Melatonin Detection and Quantification Techniques

2

Meghana Singh Rajotia, Amit Sharma, Ashish Bhatt, Vikas Mangal, Salej Sood, Ajay Kumar Thakur, Shruti Kashyap, and Lokesh Kumar Verma

Abstract

An indolic substance made from tryptophan is called melatonin (N-acetyl-5-methoxytryptamine). This substance, typically classified as a receptor or mammalian hormone, was first found in plants in 1995. Research into plant-based melatonin is an area that is expanding rapidly. Different plants contain different versions of the enzymes involved in the biosynthesis of melatonin. In the twentieth century it was discovered that several plant species can produce this molecule in large quantities and store it in specialized organs. According to endosymbiotic theory, the locations for melatonin biosynthesis in plants are chloroplasts and mitochondria. As plants similar metabolites with mammals, the metabolism of the sleep-inducing hormone melatonin in plants is less well understood. Although our understanding of the melatonin-producing enzymes in plants is still in its infancy, it has been found that plant cells are expected to be more flexible than animal cells. This chapter summarizes about melatonin discovery, evolution, and biosynthesis.

Keywords

Biosynthesis · Evolution · Melatonin · Tryptophan

M. S. Rajotia · A. Sharma
Department of Genetics and Plant Breeding, CCS HAU, Hisar, Haryana, India

A. Bhatt · S. Kashyap
Department of Genetics and Plant Breeding, GBPUA & T, Pantnagar, Uttarakhand, India

V. Mangal (✉) · S. Sood · A. K. Thakur
ICAR-Central Potato Research Institute, Shimla, Himachal Pradesh, India

L. K. Verma
University of Agricultural Sciences (UAS), Dharwad, India

R. Kumar et al. (eds.), *Melatonin in Plants: A Regulator for Plant Growth and Development*, https://doi.org/10.1007/978-981-99-6745-2_2

2.1 Introduction

Melatonin is a substance with a wide range of uses, especially in both animals and plants. The hormone indoleamine affects a variety of bodily processes, including emotions, slumber, body temperature, the retina, and sexual behaviour. The majority of these factors are controlled by or in combination with the animal's circadian schedule (Fuller et al. 2006; Jan et al. 2009; Altaf et al. 2022). It was discovered in the twentieth century that several plant species may make this molecule in large quantities and store in specific tissues. Melatonin (N-acetyl-5-methoxytryptamine) was first discovered in the bovine pineal gland by the dermatologist Lerner et al. (1958a, b). The term was first connected to its capacity to bind melanin, a pigment granule found in the chromatophores of fish and frog epidermis. Since indolamine functions as a neurohormone in the pineal gland of mammals, it was long believed that melatonin was only made there. However, it is now known that melatonin is also generated by several organisms from the Eukarya and Bacteria domains (Mannino et al. 2021a, b). It is a multifunctional signalling molecule that is widely distributed throughout a plant's many organs and is in charge of inducing a number of physiochemical reactions in response to harmful environmental circumstances in different plant systems. It functions as an essential antioxidant in animals and influences a variety of cellular processes, including circadian rhythms, body temperature, sleep, and the immune system (Pieri et al. 1994; Rodriguez et al. 1994; Jan et al. 2009). Melatonin is also an antioxidant agent that may regulate plants' reactive oxygen and nitrogen species. It also functions as an indoleamine neurotransmitter. As a signalling agent, melatonin causes several distinct physiological reactions in plants that may help improve photosynthesis, growth, carbon fixation, root growth, seed germination, and defence against various biotic and abiotic stresses (Van Tassel et al. 2001; Arnao and Hernández-Ruiz 2015; Sun et al. 2015; Wei et al. 2018; Zhang et al. 2018; Altaf et al. 2021; Arnao and Hernández-Ruiz 2019. Melatonin is also known to enhance physiological functions, such as spreading a plant's regular development and protecting emerging tissues from damage and stress signals from the environment (Erland et al. 2015; Altaf et al. 2023). This chapter explores melatonin discovery and divergent biosynthetic pathways in plants more broadly.

2.2 Discovery and Evolution of Melatonin

Melatonin is widely distributed, notably among the earliest bacteria (cyanobacteria and -proteobacteria), suggesting that it is an old molecule that has persisted throughout the history of all creatures (Manchester et al. 2015; Pshenichnyuk et al. 2017). Melatonin may have originated in bacteria before the endosymbiotic relationship, according to a popular theory. Early prokaryotes eventually developed from cyanobacteria and proteobacteria into chloroplasts and mitochondria, respectively. As a result, all unicellular and multicellular organisms eventually manufacture this essential indoleamine in these organelles (Margulis 1975; Tan et al. 2013; Behera et al. 2022; Reiter et al. 2017a, b). Melatonin is universally expanded to all creatures

with species diversity, and as a result, its functions, synthesis route, production locations, and biosynthetic control have also varied. Melatonin's detoxification of free radicals produced by photosynthesis and metabolism was thought to be its primary intent (Manchester et al. 2015; Tan et al. 1993, 2010, 2015; Galano et al. 2018). Melatonin evolved into a pleiotropic molecule with biodiversification during organismal evolution, which affects biological rhythms, reduces inflammation, etc. Melatonin also resists oxidation-related stress (Tan et al. 2010; Lochner et al. 2018; Chourasia et al. 2021; Onaolapo and Onaolapo 2018; Tamtaji et al. 2018). Organisms have created a variety of systems to control the manufacture of melatonin in order to benefit from its many biological effects. For instance, the transcription factor activator protein-1 (AP-1) stimulates the genes involved in melatonin synthesis while under stress to increase the production of melatonin (Rodriguez et al. 1994; Estrada-Rodgers et al. 1998; Korkmaz et al. 2009; Muxel et al. 2016; Cai et al. 2017).

Around 2.5 billion years ago, the Earth's atmosphere saw a surge in molecular oxygen (O_2) as a result of the persistent release of this gas by photosynthetic microorganisms that had originated about a billion years earlier (the Great Oxygenation Event). The increase in atmospheric oxygen exerted a huge selection pressure on species to evolve O_2 metabolism (Kump and Barley 2007; Reiter et al. 2017a, b; Chourasia et al. 2022). Reactive oxygen species (ROS) are inevitably produced during aerobic metabolism when oxygen takes leaky electrons from the electron transport chain (ETC).

