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Review

Is Phytomelatonin a New Plant Hormone?

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Abstract: Melatonin (*N*-acetyl-5-methoxytryptamine) is of particular importance as a chronobiological hormone in mammals, acting as a signal of darkness that provides information to the brain and peripheral organs. It is an endogenous synchronizer for both endocrine (i.e., via neurotransmitter release) and other physiological rhythms. In this work we will try to add to the series of scientific events and discoveries made in plants that, surprisingly, confirm the great similarity of action of melatonin in animals and plants. The most relevant milestones on the 25 years of phytomelatonin studies are presented, from its discovery in 1995 to the discovery of its receptor in plants in 2018, suggesting it should be regarded as a new plant hormone.

Keywords: biological clock; melatonin; photosynthesis; phytomelatonin; plant hormone; plant stress; redox network

1. Introduction

Melatonin (*N*-acetyl-5-methoxytryptamine) was discovered in 1958 in the pineal gland of a cow by Lerner and cols. [1]. This isolated, active factor lightens skin color in frogs, tadpoles, toads and certain fish, but not in mammals, as a consequence of the aggregation of melanin granules of melanocytes. For this reason, the authors proposed that the substance be called *melatonin*, and it was chemically identified in 1959 as a derivative of *N*-acetylserotonin [2].

Melatonin is of particular importance as a chronobiological hormone, acting as a signal of darkness that provides information to the brain and peripheral organs. It is an endogenous synchronizer for both endocrine (i.e., via neurotransmitter release) and other physiological rhythms, regulating sleep-wake cycles and synchronizing life activity into seasonal periods and reproductive functions [3–11].

Melatonin plays an important role in the regulation of sleep, body temperature, the state of alertness and degree of concentration or performance, and cortisol rhythms. It acts as a sleep initiator by opening the circadian sleep gate, thus acting as a sleep regulator. Melatonin adjusts the timing of or reinforces the oscillators of the central biological clock. The administration of exogenous melatonin alters the timing of bodily rhythms, including sleep, whereby phase delays are observed with the morning administration of melatonin, while phase advances are found after evening administration [12]. Many sleep disorders have been treated with melatonin: delayed sleep phase syndrome, night shift work sleep disorder, seasonal affective disorder, sleep disorders in the blind and ageing, and pathophysiological disorders of children, with notable improvements in "sleep quality" [13]. The most common disorder treated with melatonin is jet lag, a de-phasing in the sleep-wake rhythms caused by transoceanic flights [14–16].

In mammals, melatonin is secreted by the pineal gland to the cerebrospinal fluid and to the bloodstream, presenting maximal levels during the middle of the night. This circadian pattern of melatonin secretion is regulated by the biological clock that resides in mammals within the hypothalamic suprachiasmatic nucleus (SCN) [17]. The SCN is synchronized to the environmental light-dark cycle by the light perceived by the retina. Also, the SCN regulates pineal secretion through a polysynaptic network in the paraventricular nucleus of the hypothalamus [18]. Melatonin release occurs when the noradrenaline released by paraventricular nucleus fibers activate the pineal β-adrenergic receptors, stimulating, via cyclic AMP (adenosine 3-phosphate), the expression of serotonin *N*-acetyltransferase (SNAT), a key enzyme of melatonin biosynthesis, in the dark. Brief exposure to light provokes a decrease in melatonin production because of the degradation of SNAT in the pineal gland [19–21].

Until recently, it was thought that this whole process and situation had nothing to do with plant systems, and no coincidence of action was suspected. As will be seen later, the discovery of melatonin in plants, called phytomelatonin, has meant a considerable change in studies of many aspects of plant physiology. Thus, phytomelatonin has been involved in aspects such as germination, growth, rooting, fruiting, parthenocarpy, maturation, and in post-harvest. It has also been studied in key processes, such as primary/secondary metabolism, photosynthesis, senescence and CO_2 intake, and in the nitrogen, phosphorus, and sulfur cycles. Also, one of the most decisive aspects has been its recognized role as a protective and alleviating agent against stressors, both biotic and abiotic. This last aspect has opened a great field of action to be able to use melatonin in agricultural treatments, such as phytoprotective and biostimulant. However, below we will try to explain the series of scientific events and discoveries in plants that, surprisingly, testify to the great similarity of action of melatonin in animals and plants. In this respect, we explain the most relevant milestones of phytomelatonin for it to be considered as a new plant hormone.

