



A Review of Melatonin metabolism with reference to Plants

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Abstract

Melatonin, originally identified as a mammalian neurohormone, antioxidant, and signaling molecule, was later discovered in plants in 1995. The early studies on plant melatonin primarily viewed it from a human perspective, focusing on quantifying melatonin in foods and medicinal plants. Researchers questioned whether its presence could explain the medicinal properties of certain plants. Since those initial studies in the late 1990s, the field of plant melatonin research has experienced exponential growth, becoming a vibrant and actively investigated area.

Melatonin has been found to play crucial roles in various aspects of plant life, influencing responses and development at every stage of the plant life cycle, including pollen and embryo development, seed germination, vegetative growth, and stress responses.

The review covers various aspects of melatonin research in plants, including its biosynthesis and metabolism. It highlights key themes such as abiotic stress responses, root development, light responses, inter-kingdom communication, phytohormones, and plant signaling. Additionally, the review explores potential biases in the literature, particularly the divide between plant-based and medical researchers, which has influenced the direction of melatonin research in plants.

The review also identifies exciting opportunities for future research in melatonin, including investigations into non-crop and non-medicinal plant species and the characterization of melatonin signaling networks in plants. This comprehensive overview of melatonin research in plants provides valuable insights into its multifaceted roles and its potential impact on agriculture, ecosystems, and human health.

Keywords: Melatonin, Phytohormone, Metabolism, Review.

Introduction

Melatonin, initially discovered as a crucial physiological molecule in animals, serves as a multifaceted neuro-hormone, antioxidant, and signaling molecule. Subsequently, in 1995, its presence was identified in plants, sparking extensive research across various plant species. This research has unveiled melatonin as a pervasive physiological regulator, spanning from unicellular algae to higher plants (Dubbels et al., 1995; Hattori et al., 1995; Fan et al., 2018; Arnao and Hernández-Ruiz, 2019; Zhang and Zhnag, 2021; Ahmad et al., 2023).

In plants, melatonin takes on the role of orchestrating metabolic pathways crucial for growth and development. It exerts its influence on processes like seed germination, root development, overall growth, flowering timing, fruit maturation, and the regulation of leaf senescence. Melatonin is distributed throughout various plant parts, including leaves, stems, roots, fruits, and seeds. In contrast to mobile animals, plants, being sessile, rely on melatonin as a mechanism to confront environmental stresses. They adapt strategies to survive adverse conditions, a vital necessity given the array of factors, especially environmental stressors, influencing their status during growth and development. These ecological stresses encompass both biotic and abiotic factors, which can lead to yield reduction, growth impediment, senescence, and even plant mortality. It is now widely acknowledged in the scientific community that melatonin is an indispensable player in plant development and their responses to stressors (Van Tassel and O'Neill, 2001; Parades et al., 2009; Ahmad et al., 2023; Colombage et al., 2023).

Studies have revealed that melatonin in plants functions as a hormone and collaborates with other plant hormones. Its role extends beyond stress response, encompassing cold, salinity, drought, oxidative stress, and nutrient deficiency. It also plays a pivotal role in regulating plant development, including circadian rhythms, growth, senescence, root organogenesis,

flowering, and photoperiodic responses. Melatonin exhibits potent antioxidant capabilities by effectively scavenging free radicals and enhancing the activity of other free radical-scavenging enzymes like superoxide dismutase. Furthermore, it significantly influences fruit quality and preservation by promoting ripening and delaying senescence. Melatonin achieves these effects by regulating genes involved in secondary metabolism, Ethylene (ET) signaling, flavonoids, cell wall modification, senescence-related processes, carbohydrate metabolism, and the Ascorbate–Glutathione (ASC–GSH) cycle. The specific mechanisms by which melatonin operates in plants have been gradually elucidated (Lee et al, 2014a; 2014b; Arnao and Hernández-Ruiz, 2020; Zhang and Zhang 2021; Ahmad et al., 2023; Colombage et al., 2023).

The content of melatonin in plants varies by species, growth stage, and environmental conditions. Additionally, differences in extraction and detection processes can lead to variations in melatonin quantification among plant samples (Murch et al., 2004; Afreen et al., 2006; Reiter et al., 2007; Liu et al., 2022; Asif et al., 2023).