According to estimates, up to 4% of the oxygen that organisms use throughout their aerobic metabolism is eventually converted to ROS (Casteilla et al. 2001; Treberg et al. 2018). Since these high levels of ROS are hazardous to cells and organisms, elaborate and efficient methods to counteract them have been developed; this first happened in early life forms like bacteria and later unicellular creatures (Case 2017). Melatonin likely first appeared in early photosynthetic prokaryotic bacteria as an antioxidant and free radical scavenger to combat oxidative stress (Tan et al. 2013; Devi et al. 2022; Reiter et al. 2017a, b). In all living things, melatonin has maintained its capacity to reduce oxidative stress, which is brought on by the generation of free radicals during photosynthesis and respiration (Manchester et al. 2015). Based on its capacity to donate an electron or a hydrogen atom, or depending on the kind of radical, may be by other mechanisms as well, the unique structure of melatonin dictates its high efficacy in detoxifying free radicals (Shi et al. 2016). The cascade reaction, which takes place when melatonin produces derivatives that are also free radical scavengers, is at least largely responsible for its higher antioxidant potential to reduce oxidative stress (Tan et al. 2013). The molecular makeup of melatonin has not altered in billions of years, despite its extremely extensive evolutionary history and numerous roles (Reiter et al. 2017a, b). Furthermore, despite all creatures' extremely high levels of biodiversification during evolution, melatonin may have been kept by all of them. This pertains to the fact that mitochondria and chloroplasts (or both) are conserved in the majority of species' cells. Red blood cells are one exception, since they expel various organelles, including mitochondria, during erythropoiesis. Cyclic 3-hydroxymelatonin and

other melatonin metabolites are produced when melatonin interacts with different ROS. These metabolites serve as radical scavengers, sometimes even more aggressively than melatonin in their ability to neutralize ROS (Lee et al. 2016; Kumar et al. 2023a, b).

Melatonin has been shown to play a variety of roles in the growth and development of plants, including seed protection and germination, root development, fruit ripening, and senescence (Liang et al. 2017; Kumar et al. 2022b). Due to their sessile nature, plants experience more environmental challenges than mammals do. They quickly upregulate the production of melatonin as a defence against these pressures, which helps them avoid the oxidative damage that thes. In animals, quinone reductase 2 (QR2, E.C. 1.10.99.2), a cytosolic molecule, also binds directly to the catalytic site to influence the activity of this enzyme; this modulation may be either up- or downregulation (Boutin et al. 2008). Importantly, the modification in QR2 activity might also be crucial for the production or detoxification of ROS (Reybier et al. 2011).

2.3 Origin of Melatonin Receptors

The only thing the cell needed to do for melatonin to fulfil its putative original purpose, i.e., act as a direct free radical scavenger, was to place it close to where the majority of ROS are often produced. An antioxidant must be positioned in this way because free radicals have a very short half-life and instantly destroy molecules in the area around where they are generated. The initial harm caused by a highly reactive radical cannot be stopped if a free radical scavenger is not placed correctly. Evolution designed the uptake and production of melatonin in chloroplasts (Choi et al. 2017) and mitochondria (Suofu et al. 2017; Kumar et al. 2023b; Acuna-Castroviejo et al. 2018)—both significant sources of the overall oxidative burden of cells—to achieve this correct placement. Melatonin has an exceptionally wide range of physiological tools in vertebrates that are still alive today. It was essential for its binding sites/receptors and related signalling transduction mechanisms to evolve in order to increase its range of functional possibilities. The outer membrane of mitochondria has recently been linked to the MT1 receptor, which is typically thought to be restricted to the limiting membrane of cells. They developed the word "automitocrine" to describe this mechanism. According to the researchers who made this discovery, melatonin diffuses out of these structures and interacts with MT1 receptors on the outer membrane of these organelles. Melatonin produced by mitochondria may regulate the release of cytochrome c from the matrix through this receptor-mediated mechanism. This self-regulatory mechanism affects apoptosis that results from significant free radical damage. There are binding sites in the cytosol (Boutin and Ferry 2019) and the nucleus in addition to the well-studied and highly relevant cell membrane receptors that are essential for a number of melatonin's key functions (Hill et al. 2009; Wang et al. 2015; Zhao et al. 2017). Quinone reductase 2 (QR2) has been classified as receptor MT3 in the cytosol (Boutin 2016; Kumar et al. 2022a). Some of the ways that melatonin reduces

oxidative damage may be connected to the activity of this detoxifying enzyme. Additionally, melatonin interacts with calmodulin in the cytosol, which is thought to be related to the indoleamine's stated ability to prevent cancer growth (Menendez-Menendez and Martinez-Campa 2018).

Land plants have many of the antioxidant enzymes found in mammals, in addition to melatonin's direct scavenging of radicals and their byproducts. When exposed to an abiotic stress, such as a draught, heat, cold, toxin, etc., plants' melatonin-influenced enzymes are rapidly upregulated (Arnao and Hernández-Ruiz 2015; Shi et al. 2015). Melatonin receptors are thought to be involved in this upregulation, as is probably the case for mammals as well.

2.4 Melatonin Biosynthesis in Plants and Animals

Melatonin probably developed in bacteria; it has been detected in both photosynthetic cyanobacteria and in a-proteobacteria. For the first time, Lerner and colleagues reported the existence of melatonin in the bovine pineal gland in 1958 (Lerner et al. 1958a, b). After being isolated and discovered in the cow's pineal gland, melatonin was later discovered in a variety of other plants and animals (Lerner et al. 1958a, b; Kumar et al. 2023a, b; Hattori et al. 1995). Melatonin is widely distributed, particularly in cyanobacteria and a-proteobacteria, which suggests that it is an ancestral molecule that has persisted throughout the evolution of all organisms (Manchester et al. 2015) (Fig. 2.1). Its original association with the name was its capacity to bind pigment granules (melanin) in the chromatophores of fish and frog epidermis. Since indolamine functions as a neurohormone in the pineal gland of animals, it was believed for more than 30 years that melatonin was only produced there. However, it is now known that melatonin is also produced by several organisms in the Eukarya and Bacteria domains, while no information has been found for Archaea. N-acetyl-5-methoxytryptamine, also known as melatonin, was first found in 1959 (Lerner et al. 1959). Soon after, the biosynthetic route from tryptophan, using serotonin as an intermediary, was revealed (Lauber et al. 1968). Melatonin was first discovered in humans in 1959, and in the 1960s and 1970s, numerous animals and vertebrates, including birds, frogs, and fish, were found to contain it (Baker et al. 1965; Axelrod and Weissbach 1960). All living things, including microbes, yeast, fungus, animals, and plants, are believed to synthesize melatonin (Reiter et al. 2013). According to research, plants' mitochondria and chloroplasts have the greatest amounts of melatonin of any cellular compartment (Kanwar et al. 2018). This finding, along with evidence that serotonin N-acetyltransferase (SNAT), one of the rate-limiting enzymes involved in melatonin production, is localized in mitochondria and chloroplasts, points to the hypothesis that these cells are the primary locations for this indolamine's biosynthesis (Yu et al. 2019; Wang et al. 2017). Tryptophan serves as the only amino acid that goes into building this molecule. Although tryptophan is a dietary component, some species can also make it using the shikimic acid route, which begins with D-erythrose-4-phosphate, phosphoenolpyruvate, or carbon dioxide (Bochkov et al. 2012). The only amino acid used to make this protein is