2. Topics of the First Fifteen Years

As with most of the discoveries made concerning classical plant hormones, the story of events begins with its detection in plant tissues, its metabolism and regulation, the possible cellular and physiological functions, and, finally, the discovery of its receptor(s) and its action mechanism and regulation. In this respect, we recommend consulting the excellent special issue entitled *History of Plant Hormone Research*, edited by Lüthen and Ludwig-Müller (2015), for some relevant details concerning the discovery of auxin, gibberellins, cytokinins, abscisic acid, ethylene, jasmonates, and brassinosteroids [22].

Until 1995, melatonin was exclusively thought to be an animal hormone and it was one of the molecules that had been most researched and written on in the scientific press, in specialized journals, such as *Journal of Pineal Research*, established in 1984, and the most recent *Melatonin Research*. But then, in 1995, three independent research groups published the unequivocal identification of melatonin in plants [23–25]. This data caused uncertainty since the presence of an animal hormone in plant tissues was unsuspected. Since this time, successive studies have quantified the presence of melatonin in plants, and it is now fully accepted that melatonin is present in all kingdoms, from prokaryotes to eukaryotes, from animals to plants. Melatonin of plant origin is called phytomelatonin [26]. In the first years following its discovery in plants, the research focused on physiological roles similar to those that melatonin was known to have in animals. Table 1 compiles the most relevant publications in the period 1995–2009. Thus, one of the first objectives was to demonstrate its possible participation as a chrono-regulatory molecule in photomorphogenic processes, such as flowering. The Czech group of Drs. Kolář and Macháčková spent many years attempting to demonstrate the role of phytomelatonin in the flowering of *Chenopodium rubrum* L. and the influence of circadian rhythms in phytomelatonin levels, unfortunately without conclusive results [27–30]. Another interesting line of work was that developed by the group of Dr. Saxena in Canada. By 2000, working with cells in culture of St John's wort (*Hypericum perforatum* L.), they already had determined steps in the phytomelatonin biosynthesis pathway that were similar to those of animals, and they proposed that melatonin could act as an auxin in in vitro cell cultures due to the chemical similarity between the molecules melatonin and indole-3-acetic acid (IAA) (Sigma Co, Madrid, Spain) [31–33]. In 2004, using etiolated lupin (*Lupinus albus* L.) hypocotyls, it was first demonstrated that melatonin had a growth-stimulating effect, and its stimulatory potential was valued at up to 63% with respect to the effect of IAA [34]. This growth stimulating effect was subsequently confirmed in several species of *Poaceae*. The double growth-stimulating and inhibitory effect dependent on the concentration and the tissue tested (aerial or root zone), similar to that which occurs using IAA, was also demonstrated [35,36]. Also, in 2004, the first paper on the protective role of melatonin in carrot (*Daucus carota* L.) cells under cold stress was published [37]. In 2008, the effect of the melatonin-inducing germination of *Brassica oleracea* L. seeds under copper toxicity opened the door for numerous studies with the objective of demonstrating the protective effect of melatonin [38,39]. This protective effect of melatonin against diverse abiotic (drought, salinity, waterlogging, cold, heat, metal toxics, herbicides, UV radiation) and biotic (bacteria, fungi, virus) stressors has been the most widely studied aspect, featuring in numerous species and experimental situations that were all of high agronomic relevance [40–51].

Another important role for melatonin was suggested in 2007, when it was shown that melatonin could stimulate the formation of both true and adventitious roots in lupin, stimulating the formation of root primordiae in the pericycle [52].