Melatonin shares its initial biosynthesis compound with the plant growth hormone auxin, making it function as an indole-3-acetic acid-like hormone. It is also instrumental in regulating plant growth and development and conferring protection against various biotic and abiotic stresses, including salt, drought, cold, heat, and heavy metal stresses. Melatonin enhances stress tolerance through both direct pathways, where it scavenges reactive oxygen species directly, and indirect pathways, including the elevation of antioxidative enzyme activity, improvement in photosynthetic efficiency, and alteration of metabolite content. Moreover, melatonin influences gene expression in plants, thereby affecting overall plant performance. Recent investigations underscore melatonin's widespread and multifunctional role in the plant kingdom (Dubbels et al., 1995; Earland et al., 2015; Chen et al., 2017; Chio et al., 2019; Arnao et al., 2022).

This review article delves into the metabolic processes, including biosynthesis pathways, regulation of growth and development, and responses to environmental stress, of melatonin in plants. It also outlines future research directions and priorities in understanding the role of melatonin in plants.

Brief review of literature

Our study has revealed a notable divergence within the field of plant melatonin research, resulting in distinct clusters of authors and specialized areas of focus. These divergent paths of inquiry have enriched our understanding of the multifaceted role of melatonin in plants.

1. Medical and Human Health Perspective:

Researchers with backgrounds in medicine and human health, where melatonin serves as a master regulator of circadian rhythms, initially drew inspiration from mammalian systems. Their primary focus was on exploring the implications of dietary sources of melatonin for human health. This line of research has borne fruit, contributing significantly to our comprehension of the health effects associated with the consumption of melatonin-rich plants by humans and animals. Such plants have been investigated for their potential as foods and medicines, and their role as a neurohormone in humans has spurred interest in melatonin's bioactivity and synergy with other bioactives in medicinal plants, herbal products, and dietary supplements. For instance, melatonin has been studied in conjunction with sleep aids, medicinal herbs (e.g., valerian, passionflower, chamomile), psychoactive plants (e.g., Cannabis, Datura, Papaver), and even in the treatment of neurological conditions like migraines. Additionally, the rise of plant-based melatonin supplements has gained popularity, especially in response to the increased demand for melatonin during the treatment of coronavirus disease-19 ((Dubbels *et al.*, 1995; Hattori *et al.*, 1995; Vogler *et al.*, 1998; Reiter *et al.*, 2005; Murch *et al.*, 2009; Allegrone *et al.*, 2019; Back, 2020).

2. Plant Sciences Perspective:

Concurrently, scientists well-versed in plant sciences were intrigued by the structural similarity between melatonin and the plant growth regulator indole-3-acetic acid (IAA), also known as auxin. This led to in-depth investigations into melatonin's role in fundamental plant processes such as root growth, seed germination, and the control of plant morphology. Research in this domain has significantly expanded our knowledge of how melatonin influences these critical aspects of plant biology (Pelagio-Flores *et al.*, 2012; Zhang *et al.*, 2014; Erland *et al.*, 2018).

3. Ecological Emphasis:

Another distinct line of inquiry has emerged, focusing on the ecological implications of melatonin in plants. Researchers in this field have explored the broader ecological functions of melatonin, including its role in plant adaptation, evolution, and its ability to mitigate the impact of environmental stresses. This perspective has shed light on how melatonin contributes to the resilience of plant species in the face of changing environmental conditions (Tan *et al.*, 2014; Arnao and Hernández-Ruiz, 2019c).

In this comprehensive review, our primary aim has been to harmonize these diverse research approaches and viewpoints, fostering a cross-disciplinary understanding of the synergies that exist at the intersections of these specialized fields. By doing so, we hope to unlock new possibilities for innovation and collaboration in the study of melatonin's multifaceted roles in plants. This collaborative approach promises to yield valuable insights with far-reaching implications for both human health and plant biology.