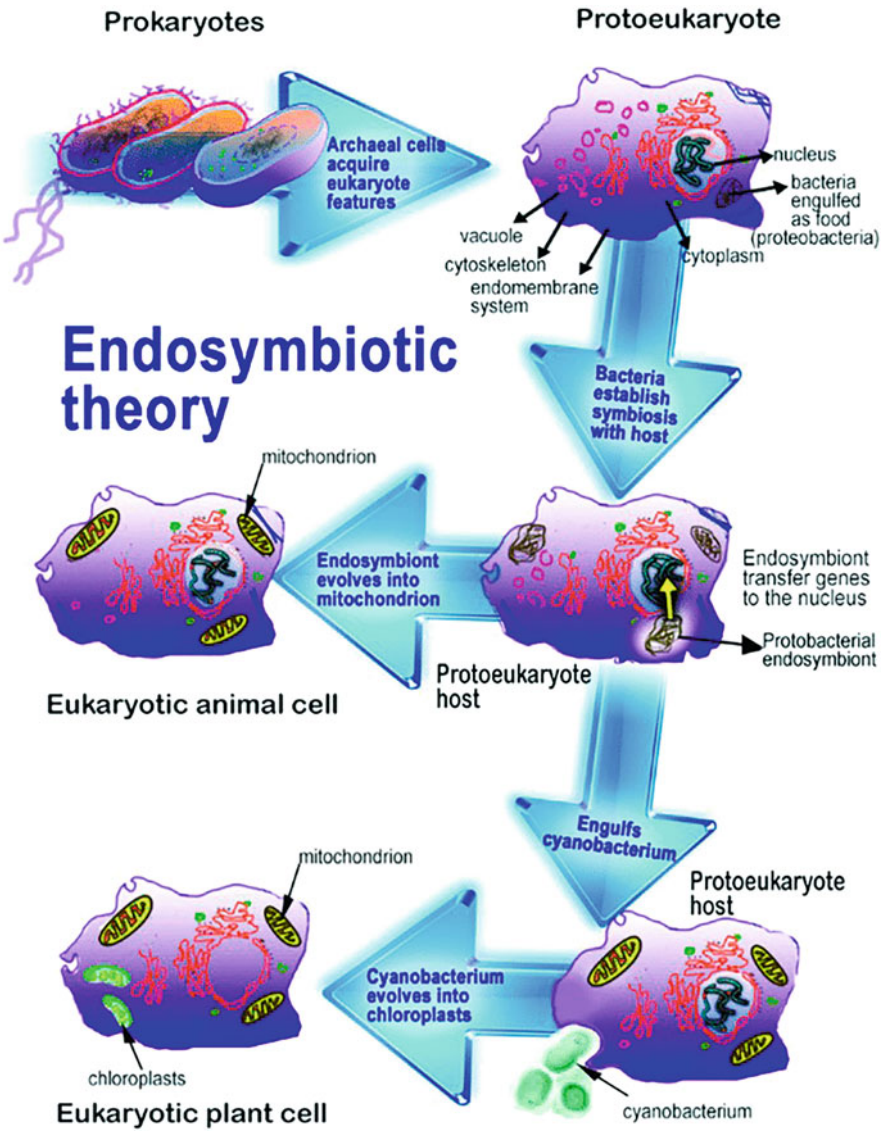

Fig. 2.1 This figure illustrates the endosymbiotic origin of mitochondria and chloroplasts. a-Proteobacteria (Source: Zhao et al. 2019)

tryptophan. Although tryptophan is a dietary component, some species also have the ability to synthesize it using the shikimic acid route, which begins with Derythrose-4-phosphate, phosphoenolpyruvate, or carbon dioxide (Bochkov et al. 2012; Lal et al. 2021b). Bacteria, fungi, and plants maintained the capacity to synthesize tryptophan with the evolution of organisms (apart from animals). Conversely,

animals can only get the essential amino acid tryptophan through eating. When tryptophan levels are lower than they are in plants, mammals produce significantly less melatonin than do plants. Since plants are unable to behaviourally prevent highly stressful situations, they need additional stress protection. In order to ensure that melatonin is available to reduce oxidative stress levels under stressful environmental circumstances, tryptophan biosynthesis is likely maintained in plants. Serotonin is first produced by decarboxylation and hydroxylation of tryptophan. There are two methods for serotonin synthesis that result in the production of melatonin in various taxa. Microorganisms and plants have a distinct serotonin biosynthetic pathway than mammals do. In plants, tryptophan is converted to tryptamine by the enzyme tryptophan decarboxylase (TDC), which is followed by the enzyme tryptamine 5-hydroxylase (T5H), which catalyses the serotonin biosynthesis (Park et al. 2008). However, animals first hydroxylate tryptophan using tryptophan hydroxylase (TPH) to form 5-hydroxytryptophan, which is then decarboxylated by aromatic amino acid decarboxylase (AADC) to produce serotonin. This is in contrast to humans, who first produce tryptophan through the decarboxylation of the amino acid. Serotonin is a crucial intermediate between tryptophan and melatonin, following which the biosynthetic process uses two potential pathways, each of which involves two consecutive enzymatic processes that produce melatonin (Back et al. 2016). These processes use the enzymes serotonin N-acetyltransferase (NAT) and acetylserotonin O-methyltransferase (ASMT; formerly known as hydroxyindole-O-methyltransferase, HIOMT) to catalyse the conversion of serotonin into the end product, melatonin. While the final enzyme, ASMT, catalyses NAS to produce melatonin, the penultimate enzyme, NAT, plays a critical part in the conversion of serotonin to N-acetylserotonin (Byeon et al. 2016).

Tryptophan and the other aromatic amino acids can be biosynthesized in plants through this pathway, which comprises seven distinct stages (Mannino et al. 2021a, b) as shown in Fig. 2.2.

In all species, melatonin production involves four enzymatic stages starting with tryptophan. The melatonin production rhythm evolved over billions of years, becoming more diverse. There are two stages in the production of melatonin from tryptophan (Fig. 2.3). Serotonin is produced from tryptophan in the first stage of the melatonin biosynthesis pathway in plants.