In 2009, another aspect of great relevance was suggested for melatonin. Barley leaves incubated with melatonin clearly retarded their loss of dark-induced chlorophylls [53]. It was later shown that, in leaf senescence, melatonin regulates transcription factors linked to senescence and chlorophyll metabolism [54]. Also, in 2009, the role of melatonin in stress situations was demonstrated, since an increase in endogenous phytomelatonin levels was recorded in a variety of stress situations, accompanied by a consequent anti-stress response [55]. All induced stresses activate the biosynthesis of phytomelatonin in tissues and are generally associated with a burst in reactive oxygen and nitrogen species (ROS/RNS). Induced stresses also up regulate the gene expression of the melatonin biosynthesis enzymes tryptophan 5-hydroxylase (T5H), tryptophan decarboxylase (TDC), serotonin *N*-acetyltransferase (SNAT), acetylserotonin methyltransferase (ASMT) and caffeic acid *O*-methyltransferase (COMT) [42,47,56].

Table 1. Most relevant studies on melatonin in plants in the period 1995–2009.

Year	Specie	Study Field	Reference
1995	Edible plants *Chenopodium rubrum* L.	Discovery of melatonin in plants	[23–25]
1997	*Chenopodium rubrum* L.	First studies on flowering and rhythms	[27]
2000	*Hypericum perforatum* L.	First studies on biosynthesis and possible regulator role	[31]
2004	*Lupinus albus* L.	First demonstration as growth promoter	[34]
	Daucus carota L.	First proposal as stress protector agent	[37]
2007	*Lupinus albus* L.	First demonstration as rooting promoter	[52]
2008	*Brassica oleracea* L. *Cucumber sativus* L.	First demonstration as germination promoter in stress	[38] [39]
2009	*Hordeum vulgare* L.	First demonstration as foliar senescence retardant	[53]
	Hordeum vulgare L.	First demonstration of endogenous melatonin biosynthesis in several stress conditions	[55]

Outside the field of plant physiology, this period saw the first papers on the effect of human plasma on the consumption of fruits and vegetables rich in phytomelatonin, and the beneficial effects on the antioxidant status and improvements in sleep parameters were described [57–61].

This first exciting period (1995–2009) was characterized by the search for the unknown effects of melatonin in plants, sometimes based on existing knowledge of its role in animals, but on many other occasions as a result of unexpected discoveries. Figure 1 illustrates the evolution in the number of articles (papers and others) published on melatonin in plants. As can be seen from the first articles published in 1995, only 35 articles were published up to 2005 (an average of 3.2 per year). Since 2010, the publications on melatonin in plants have shown an exponential increase, reaching a maximum in 2019 with 88 articles. It is expected that in the forthcoming years, this number may well be exceeded.

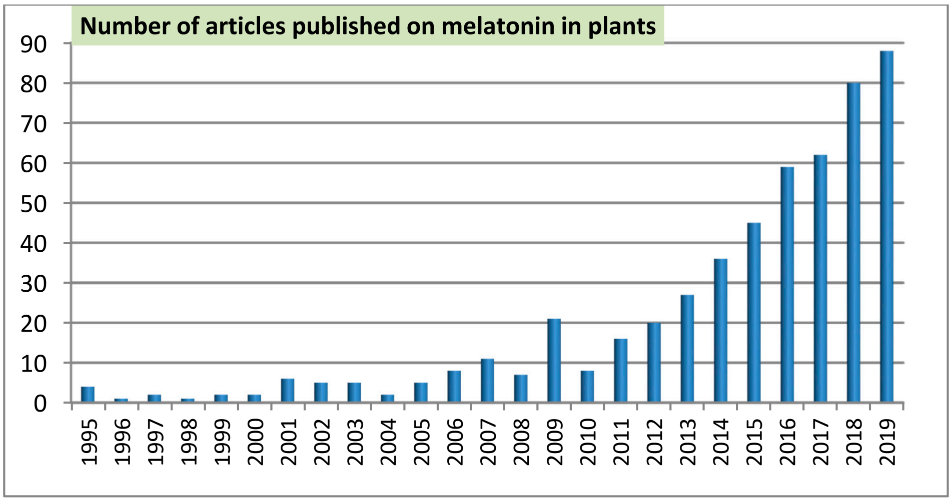

Figure 1. Evolution of the number of articles related with melatonin in plants since its discovery in 1995. For 2019, the data are based on an extrapolation of the data available to date (first 10 months).

