorophyll catabolite reductase (*RCCR*), 7-hydroxymethyl chlorophyll a reductase (*HCAR*), Non-Yellowing Coloring 1 like (NOL), and Non-Yellowing Coloring 1 (*NYC1*). Additionally, melatonin restricts the activity of enzymes involved in chlorophyll catabolism, such as chlorophyllase (CLH) and PPH [26-28]. Wu *et al.* [28] found that treating broccoli (*Brassica oleracea* L. var. Italica, cv. Youxiu) with melatonin caused a down-regulation in the expression of genes responsible for breaking down chlorophyll. These genes included *NYC1, NOL, CLH, PPH, PAO, RCCR*, and Stay-Green 1 (*SGR1*). Furthermore, melatonin has been found to be essential in controlling the transcriptional reprogramming of senescing leaves, i.e., *NACs, WRKYs,* and DREBs [20]. In another study, Martinez *et al.* [29] found that the application of melatonin to apple plants resulted in a delay in leaf senescence. This delay was achieved by inhibiting the expression of specific genes involved in chlorophyll degradation, including notably senescence-associated gene 12 (*SAG12*) and auxin-resistant 3 (*AXR3*)/indole-3-acetic acid inducible 17 (*IAA17*). Moving on from the topic of leaf senescence, it is critical to investigate how melatonin's protective properties apply to various environmental stressors, beginning with drought stress.

3. Melatonin and Alleviating of Drought Stress

Drought stress has a severe impact on plant growth and yield. Drought stress is a major environmental factor that limits crop productivity and threatens global food security [30]. It has been found that applying melatonin externally can reduce oxidative damage caused by drought, regulate stomata closure, and improve water utilization efficiency in plants [2, 22, 31]. Under water deficit conditions, melatonin regulates the expression of various genes responsible for producing plant hormones such as ABA, IAA, GAs, CKs, ethylene jasmonic acid (JA), and brassinosteroids. This regulation occurs by increasing the expression of hormone receptors, associated signaling elements, and biosynthesis enzymes [32]. Moreover, melatonin has been found to upregulate specific aquaporins, membrane proteins responsible for water transport, facilitating water uptake and its distribution throughout the plant tissues [32]. In this respect, it has been found that exogenous melatonin enhanced the leaf pressure potential (Lpr) and the water conductivity of the plant (K_{plant}) in maize plants by upregulating PIP aquaporin genes, which are responsible for water transport in the presence of drought stress [33]. It was also reported that the rhizospheric application of melatonin increases the mRNA expression level of TIP aquaporins and prevents water loss in barley [34]. According to Xia *et al.* [35], melatonin can also increase the expression levels of the MAPKs Asmap1 and *Aspk11*, as well as the *WRKY1*, *DREB2*, and *MYB* transcription factor genes in oat seedlings under drought stress. These findings suggest that activating the MAPK cascade may be necessary for melatonin to induce the antioxidant response and regulate the expression of genes relevant to antioxidants. Besides, melatonin has been reported to modify root morphology and promote root elongation, enabling plants to explore deeper soil layers with higher water availability [36]. On the other hand, melatonin has been shown to regulate stomatal closure during drought stress, allowing plants to strike a balance between water conservation and efficient CO_2 fixation [37]. This modulation occurs through melatonin-mediated regulation of abscisic acid (ABA), an essential hormone involved in stomatal movement, suggesting a potential interplay between melatonin and other signaling molecules to fine-tune stomatal responses and optimize plant water-use efficiency [38]. After discussing drought stress, we will look at how melatonin might assist in combating salt stress, another common environmental challenge.

4. Melatonin and Alleviating of Salt Stress

Salt stress impairs plant health by creating ionic imbalance and osmotic stress. Exogenous melatonin has been found to mediate salt tolerance in plants by several interactions with MAP kinase signaling pathways. In this regard, melatonin has been found to upregulate significantly the expression of antioxidant enzyme genes, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase genes, mitogen-activated protein kinase (MAPK) genes (*MAPK3, MAPK4, MAPK6*) and salt overly sensitive (SOS) genes (*SOS1, SOS2, SOS3*) in salt-stressed cucumber plants [39]. Furthermore, melatonin can promote ion homeostasis, specifically the Na/K ratio under salt stress. This response is associated with the upregulation of several genes, such as *NHX, SOS,* and *AKT* [40]. Li *et al.* [41] found that exogenous melatonin significantly increased the expression of *MdNHX1* and *MdAKT1* genes in the salt-stressed seedlings of *Malus hupehensis.* This observation was in line with elevating the levels of potassium (K^+) and the ratio of K^+ to sodium (Na^+) in plant issues. On the other hand, exogenous melatonin can induce an elevation in endogenous melatonin levels through activation of the phyto-melatonin receptor CAND2/PMTR1 [41]. Melatonin has been found to synergize with polyamines and reduce their catabolism in snap bean seedlings under salinity stress, leading to multiple protective effects against salt stress [7]. Melatonin also interacts with the other phytohormones by affecting their biosynthetic-related genes. For example, exogenous melatonin has been found to down-regulate *NCED1* and *CsNCED2,* which serve as ABA synthesis-related genes. At the same time, ABA catabolism-related genes and GA biosynthesis-related genes (*GA20ox* and *GA3ox*) were upregulated [40]. One key mechanism through which melatonin modulates salt stress is by enhancing antioxidant defense systems [42]. In this context, Zhang *et al.* [43] found that exogenous melatonin increased the expression of genes associated with the removal of reactive oxygen species (ROS), including *CsCu-ZnSOD*, *CsFe-ZnSOD*, *CsPOD,* and *CsCAT* in salt-stressed cucumber seedlings. Moreover, melatonin promotes the accumulation of compatible solutes, such as proline and free amino acids and total soluble sugars, which protect plants from osmotic stress caused by high salt concentration [7, 38, 44]. Additionally, previous studies have shown that melatonin enhances the activity of critical enzymes that are involved in photosynthesis, such as Rubisco and ATP synthase, thus ensuring efficient energy production in the presence of salt stress by enhancing the efficiency of the electron transport chain, which increases ATP production and thereby facilitates plant resilience under salt stress [45, 46]. Temperature extremes, in addition to salt stress, are a critical stress factor that affects plant health. Let's look at how melatonin helps with both low and high-temperature stress.