2.5 Melatonin Detection and Quantification

Melatonin (N-acetyl-5-methoxy-tryptamine) was initially discovered in 1958 and it was given that name because it could counteract the melanocyte stimulating hormone (MSH)-induced darkening. It is a ubiquitous chemical found in both plants and mammals. It has been found at various levels in many types of plants and organs.

Melatonin operates as a hormone similar to indole-3-acetic acid because it has the same starting biosynthesis component with auxin in plants (Fig. 2.4). In lupin hypocotyls, as well as in monocot species like canary grass, wheat, barley, and oat (Hernández-Ruiz et al. 2005; Lal et al. 2022b; Arnao and Hernández-Ruiz 2007),

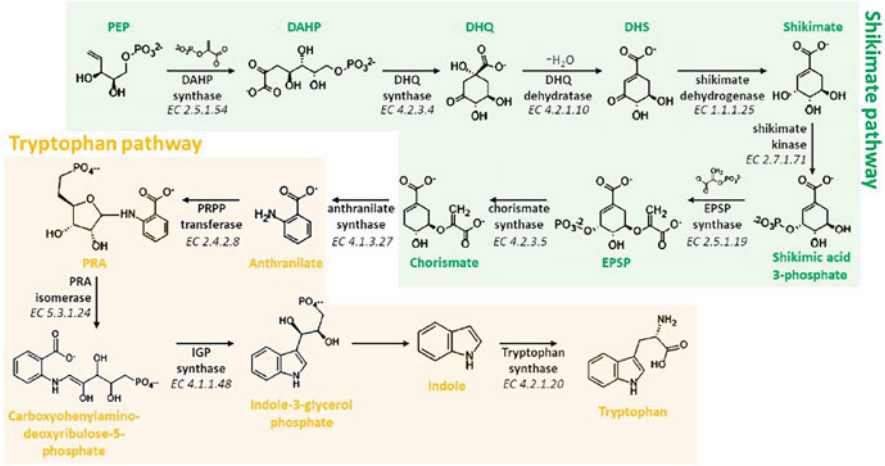

Fig. 2.2 Biosynthetic pathway involved in the synthesis of tryptophan, the key compound of melatonin in plants. *DAHP* 3-Deoxy-D-arabino-heptulosonate 7-phosphate, *DHQ* 3-Dehydroquinate, *DHS* 3-Dehydroshikimate, *EPSP* 5-Enolpyruvylshikimate 3-phosphate; IGP synthase, Indole-3-glycerol phosphate synthase, *PEP* phosphoenolpyruvate, *PRA* Phosphoribosyl anthranilate, *PRPP* 5-Phospho-ribosyl 1-pyrophosphate

and dicot species like Arabidopsis, melatonin is thought to be a growth-promoting chemical, similar to auxin. As such, it is an auxinic hormone in plants. By directly scavenging reactive oxygen species and through indirect mechanisms that boost antioxidative enzyme activity, photosynthetic efficiency, and metabolite content, melatonin increases plants' ability to withstand stress. It also plays an important role in regulating gene expression.

A plant's melatonin production is thought to be for its own defence against free radicals produced by environmental or metabolic activities, such as photosynthesis (Manchester et al. 2000). To corroborate this, it has been shown that the sensitivity of *Nicotiana tabacum* leaves to ozone (a free radical producer) damage varies among kinds, with the susceptibility decreasing in leaves with the greatest melatonin contents (Dubbels et al. 1995). This is in line with the theory that melatonin serves as an antioxidant in both plants and mammals. The seeds of edible plants have also been shown to contain significant quantities of melatonin (Manchester et al. 2000). Melatonin is thought to be crucial for seeds' ability to protect germ and reproductive organs from oxidative damage brought on by UV radiation, drought, extremely high or low temperatures, and other environmental factors.

To gain deeper understanding of melatonin's involvement in plant physiology and ecology, it is fundamental to establish more dependable analytical methods for melatonin detection and quantification. For materials ranging from algae to higher plants, melatonin was extracted, purified, and measured using a variety of techniques. Simple extraction solvents such ethanol, 10% Na2CO3, phosphate-buffered saline, or potassium phosphate buffer were employed by several writers (Dubbels et al. 1995; Hattori et al. 1995; Lal et al. 2021a; Manchester et al. 2000).

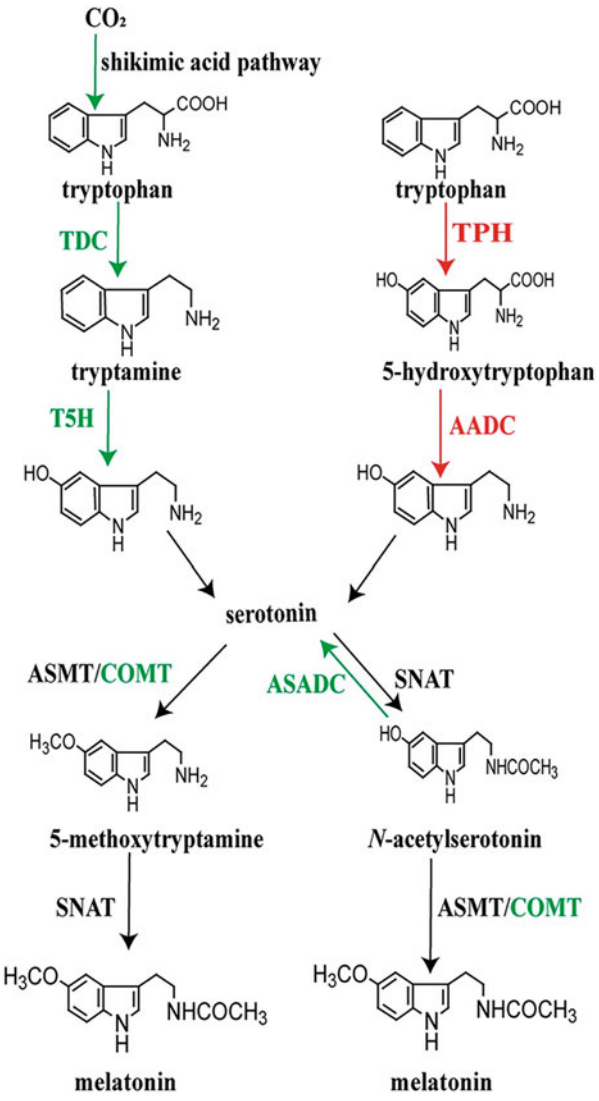

Fig. 2.3 Pathways of melatonin synthesis in different plant (left) and animal (right) sources; (Zhao et al. 2019). *AADC* aromatic L-amino acid decarboxylase, *ASMT* acetylserotonin O-methyltransferase, *COMT* catechol-O-methyltransferase, *SNAT* serotonin N-acetyltransferase, *T5H* tryptamine 5-hydroxylase, *TPH* tryptophan hydroxylase