Biosynthesis of plant melatonin via multiple pathways:

Our research underscores the intricate nature of melatonin biosynthesis in plants, which is notably more complex than in animals. It's noteworthy that plants possess a remarkable capacity to

synthesize larger quantities of melatonin compared to animals. Within plant cells, melatonin biosynthesis predominantly occurs in the mitochondria and chloroplasts, with a primary focus on chloroplasts. Interestingly, if the chloroplast pathway for melatonin production is obstructed, plants activate the mitochondrial pathway to maintain melatonin homeostasis. Depending on the specific tissue and crop under examination, melatonin levels in plants can range from picograms to micrograms per gram of tissue (Huerto-Delgadillo et al., 1994; Zhao et al., 2019; Tan et al., 2020).

Tryptophan, the Precursor:

A key precursor in the enzymatic steps leading to the production of melatonin and phytomelatonin, both in plants and animals, is tryptophan (Arnao et al., 2022; Liu et al., 2022....). The primary biosynthesis processes of melatonin revolve around two critical conversions: the transformation of tryptophan into serotonin and the conversion of serotonin into melatonin.

Enzymatic Players:

The biosynthesis of phytomelatonin in plants involves at least six key enzymes, which include Tryptophan hydroxylase (TPH), tryptophan decarboxylase (TDC), tryptamine 5-hydroxylase (T5H), serotonin N-acetyltransferase (SNAT), N-acetylserotoninmethyltransferase (ASMT), and caffeic acid O-methyltransferase (COMT) (Arnao et al., 2022; G. Liu et al., 2022; Liu et al., 2022). It's worth noting that, with the exception of TPH, all these enzymes have been successfully cloned in plants. SNAT and ASMT were formerly known as hydroxyindole O-methyltransferase (HIOMT) and aralkylamine N-acetyltransferase (AANAT), respectively (Kolar et al., 1997; Kolar et al., 2003).

Divergence from Mammalian Pathways:

While it was initially believed that plants and mammals shared identical biochemical processes for melatonin production, subsequent research revealed distinct pathways for each. In plants, melatonin is synthesized from the aromatic amino

acid tryptophan. Radio-labeling experiments using ¹⁴C-tryptophan demonstrated rapid conversion to melatonin in in-vitro grown plantlets over two decades ago (Murch et al., 2000; Armo et al., 2019a; Armo et al., 2020). Over the years, molecular investigations have uncovered the complete pathway for melatonin biosynthesis in plants, as well as several alternative mechanisms.

The Primary Pathway:

In the principal pathway, tryptophan decarboxylase (TDC) catalyzes the decarboxylation of tryptophan into tryptamine (TDC; Zhou et al., 2020). Notably, some *Arabidopsis* ecotypes lack TDC1, and this diversity in *Arabidopsis* ecotypes' response to melatonin exposure suggests that this mechanism may not be conserved across all plant species (Zia et al., 2019). Subsequently, tryptamine-5-hydroxylase converts tryptamine into serotonin (5HT; 5-hydroxytryptamine) (Kang et al., 2007)(Fig. 1).

Melatonin Production:

The conversion of serotonin (5HT) to melatonin in plants takes place through two primary intermediates. One involves the formation of N-acetylserotonin (NAS), catalyzed by serotonin-N-acetyltransferase (SNAT), which follows a pathway similar to that in animals (Kang et al., 2013). The other pathway leads to the creation of 5-methoxytryptamine (5-MT), catalyzed by caffeic acid-O-methyltransferase (COMT) (Lee et al., 2014). SNAT can catalyze the acetylation of 5-MT to form melatonin and utilize tryptamine as a substrate for NAS production, eliminating the necessity to produce 5HT (Byeon et al., 2013). Recently, a new enzyme called NAS deacetylase (ASDAC) has been characterized, enabling the conversion of NAS to 5HT or melatonin to 5-MT, indicating the potential for interconversion between 5HT and melatonin (Lee et al., 2018). The final step in the primary pathway involves the methylation of NAS to melatonin, catalyzed by the enzyme NAS methyltransferase (ASMT) or COMT (Byeon et al., 2014).

Subcellular Synthesis:

Melatonin biosynthesis occurs within plant mitochondria and chloroplasts, with some involvement in the cytosol (Zheng et al., 2017; Wang et al., 2017). Nevertheless, the characterization of melatonin transport proteins in plants remains an area that requires further investigation.