5. Melatonin and Alleviating of Heat Stress: Low and High Temperatures

Extreme temperatures, both high and low, could significantly impact plant metabolism and growth. Low temperatures (chilling stress) significantly impact plant cell membrane integrity, critical for preserving cellular functioning [47]. The physical characteristics of the membrane's lipids lose some of their fluidity and may go through a phase change, increasing its vulnerability to cold injury [48-50]. In a previous study on tomato fruits during cold storage, exogenous melatonin (100 μM) has been found to decrease the chilling injury by supplying enough intracellular ATP and enhancing the activities of H^+-ATPase, Ca-ATPase, cytochrome C oxidase (CCO), and succinate dehydrogenase (SDH) [51]. At the same time, these responses were associated with preserving the integrity of the cellular membranes by achieving a higher ratio of unsaturated to saturated fatty acids by increasing the expression of the *FAD3* and *FAD7* genes and decreasing *PLD* and *LOX* genes [51]. Moreover, applied melatonin has been found to stimulate the phenylpropanoid pathway by promoting the activities of phenylalanine ammonia-lyase (PAL), 4-coumarate-coenzyme A ligase (4CL), cinnamate-4-hydroxylase (4CH) and peroxidase (POD), and accompanied by higher contents of total phenols and lignin, which might be contributed to improving the temperature tolerance in plum fruit during storage [52]. The antioxidant property of melatonin can also prevent cellular damage and maintain cell membranes' structural and functional integrity under low-temperature conditions [53-56].

On the other hand, high temperatures have detrimental effects on different physiological processes, decreasing plant growth and even leading to cell death [57]. It can disrupt plant water balance, leading to dehydration and wilting [58]. Melatonin has been found to enhance the accumulation of compatible solutes, such as proline and soluble sugars, which act as osmoprotectants under heat stress [3, 14, 59]. Also, applied melatonin can increase plant thermotolerance by modulating the expression of heat shock proteins (HSPs) [60]. In this context, melatonin significantly stimulated the expression of the carotenoid biosynthesis gene in the presence of 10 *de novo* HSPs in kiwifruit [61]. Furthermore, melatonin can protect plant cells from heat-induced damage by affecting protein folding and preventing its denaturation [62].

Additionally, melatonin has been demonstrated to increase the antioxidative capacity of *Camellia sinensis* L under heat stress by increasing the transcript levels of catechins biosynthesis genes, including *CsCHS, CsCH1, CsF3H, CsDFR, CsANS, CsLAR,* and *CsANR* [63]. In addition to temperature, contamination by heavy metals in soils is another significant stressor. The following section explores how melatonin helps plants deal with heavy metal stress.

6. Melatonin and Alleviating of Heavy Metal Stress

Heavy metal stress occurs when harmful metals accumulate in plant tissues, inducing oxidative damage and diminished physiological functioning. Heavy metals are toxic elements that can accumulate in plants and pose serious health risks to humans and ecosystems [64]. Melatonin has been shown to play a crucial role in regulating heavy metal accumulation in plants [65]. Research suggests that melatonin can mitigate the harmful effects of heavy metals by reducing metal uptake and translocation within the plant [66]. This hormone acts as a chelator, binding to heavy metals and forming less toxic complexes and more easily excreted [67].

Additionally, melatonin can enhance the activity of antioxidant enzymes, which help combat the oxidative stress induced by heavy metal toxicity [68]. By regulating metal accumulation, melatonin contributes to plants' overall health and resilience in metal-contaminated environments. Furthermore, melatonin possesses a unique ability to induce metal detoxification mechanisms in plants. Studies have found that melatonin can upregulate the expression of genes involved in metal detoxification, including metallothioneins and transporters that facilitate metal sequestration in vacuoles [69]. This upregulation enhances the plant's ability to cope with heavy metal stress and reduces the toxic effects caused by metal accumulation in vital plant tissues.