Poeggeler and Hardeland (1994) drew attention to the fact that material from unicellular eukaryotes and plants frequently includes substances (for instance, chelated iron or redox-active proteins) that encourage melatonin breakdown by photooxidation or free radical-mediated oxidation. Methods that had been used to measure melatonin in animals were applied to plants. The sensitivity and specificity of the approaches vary. Although HPLC with fluorescence detection was successfully utilized to measure melatonin in Chinese medicinal herbs, it was not sensitive enough to demonstrate its presence in *C. rubrum* shoots (Chen et al. 2003). Melatonin has recently been identified subjectively and quantitatively in edible plants and

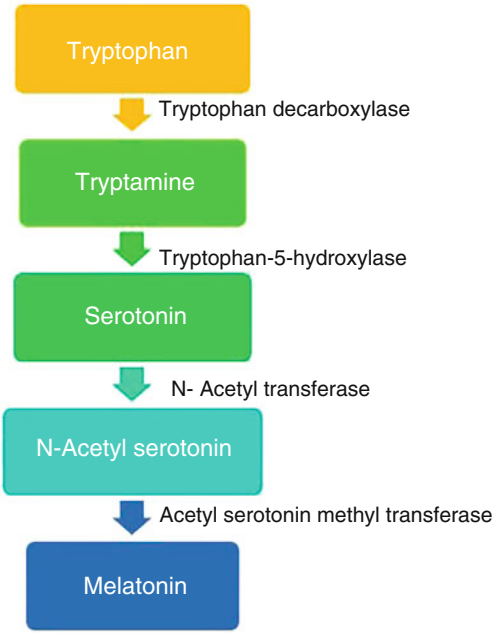

Fig. 2.4 Biosynthesis of melatonin

animal diets. Many fruits and vegetables contain melatonin, according to researchers such as blackberry, black mulberry, white mulberry, radish, jujube, clove, and sweet cherry (Riga et al. 2014; González-Gómez et al. 2009). Analytical methods are required for the quick and precise measurement and quantification of melatonin in soporific medications due to the numerous favourable benefits of melatonin on human health, most notably its intense usage in avoiding sleeplessness. Numerous techniques have been published for measuring melatonin in various types of matrix, such as plasma, saliva, pineal gland, and biological materials using GC-MS chemical ionization (Fourtillan et al. 1994), HPLC chemiluminescence (Lu et al. 2002), HPLC-FLD (Rizzo et al. 2002), LC-MS/MS (Eriksson et al. 2003), and HPLC-electrochemical detector (Chanut et al. 1998). There are many more approaches for quantifying melatonin such as electrochemical, bioanalytical, and analytical (Stege et al. 2010; Lal et al. 2022a; Radi and Bekhiet 1998). None of the methods employs ambient mass spectrometry, although it would provide a cheap and fast alternative to conventional methods (Black et al. 2016). Out of them, the liquid chromatography approach has been frequently utilized. In contrast, HPLC with electrochemical detection is more sensitive and was often utilized in algae and higher plants. Despite having a very low specificity, melatonin may have retention periods that are extremely similar to those of other substances with comparable oxidation potential. Melatonin levels in plants measured solely by RIA and not verified by other techniques may therefore be exaggerated, as was shown, for instance, for Pharbitis nil and tomato. Melatonin RIA is therefore not a valid approach in plants as opposed to mammals. The issues raised above can be resolved by using gas chromatography-

mass spectrometry (GC-MS) or low-cost mass spectrometry (LC-MS), which provide high sensitivity and great detection specificity (Dubbels et al. 1995; Van Tassel et al. 2001). Another one, AnFD has low limits of detection and quantification, is adaptable and sensitive enough to quantify melatonin in samples with low melatonin levels (Milenkovic-Andjelkovic et al. 2015; Setyaningsih et al. 2015). The extraction of melatonin can be greatly impacted by a variety of factors, including the extraction solvent and extraction time. The polarity and diffusivity of the solvent used determine how well target chemicals are extracted from plant samples. Depending on the polar characteristics of the substance to be extracted, the polarity of the solvent influences the extraction (Setyaningsih et al. 2015).

2.6 Quantification

A method where representable units are selected from a large sample is quantification. A number of plant-derived chemicals may interact with related antibodies and enzymes, leading to an overestimation of the true levels of melatonin.

2.6.1 Chromatographical Procedures

Chromatographic approach is the most used separation method for melatonin. The process of separating, purifying, and analysing chemicals is known as chromatography. The word "chromatography" comes from the Greek words "chroma" and "graphein," which in turn mean "to write".

2.6.2 Brief Procedure of Chromatography

The mixture to be separated is applied to a stationary phase (solid or liquid) in this procedure, and a pure solvent—such as water or any gas—is then allowed to move slowly across the stationary phase, transferring the components separately according to their solubility in the pure solvent.

Advantage of GC-MS is that it provides great sensitivity and specificity, and the drawback is the requirement for derivation. HPLC techniques are more effective and precise, and they do not need to be derivatized. For melatonin separation, the majority of HPLC techniques have utilized reverse-phase columns (RP C18 or RP C8), and two distinct detectors, ECD and FD, have been utilized in fruits (Table 2.1). By using HPLCeECD (Table 2.1) and acetonitrile in an 80:20 ratio with 0.1 M potassium phosphate buffer (pH 14 4.5) at a flow rate of 1 mL/min, the presence of melatonin in tart cherries was determined. Garcia-Parrilla et al. (2009) found that HPLCeFD was sensitive and versatile in its capacity to measure melatonin in fruits and had a low limit of detection and quantification. MV-Rainin instead of Zorbax was proved to be more selective towards matrix compounds present in the grappa (Mercolini et al. 2012). The mobile phase typically comprised of acetonitrile and

Table 2.1 Methods that have been adopted in various crops for melatonin extraction