In conclusion, the diverse biosynthetic pathways for melatonin in plants present significant

challenges and opportunities for future research. The existence of alternative pathways, along with the potential for convergent or divergent evolution between plant families and species, underscores the complexity of melatonin biosynthesis in plants. Further exploration is essential to comprehensively understand the significance of these various mechanisms and their implications for plant function and adaptation.

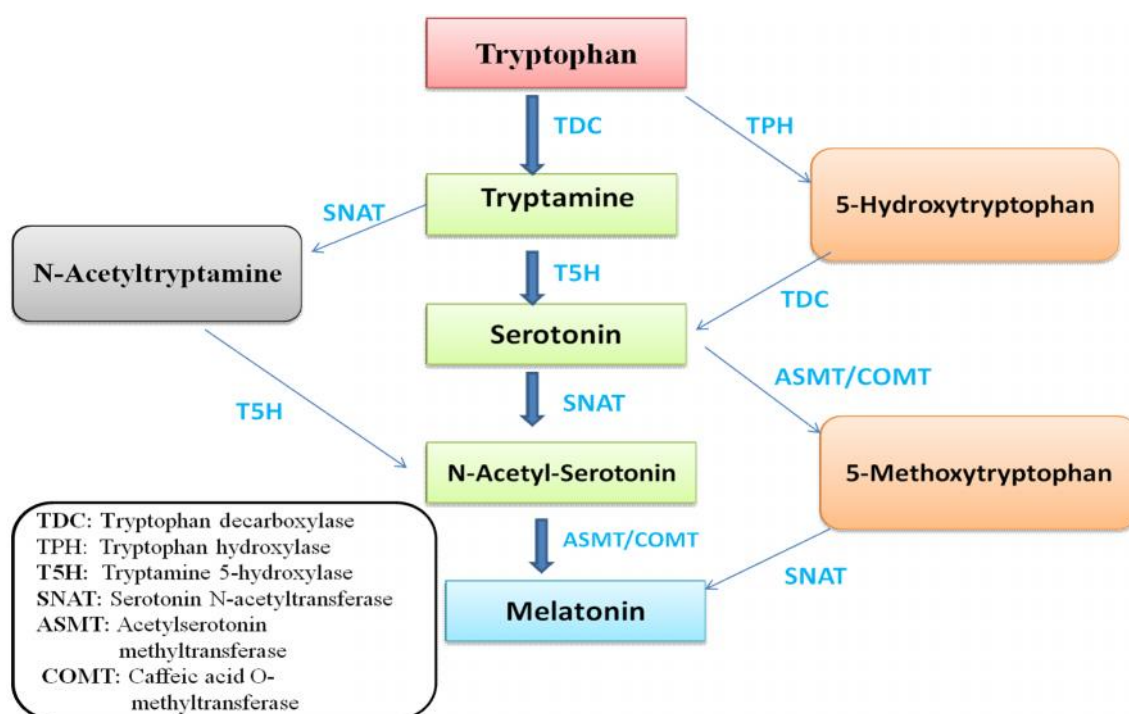


Fig. 1. Melatonin biosynthesis pathway of in plants.

Melatonin a precursor of bioactive metabolites

In the realm of plant melatonin metabolism, the compound undergoes transformations to yield a range of significant bioactive molecules, broadly categorized into (a) conjugates and derivatives, (b) catabolic products, and (c) products generated through oxidation reactions.

Oxidation Products:

Among these derivatives, a set of 5-methoxytryptamine (5-MT) derivatives, including

nitrosomelatonin, N-acetyl-N-formyl-5-methoxykynuramine (AFMK), and N-acetyl-5-methoxykynuramine (AMK), emerge as byproducts of oxidation reactions. Notably, AFMK and AMK were the first melatonin metabolites identified in plants. These compounds exhibit the remarkable ability to quench both reactive oxygen species (ROS) and reactive nitrogen species (RNS), contributing to their role as crucial antioxidants (Tan et al., 2007b; Schaefer and Hardeland, 2009; Armo et al., 2019a; Armo et al., 2020).

Oxidation Mechanisms:

The precise mechanisms underlying the generation of AFMK, whether enzymatic or non-enzymatic, remain subjects of debate. Some research suggests that indole-2,3-dioxygenase (IDO) may catalyze this conversion, although controversies surround this hypothesis, given that tryptophan is typically the primary substrate for IDO (Okazaki et al., 2010). The correlation between AFMK levels and melatonin levels in plants further adds complexity to this discussion (Tan et al., 2007a).