Moreover, melatonin can stimulate the synthesis of phytochelatins, small proteins that bind to heavy metals, and enhance their sequestration and detoxification within plants [70]. In a previous study on copper toxicity in tomato seedlings, applied melatonin improved the expression of several defense genes (CAT, APX, GR, and MDHAR) and melatonin biosynthesis-related genes, i.e., *TDC, SNAT, and COMT* [71]. Under nickel toxicity, Jahan *et al.* [26] found that tomato seedlings treated with melatonin effectively inhibited the generation of hydrogen peroxide (H_2O_2) and superoxide radicals. It also raised the expression of *RBOH* and restored cellular integrity by reducing malondialdehyde levels and electrolyte leakage. This effect was achieved by activating antioxidant enzymes and regulating the AsA-GSH pools. The study found that nickel-induced oxidative stress was successfully reduced by upregulating the expression of many defense genes (*SOD, CAT, APX, GR, GST, MDHAR, DHAR*) and genes associated with melatonin production (*TDC, T5S, SNAT, ASMT*). Yet another stressor to consider is waterlogging, which may also harm plant life. The next part will address how melatonin assists in alleviating waterlogging stress.

7. Melatonin and Alleviating Waterlogging

Plants under wet conditions experience hypoxia or low oxygen levels, which set off a series of physiological and biochemical reactions [72]. Melatonin uses a variety of regulatory systems to assist plants in lessening the negative consequences of waterlogging. Plants experience oxidative stress due to the overproduction of reactive oxygen species (ROS) brought on by waterlogging. Melatonin, a potent antioxidant, is essential for scavenging ROS and decreasing oxidative damage in a variety of plant species, including wheat [73], alfalfa [74], kiwifruit [75], and maize [76]. Previous research showed that the MDA content of maize seedlings decreased when melatonin was used under waterlogging stress [76]. Several studies have indicated that melatonin increases the activity of antioxidant enzymes like SOD, POD, and CAT [22, 77]. In recent work on cotton grown under waterlogging, melatonin also boosted leaf chlorophyll content, photosynthetic rate, IAA and gibberellic acid (GA) levels, as well as SOD, POD, and CAT activity [72]. Melatonin, on the other hand, lowered the concentrations of H_2O_2, MDA, and ABA, as well as the activities of alcohol dehydrogenase (ADH) and pyruvate decarboxylase (PDC), when compared to waterlogging without using melatonin [72].

Additionally, melatonin increased the expression of the melatonin biosynthesis genes *GhSNAT1* and *GhCOMT* and the gibberellin biosynthesis gene *GhGA20ox1,* compared to non-waterlogged cotton. Melatonin, on the other hand, reduced the expression of the ABA synthesis gene *GhNCED2*, the H_2O_2 generating gene *GhRBOHC*, and the glycolysis and fermentation gene *GhADH2* [72]. In alfalfa, melatonin inhibited ethylene production by downregulating ethylene biosynthesis-related genes and preventing waterlogging-induced growth decrease, chlorosis, and early senescence in plants. Also, melatonin boosts polyamine levels by increasing polyamine metabolism enzymes' activity and gene expression [74]. These reactions allow plants to adapt to and endure extended durations of water saturation.

8. Conclusion and Future Prospective

In conclusion, melatonin is a crucial hormonal regulator of gene expression in plants, playing a significant role in plant development, growth, and stress response. Its ability to interact with transcription factors and modulate epigenetic mechanisms gives plants a dynamic and flexible way to adapt to changing environmental conditions. Besides, the molecular mechanisms behind melatonin's plant activities are still unknown. Despite enormous advances, more extensive investigations are needed to explain the mechanisms involved and identify melatonin's direct targets in plant cells. Further research into the specific genes and pathways regulated by melatonin in plants will uncover more insights into its role in plant biology. Additional research is required to fully understand the intricate molecular mechanisms underlying this relationship. Still, the findings offer promising avenues for remediation strategies in metal-contaminated soils and environments. By harnessing melatonin's potential, we may develop innovative approaches to mitigate heavy metal toxicity in plants and promote ecological sustainability. Another point of contention is whether melatonin occurs naturally in plants. Some researchers wonder whether the quantities of melatonin found in plants can produce the documented protective effects or if the high doses utilized in experiments artificially enhance the molecule's influence. Still, the possible ecological and environmental consequences of broad melatonin use in agriculture are in doubt. The long-term implications on plant health, soil microbiology, and overall ecosystem balance should be further investigated. By addressing these unaddressed issues and improving our understanding of melatonin's mechanisms, we can better take advantage of its benefits to boost plant resilience and productivity in agriculture.

Author Contributions

B. O. S. Al-Falahi, I. Lamdjad conceived the idea; M. Al-Nujaifi and N. A. Alheety visualisation, A. Qayyum resources B. O. S. Al-Falahi, funding B. O. S. Al-Falahi and I. Lamdjad, revision; B. O. S. Al-Falahi, I. Lamdjad wrote the draft of manuscript, A. Qayyum supervision; all authors contributed to writing the manuscript.

Competing Interests

The authors have declared that no competing interests exist.

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