Crops	Extraction solvent	Analytical method
Hordeum vulgare	Chloroform	LC-FLD
Lupinus spp.	Chloroform	LC-FLD
Oryza sativa	Methanol	LC-FLD
	Methanol	LC-MS
Datura metel (seed and flower)	80% methanol	LC-MS
Helianthus annus L.	1 M Tris-HCl, 0.4 M perchloric acid, 0.1%EDTA, 0.05% Na2S2O5, 10 M ascorbic acid	LC-UV
Arabidopsis thaliana	50% methanol	LC-MS
Cynodon dactylon	89% acetone, 10% methanol	ELISA
Musa sp.	10%Na_2CO_3 and diethyl ether	RIA and GC-MS
Malus pumila, *Ananas comosus*	10 mm PBS buffer	RIA
Ananas comosus, *Mangifera indica*	Methanol and C18 cartridges	HPLC-FD and ELISA
Musa sp., *Ananas comosus, Punica granatum*	10%Na_2CO_3 and diethyl ether	GC-MS
Vitis Vinifera	Methanol and C18 cartridges	HPLC-FD and ELISA
Vitis Vinifera	5 g/L tartaric acid in water/ethanol mixture and C8 sorbent	HPLC-FD
Prunus avium	50 mm Pbs buffer and chloroform	HPLC-MS
Fragaria ananassa	Acetone and C18 cartridges	HPLC-MS
Montmorency, Balaton tart cherry	Methanol and C18 cartridges	HPLC-MS
Montmorency, Balaton tart cherry	50 mm K_3PO_4 buffer and chloroform	HPLC-ECD

LC-FLD liquid chromatography with fluorescence detection, *LC-MS* liquid chromatography-mass spectrometry, *LC-UV* liquid chromatography with ultraviolet detection, *ELISA* enzyme-linked immunosorbent assay, *RIA* radioimmunoassay, *GC-MS* gas chromatography-mass spectrometry, *HPLC-FD* high-performance liquid chromatography with fluorescence detection, *HPLC-ECD* high-performance liquid chromatography with electrochemical detection

water in varying ratios. To reduce the retention period, it is preferable to raise the concentration of organic solvents in the mobile phase because there is no upper limit for their concentration in HPLCeFD (Huang and Mazza 2011). Consequently, compared to HPLCeECD, HPLCeFD provides a superior potential for melatonin detection.

2.6.3 Extraction of Melatonin

For purification and to prevent clogging of the HPLC column, C18 solid phase extraction (SPE) can be combined with acetone and PCA extraction techniques. Many medicinal plants were found to have substantially greater melatonin concentrations, as shown by experiments using SPE and HPLC (Chen et al. 2003). The intrinsic selectivity of this HPLC application is enhanced by combining melatonin derivatization with HPLC purification to produce a product with a distinct fluorescence spectrum and retention time under the same chromatographic conditions. For the first time, this technique was utilized to quantify melatonin in photoautotrophic organisms. It involves the conversion of melatonin to 6-MOQMA (Iinuma et al. 1999).

Liquid extraction using 10% Na_2CO_3 and diethyl ether was used to extract melatonin from bananas. RIA (radioimmunoassay) kits were also used in cabbage, spinach, radish, etc. (Dubbels et al. 1995). Melatonin was extracted from apples, pineapples, strawberries, and pomegranates using a similar sequential process (Badria 2002). Using phosphate buffer and chloroform, melatonin in cherries was extracted, and the recovery rates from sour and sweet cherries, respectively, were 60% and 70.7% (Burkhardt et al. 2001; González-Gómez et al. 2009).

Melatonin was isolated from grape skins, strawberries, and mangoes using SPE with C18 cartridges (Iriti et al. 2006; Sturtz et al. 2011; Johns et al. 2013). Melatonin may be absorbed by SPE, and its expensive extraction is a significant drawback. According to a different research, the sample pretreatment process known as microextraction by packed sorbent (MEPS) is quicker and less expensive than standard SPE. It also needs less sample and solvent volume for melatonin extraction (Mercolini et al. 2012). It revealed that all examined samples had melatonin recovery rates with MEPS pretreatment that above 90%. Microwave-assisted extraction (MAE) was developed by Setyaningsih et al. (2012) for very accurate melatonin extraction from rice. Because of the novel extraction technique used, they claimed that the average quantity of melatonin in short grain varieties (54.17 13.48 ng/g) is significantly greater than the fig. (1.0 0.06 ng/g) reported by Hattori et al. (1995).

According to Stege et al. (2010), sonication can cause cavitations, which produce microenvironments with high temperatures and high pressures and speed up the removal of analytes from complicated matrices. So, melatonin extraction may also be done with the use of ultrasonography.The whole extraction time can take anywhere between 15 min and more than 16 h, and in most situations, the reader is left to infer the total extraction time based on the length of time for separate procedures like shaking, sonication, or drying.

Light is a major factor that contributes to the degradation of melatonin. Since sonication generates heat even when done in an ice bath, the study conducted by Maharaj and Dukie (2002), found that heat and to a lesser extent sonication had the greatest impact on the stability of melatonin, indicating the importance of temperature on melatonin stability.

2.7 Conclusion

Melatonin functions as a circadian regulator, cytoprotector, and growth promoter in plants, where it has been documented to be engaged in a number of physiological processes. The information presented in this study explains the melatonin's chemical properties as well as the usual biosynthetic routes used by both plants and animals. Melatonin, which is thought to have initially developed to offer molecular defence against free radicals, has acquired additional functions over a very long evolutionary period. Melatonin is thought to have first evolved in microorganisms about 3.0–2.5 billion years ago. Rhizogenesis, cellular growth, and stress defence are additional functions of this compound. In this regard, a number of evaluations with condensed data can be examined. Moreover, the main biochemical and biomolecular differences were highlighted. In fact, the benefits found in previous studies and the lack of toxicity at large doses support the use of this indolamine as a dietary additive for animals and plants. A plant's melatonin production is thought to be for its own defence against free radicals produced by environmental or metabolic activities, such as photosynthesis. To corroborate this, it has been shown that the sensitivity of *Nicotiana tabacum* leaves to ozone (a free radical producer) damage varies among kinds, with the susceptibility decreasing in leaves with the greatest melatonin contents. This is in line with the theory that melatonin serves as an antioxidant in both plants and mammals. Melatonin in significant concentrations has also been found in seeds of edible plants. Hence, melatonin in seeds has been found to be crucial for shielding germ and reproductive organs from oxidative damage brought on by UV radiation, drought, temperature fluctuations, and environmental pollutants.