3. Current Topic Status

The period from 2010 to the present has been very productive in terms of achievements. During this time, many of the ideas that were only suggested in the previous period have been demonstrated, and there is a very active and enthusiastic research body. Table 2 shows the most outstanding events in this second period.

In this period, many more phytomelatonin determinations/quantifications have been made by studying the phytomelatonin content of many plant species, both edible and wild type, and in various plant organs (roots, leaves, stems, flowers, fruits, and seeds). The same is true for foods of plant origin and their processed and fermented products (juices, musts, wines, infusions, etc.). Additionally, many suggestions have been made regarding its nutraceutical potential [26,62–70].

The phytomelatonin biosynthesis route has been completed with great accuracy, mainly due to the works of Dr. K. Back and his team, in rice and *Arabidopsis* plants [71–83]. One aspect of great interest has been the discovery that some melatonin catabolites, such as 2-hydroxymelatonin, also have physiological activity, a topic that merits further study [84–88].

Table 2. Pioneering studies on melatonin in plants in the period 2010–2019.

Year	Study Field	Reference
2010–2018	Biosynthesis and catabolic route	[83,89]
2012	Confirmation that melatonin induces lateral rooting independent of auxin signal	[90]
2013	Growth conditions determine endogenous phytomelatonin level	[91,92]
2013–2014	Melatonin determines many changes in gene expression	[93,94]
2012–2013	Melatonin positively affects chlorophyll and carotenoid levels, photosynthesis, water economy, carbon, nitrogen, sulfur and phosphorous metabolism and secondary metabolism	[54,95–101]
2013–2014	Melatonin improves resistance to plant diseases and activates the immune response	[102–104]
2014	Many stress response factors are activated by melatonin	[105,106]
2014–2015	Plant hormone gene expression is regulated by melatonin	[104,107,108]
2015	Melatonin induces the nitric oxide pathway in innate immunity pathogen infection	[109]
2015–2016	Melatonin regulates its own biosynthesis genes (SNAT, ASMT and COMT)	[108,110]
2016	Melatonin levels are regulated by diurnal cycles and it is related with biological clock and stress gene elements	[111]
2015–2017	Melatonin improves the quality of fruits and flowers during post-harvest	[112–115]
2018	Melatonin induces parthenocarpy	[116]
2018	First phytomelatonin receptor (PMTR1) is identified and characterized	[117]
2019	Melatonin aids in the eradication of apple stem grooving virus	[118]

The physiological aspects in which melatonin exerts some beneficial action are shown in Figure 2 and are commented on below:

- Improvements in photosynthesis efficiency, preserving chlorophylls and carotenoids, reducing photorespiration, stomatic conductance and optimizing water economy; improving the yield of seeds and fruits in adverse conditions. Osmoregulation balance, the regulation of ion exchange and adjustments of osmotic and water potentials.
- The regulation of the different metabolisms of carbohydrates, lipids, nitrogen compounds, and sulfur and phosphorus cycles; the induction of the biosynthesis of flavonoids, anthocyanins, and carotenoids, among others, in the secondary metabolism, generally in stress conditions.
- In hormonal homeostasis, interventions in the regulation of all plant hormones, up- or down-regulating the gene biosynthesis/catabolic expression of auxin (IAA), cytokinins (CKs), gibberellins (GAs), abscisic acid (ABA), salicylic acid (SA), jasmonic acid (JA), ethylene, brassinosteroids, strigolactone, and polyamines.
- Melatonin regulates its own biosynthesis, upregulating the gene expression of phytomelatonin biosynthesis genes, mainly SNAT, ASMT, and COMT.
- Melatonin levels are regulated by diurnal cycles in *Arabidopsis* and it is related with *CIRCADIANCLOCK ASSOCIATED 1* (*CCA1*), a main biological clock of elements. Also, *C-repeat-binding factors* (*CBFs*)/*Drought response element Binding 1 factors* (*DREB1s*) were co-regulated by exogenous melatonin and diurnal changes, indicating the possible correlation among clock, endogenous melatonin level, *AtCBFs* expressions, and plant immunity.
- In the rooting processes of primary, secondary and adventitious roots, melatonin regulates the expression of many factors, such as PIN auxin transporters and AUX1, among others.
- In the processes of foliar senescence, melatonin regulates the expression of chlorophyll degradation-related and senescence-induced genes.
- In the post-harvest control of fruits, melatonin increases the ethylene and lycopene content, and regulates many enzymes of the cell wall, ethylene biosynthesis and of the primary and secondary metabolism. It also helps preserve cut flowers.
- Melatonin induces parthenocarpy in pear, increasing GAs level.
- Of great importance is its role in bacterial, fungal, and viral pathogen infections, with relevant responses, slowing damage and stimulating systemic acquired resistance (SAR), to favor crop health.