Less Explored Derivatives:

Relatively less attention has been devoted to exploring the 5-MT metabolites 5-methoxytryptophol (5-ML) and 5-methoxyindole-3-acetaldehyde (5-MIAA) in plants, although their roles as products of melatonin catabolism in dinoflagellates are somewhat understood (Hardeland, 2014).

Antioxidant Role:

In plants, melatonin oxidation products, as well as nitrosomelatonin, serve pivotal roles as antioxidants. Additionally, conjugates formed may act as forms of storage or sequestration. Although melatonin-phenolic compound existence and function in plants have not been definitively established, phenolic-conjugates of the melatonin precursor, serotonin (5HT), have been demonstrated to play roles in plant defense mechanisms (Ishihara et al., 2008; Erland et al., 2020b).

Hydroxymelatonin Isomers:

Another intriguing facet of plant melatonin metabolism involves hydroxymelatonin isomers, with "hydroxymelatonin" and "isomer" mentioned in 14 titles and abstracts each. Among these, 2-hydroxymelatonin (2-OHM) emerges as the most frequently cited term, appearing in 12 titles and abstracts. Some studies propose that certain metabolites, particularly 2-OHM and 3-hydroxymelatonin (3-OHM), produced by the

enzymes melatonin 2-hydroxylase (M2H) and melatonin 3-hydroxylase (M3H), respectively, may serve as the predominant forms of melatonin in plants (Iriti and Vigentini, 2015; Hu et al., 2020).

Functions of Hydroxymelatonin Isomers:

2-OHM has been linked to imparting tolerance to various abiotic stresses, including cold, drought, salt, and heavy metal stress. It achieves this through both direct antioxidant activities and the upregulation of antioxidant enzymes. Additionally, 2-OHM has been associated with modulating gene expression related to stress-related transcription factors, transport proteins, and activating MAPK signaling cascades (Ishihara et al., 2008; Beyon et al., 2015a, 2015b; Hwang et al., 2018).

In summary, while the existence of melatonin metabolites in plants is well-established, their precise functions remain a subject of ongoing research. Given the myriad potential roles and interactions, further investigations into the functions and quantification of these compounds are imperative. Future research should aim to unravel the complexities of these metabolites and isomers in plant metabolism to gain deeper insights into their significance.

Conclusions

The presence of small molecule melatonin in plant cells, with its diverse properties including antioxidant effects, growth regulation, and signaling capabilities, underscores the significance of melatonin in plant biology. The secretion of melatonin in plants primarily occurs in the cytoplasm, and the entire secretion pathway is intricate and multifaceted.

The field of plant melatonin research is rapidly expanding, and it will continue to be an active area of study with far-reaching implications for ecosystems, agriculture, and human health. However, there are notable gaps and biases in the existing literature that warrant attention.

Future research in plant melatonin should consider:

Non-Medicinal and Non-Crop Species: While much of the existing research has focused on medicinal and crop species, there is a need to explore the role of melatonin in a broader range of plant species, including those not traditionally studied for their medicinal or economic value. Understanding melatonin's function in various plant types can provide valuable insights into its ecological significance.

Functional Mechanisms: In addition to identifying the presence of melatonin, future research should emphasize understanding the specific functions and mechanisms of action of melatonin in plants. How does it modulate various physiological processes, and what are the underlying molecular pathways?

Melatonin Signaling Cascades: Investigating melatonin signaling cascades in plants is crucial. This involves identifying the downstream components that mediate melatonin's effects on gene expression, growth, and stress responses.

Melatonin Receptors: The existence and characterization of melatonin receptors in plants remain an important area of study. Identifying these receptors and understanding how they interact with melatonin can provide insights into the specificity of melatonin's actions.

Melatonin Interacting Proteins: Exploring the proteins that interact with melatonin in plant cells can reveal additional layers of melatonin's regulatory functions.

These areas represent just a few of the many promising avenues for future research in plant melatonin. As our understanding of plant melatonin deepens, it will contribute to a more comprehensive picture of its roles in plant biology and its broader ecological and agricultural implications.


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