References

Acuna-Castroviejo D, Noguiera-Navarro MT, Reiter RJ, Escames G (2018) Melatonin actions in the heart: more than a hormone. Melaton Res 1:21–26. https://doi.org/10.32794/mr11250002

Alkozi HA, Sánchez JM, Doadrio AL, Pintor J (2017) Docking studies for melatonin receptors. Expert Opin Drug Discov 13:241–248. https://doi.org/10.1080/17460441.2018.1419184

Altaf MA, Shahid R, Kumar R, Altaf MM, Kumar A, Khan LU, Saqib M, Azher Nawaz M, Saddiq B, Bahadur S, Tiwari RK, Lal MK, Naz S (2022) Phytohormones mediated modulation of abiotic stress tolerance and potential crosstalk in horticultural crops. J Plant Growth Regul 1–27:4724. https://doi.org/10.1007/S00344-022-10812-0

Altaf MA, Shahid R, Ren MX, Khan LU, Altaf MM, Jahan MS, Nawaz MA, Naz S, Shahid S, Lal MK, Tiwari RK, Shahid MA (2021) Protective mechanisms of melatonin against vanadium Phytotoxicity in tomato seedlings: insights into nutritional status, photosynthesis, root architecture system, and antioxidant machinery. J Plant Growth Regul 1–17:3300. https://doi.org/10.1007/s00344-021-10513-0

Altaf MA, Sharma N, Singh J, Samota MK, Sankhyan P, Singh B, Kumar A, Naz S, Lal MK, Tiwari RK, Kumar R (2023) Mechanistic insights on melatonin-mediated plant growth regulation and hormonal cross-talk process in solanaceous vegetables. Sci Hortic 308:111570. https://doi.org/10.1016/J.SCIENTA.2022.111570

Arnao MB, Hernández-Ruiz J (2007) Melatonin promotes adventitious-and lateral root regeneration in etiolated hypocotyls of Lupinus albus L. J Pineal Res 42:147–152

Arnao MB, Hernández-Ruiz J (2015) Functions of melatonin in plants: a review. J Pineal Res 59: 133–150

Arnao MB, Hernández-Ruiz J (2019) Melatonin: a new plant hormone and/or a plant master regulator?. Trend Plant Sci 24(1):38–48

Axelrod J, Weissbach H (1960) Enzymatic O-methylation of N-acetylserotonin to melatonin. Science 131(3409):1312

Back K, Tan DX, Reiter RJ (2016) Melatonin biosynthesis in plants: multiple pathways catalyze tryptophan to melatonin in the cytoplasm or chloroplasts. J Pineal Res 61:426–437

Badria FA (2002) Melatonin, serotonin, and tryptamine in some Egyptian food and medicinal plants. J Med Food 5:153–157

Baker PC, Quay WB, Axelrod J (1965) Development of hydroxyindole-O-methyl transferase activity in eye and brain of the amphibian, Xenopus laevis. Life Sci 4(20):1981–1987

Behera B, Kancheti M, Raza MB, Shiv A, Mangal V, Rathod G, Altaf MA, Kumar A, Aftab T, Kumar R, Tiwari RK, Lal MK, Singh B (2022) Mechanistic insight on boron- mediated toxicity in plant Vis-a-Vis its mitigation strategies: a review. Int J Phytoremediation 25:9. https://doi.org/10.1080/15226514.2022.2049694

Black C, Chevallier OP, Elliott CT (2016) The current and potential applications of ambient mass spectrometry in detecting food fraud. TrAC Trends Anal Chem 82:268–278

Bochkov DV, Sysolyatin SV, Kalashnikov AI, Surmacheva IA (2012) Shikimic acid: review of its analytical, isolation, and purification techniques from plant and microbial sources. J Chem Biol 5:5–17

Boutin JA (2016) Quinone reductase 2 as a promising target of melatonin therapeutic actions. Expert Opin Ther Targets 20:303–317

Boutin JA, Ferry G (2019) Is there sufficient evidence that the melatonin binding site MT3 is Quinone reductase 2? J Pharmacol Exp Ther 368:59–65

Boutin JA, Saunier C, Guenin SP, Berger S, Moulharat N, Gohier A et al (2008) Studies of the melatonin binding site location onto quinone reductase 2 by directed mutagenesis. Arch Biochem Biophys 477:12–19

Burkhardt S, Tan DX, Manchester LC, Hardeland R, Reiter RJ (2001) Detection and quantification of the antioxidant melatonin in Montmorency and Balaton tart cherries (Prunus cerasus). J Agric Food Chem 49:4898–4902

Byeon Y, Lee HJ, Lee HY, Back K (2016) Cloning and functional characterization of the Arabidopsis N-acetylserotonin O-methyltransferase responsible for melatonin synthesis. J Pineal Res 60:65–73

Cai SY, Zhang Y, Xu YP, Qi ZY, Li MQ, Ahammed GJ et al (2017) HsfA1a upregulates melatonin biosynthesis to confer cadmium tolerance in tomato plants. J Pineal Res 62:e12387

Case A (2017) On the origin of superoxide dismutase: an evolutionary perspective of superoxide-mediated redox signaling. Antioxidants 6:82

Casteilla L, Rigoulet M, Pénicaud L (2001) Mitochondrial ROS metabolism: modulation by uncoupling proteins. IUBMB Life 52:181–188

Chanut E, Nguyen-Legros J, Versaux-Botteri C, Trouvin JH, Launay JM (1998) Determination of melatonin in rat pineal, plasma and retina by high-performance liquid chromatography with electrochemical detection. J Chromatogr B Biomed Sci Appl 709(1):11–18

Chen G, Huo Y, Tan DX et al (2003) Melatonin in Chinese medicinal herbs. Life Sci 73:19–26

Choi GH, Lee HY, Back K (2017) Chloroplast overexpression of rice caffeic acid O-methyltransferase increases melatonin production in chloroplasts via the 5-methoxytryptamine pathway in transgenic rice plants. J Pineal Res 63:e12412

Chourasia KN, Lal MK, Tiwari RK, Dev D, Kardile HB, Patil VU, Kumar A, Vanishree G, Kumar D, Bhardwaj V, Meena JK, Mangal V, Shelake RM, Kim JY, Pramanik D (2021) Salinity stress in potato: understanding physiological, biochemical and molecular responses. Life 11(6):545. https://doi.org/10.3390/life11060545

Chourasia KN, More SJ, Kumar A, Kumar D, Singh B, Bhardwaj V, Kumar A, Das SK, Singh RK, Zinta G, Tiwari RK, Lal MK (2022) Salinity responses and tolerance mechanisms in

underground vegetable crops: an integrative review. Planta 255(3):1–25. https://doi.org/10.1007/S00425-022-03845-Y

Devi R, Behera B, Raza MB, Mangal V, Altaf MA, Kumar R, Kumar A, Tiwari RK, Lal MK, Singh B (2022) An insight into microbes mediated heavy metal detoxification in plants: a review. J Soil Sci Plant Nutr 22(1):914–936