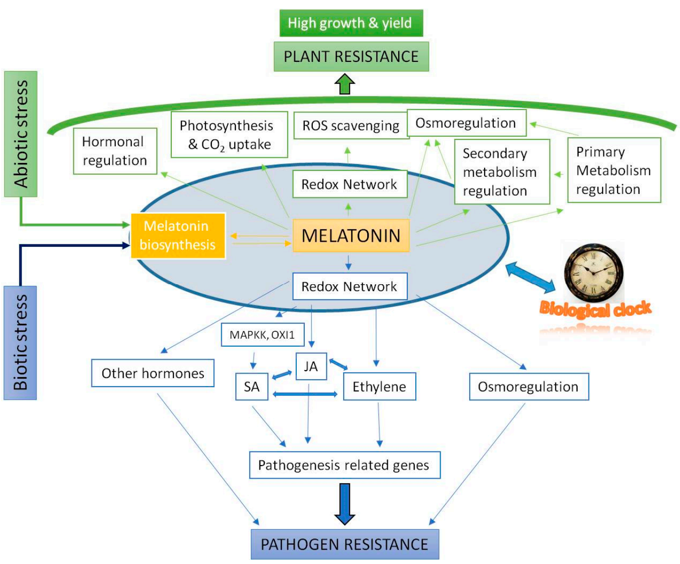

Figure 2. Model of phytomelatonin action regulating redox network in abiotic and biotic stress responses.

Figure 2 shows an overview of the protective role of phytomelatonin against abiotic and biotic stressors. Melatonin acts as a master regulator of the redox network, activating many responses mainly through the nitric oxide pathway, among others. Several recent reviews can be consulted [42,43,46–51,56,119–124].

4. Aspects that Lead One to Consider Melatonin as a New Plant Hormone

The first proposals about the possible role of phytomelatonin concerned its antioxidant potential. Chemically, melatonin is an excellent antioxidant, presenting an antioxidant potential many times greater than classical antioxidants, such as ascorbic acid, vitamin E, and others. Its capacity as a regulator of gene expression soon opened the door to new hypotheses. For a molecule to be considered as a plant hormone implies knowledge of its biosynthesis, degradation, possible conjugation, transport, receptor(s), signal transduction chain, and physiological effect(s). Many of these requisites were well documented, but the detection of a phytomelatonin receptor proved more elusive [42,56], and it was not until 2018 that Dr. Chen's group first detected and characterized the phytomelatonin receptor called PMTR1. Localized in the plasma membrane of *Arabidopsis thaliana*, it presents a receptor-like topology. It interacts with the G-protein a subunit (GPA1), while its expression in different tissues can be induced by melatonin. PMTR1-phytomelatonin binding triggers the dissociation of Gγb and Gα, which activates a NADPH oxidase-dependent H_2O_2 production (RBOH), enhancing Ca^{2+} influx and promoting K^+ efflux, all of which finally results in stomatal closure [117]. This was a crucial step for starting to consider the hormone nature of phytomelatonin. However, the consequent description of the phytomelatonin receptor in other plant species also seems to be an essential requirement. It was known that phytomelatonin exerted a regulatory role on the redox network, mobilizing a large amount of genetic resources in stress situations to restore redox homeostasis. Some detailed models, in which phytomelatonin is considered as a plant master regulator of the redox network, have been suggested [42,47,56,124]. In Figure 3 we proposed a model in which core clock, phytomelatonin and the receptor PMRT1 are integrated in the coordination and response to the redox network. Although there are data on the role of phytomelatonin as a chronoregulator in plants [41,111], this piece of the puzzle between biological clock and redox network, is yet to be confirmed experimentally, with researchers currently in its study. If this last idea is confirmed, phytomelatonin worked in transferring biological clock oscillations to the redox network and, as a plant master regulator (plant master hormone), provides the adequate response to reach redox homeostasis in stress situations, in a similar way to animal melatonin.

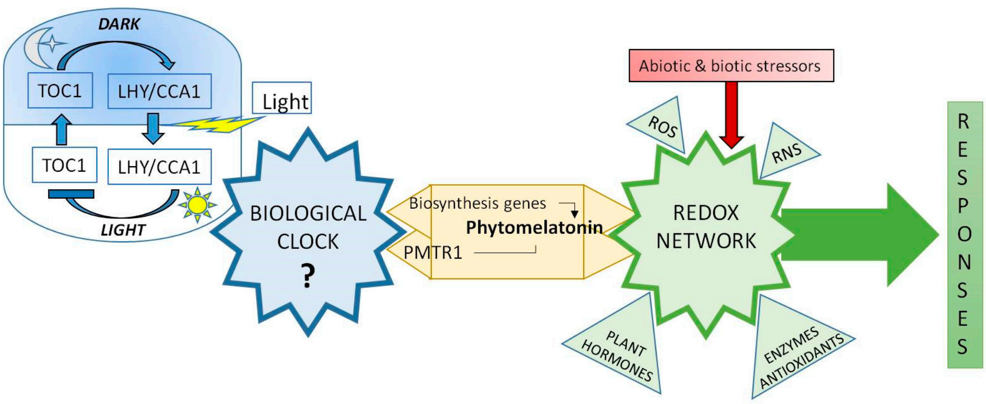

Figure 3. Possible relationship of the triad: core biological clock-Phytomelatonin-Redox network.

5. Perspectives

Since the discovery of phytomelatonin in plants 25 years ago, much progress has been made in improving our knowledge. Its possible role as a chronobiological plant hormone, coordinating the biological clock with redox homeostasis, can explain its importance in stress responses and in regulating the levels of other plant hormones in many actions. It also explains its role in the optimization of the photosynthetic system, including the aspects of water economy and the assimilation of CO_2, all of which are regulated by the biological clock.

However, all of the above lead to more questions and objectives, such as: what changes does exogenous melatonin treatment cause in the triad core clock-phytomelatonin-redox network? And what changes does it cause in the stress agents? Is there only one type of receptor for phytomelatonin? And does this regulatory triad exist in other species? In CAM (Crassulaceae Acid Metabolism) plants, which open their stomata at night, what differences exist from the model described for *Arabidopsis*? The answers to these and many other questions will throw further light on the fascinating world of this universal molecule.

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Abbreviations

AUX1	auxin transporter-like protein
ASMT	N-acetylserotonin methyltransferase
CAM	Crassulaceae acid metabolism
CCA1	circadian clock associated-1
COMT	caffeoyl-O-methyl transferase
GAs	gibberellins
IAA	indole-3-acetic acid
LHY	late elongated hypocotyl
PIN	auxin efflux transporters
PMTR1	phytomelatonin receptor
RBOH	NADPH oxidase-dependent H_2O_2 production
RNS	reactive nitrogen species; ROS, reactive oxygen species
SAR	systemic acquired resistance
SCN	suprachiasmatic nucleus
SNAT	serotonin *N*-acetyltransferase
T5H	tryptophan 5-hydroxylase
TDC	tryptophan decarboxylase
TOC1	timing of CAB expression-1

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