Dubbels R, Reiter RJ, Klenke E et al (1995) Melatonin in edible plants identified by radioimmunoassay and by high performance liquid chromatography-mass spectrometry. J Pineal Res 18:28–31

Dubocovich ML, Delagrange P, Krause DN, Sugden D, Cardinali DP, Olcese J (2010) International Union of Basic and Clinical Pharmacology. LXXV nomenclature, classification, and pharmacology of G protein coupled melatonin receptors. Pharmacol Rev 62:343–380

Eriksson K, Östin A, Levin JO (2003) Quantification of melatonin in human saliva by liquid chromatography–tandem mass spectrometry using stable isotope dilution. J Chromatogr B 794(1):115–123

Erland LA, Murch SJ, Reiter RJ, Saxena PK (2015) A new balancing act: the many roles of melatonin and serotonin in plant growth and development. Plant Signal Behav 10:e1096469

Estrada-Rodgers L, Levy GN, Weber WW (1998) Characterization of a hormone response element in the mouse N-acetyltransferase 2 (Nat2∗) promoter. Gene Expr 7:13–24

Fourtillan JB, Gobin P, Faye B, Girault J (1994) A highly sensitive assay of melatonin at the femtogram level in human plasma by gas chromatography/negative ion chemical ionization mass spectrometry. Biol Mass Spectrom 23(8):499–509

Fuller PM, Gooley JJ, Saper CB (2006) Neurobiology of the sleep-wake cycle: sleep architecture, circadian regulation, and regulatory feedback. J Biol Rhythm 21(6):482–493

Galano A, Reiter RJ (2018) Melatonin and its metabolites vs. oxidative stress: from individual actions to collective protection. J Pineal Res 65:e12514

Galano A, Tan DX, Reiter RJ (2018) Melatonin: a versatile protector against oxidative DNA damage. Molecules 23:E530

Garcia-Parrilla MC, Cantos E, Troncoso AM (2009) Analysis of melatonin in foods. J Food Compos Anal 22:177–183

González-Gómez D, Lozano M, Fernández-León MF (2009) Eur Food Res Technol 229:223–229

Hardeland R (2016) Melatonin in plants—diversity of levels and multiplicity of functions. Front Plant Sci 7:198

Hattori A, Migitaka H, Iigo M et al (1995) Identification of melatonin in plants and its effects on plasma melatonin levels and binding to melatonin receptors in vertebrates. Biochem Mol Biol Int 35:627–634

Hernández-Ruiz J, Cano A, Arnao MB (2005) Melatonin acts as a growth-stimulating compound in some monocot species. J Pineal Res 39:137–142

Hill SM, Frasch T, Xiang S, Yuan L, Duplessis T, Mao L (2009) Molecular mechanisms of melatonin anticancer effects. Integr Cancer Ther 8:337–346. https://doi.org/10.1177/1534735409353332

Huang X, Mazza G (2011) Application of LC and LCeMS to the analysis of melatonin and serotonin in edible plants. Crit Rev Food Sci Nutr 51:269–284

Iinuma F, Hamase K, Matsubayashi S et al (1999) Sensitive determination of melatonin by precolumn derivatization and reversed-phase high-performance liquid chromatography. J Chromatogr A 835:67–72

Iriti M, Rossoni M, Faoro F (2006) Melatonin content in grape: myth or panacea? J Sci Food Agric 86:1432–1438

Jan JE, Reiter RJ, Wasdell MB, Bax M (2009) The role of the thalamus in sleep, pineal melatonin production, and circadian rhythm sleep disorders. J Pineal Res 46(1):1–7

Jockers R, Delagrange P, Dubocovich ML, Markus RP, Renault N, Tosini G et al (2016) Update on melatonin receptors: IUPHAR review 20. Br J Pharmacol 173:2702–2725

Johns NP, Johns J, Porasuphatana S, Plaimee P, Sae-Teaw M (2013) Dietary intake of melatonin from tropical fruit altered urinary excretion of 6-sulfatoxymelatonin in healthy volunteers. J Agric Food Chem 61:913–919

Kanwar MK, Yu J, Zhou J (2018) Phytomelatonin: recent advances and future prospects. J Pineal Res 65:e12526

Korkmaz A, Reiter RJ, Topal T, Manchester LC, Oter S, Tan DX (2009) Melatonin: an established antioxidant worthy of use in clinical trials. Mol Med 15:43–50

Kumar R, Kaundal P, Tiwari RK, Lal MK, Kumari H, Kumar R, Naga KC, Kumar A, Singh B, Sagar V, Sharma S (2023a) Development of reverse transcription recombinase polymerase amplification (RT-RPA): a methodology for quick diagnosis of potato Leafroll viral disease in potato. Int J Mol Sci 24:2511. https://doi.org/10.3390/ijms24032511

Kumar R, Kaundal P, Tiwari RK, Siddappa S, Kumari H, Lal MK, Naga KC, Sharma S, Sagar V, Kumar M (2022a) Establishment of a one-step reverse transcription recombinase polymerase amplification assay for the detection of potato virus S. J Virol Methods 307:114568. https://doi.org/10.1016/j.jviromet.2022.114568

Kumar D, Lal MK, Dutt S, Raigond P, Changan SS, Tiwari RK, Chourasia KN, Mangal V, Singh B (2022c) Functional fermented probiotics, prebiotics, and synbiotics from non-dairy products: a perspective from nutraceutical. In: Molecular nutrition and food research, vol 66. Wiley, Hoboken, NJ, p 2101059. https://doi.org/10.1002/mnfr.202101059

Kumar A, Lal MK, Sahoo U, Sahoo SK, Sah RP, Tiwari RK, Kumar R, Sharma S (2023b) Combinatorial effect of heat processing and phytic acid on mineral bioavailability in rice grain. Food Chem Adv 2:100232. https://doi.org/10.1016/j.focha.2023.100232

Kumar A, Sahoo U, Lal MK, Tiwari RK, Lenka SK, Singh NR, Gupta OP, Sah RP, Sharma S (2022b) Biochemical markers for low glycemic index and approaches to alter starch digestibility in rice. J Cereal Sci 106:103501. https://doi.org/10.1016/j.jcs.2022.103501

Kump LR, Barley ME (2007) Increased subaerial volcanism and the rise of atmospheric oxygen 2.5 billion years ago. Nature 448:1033–1036

Lal MK, Kumar A, Raigond P, Dutt S, Changan SS, Chourasia KN, Tiwari RK, Kumar D, Sharma S, Chakrabarti SK, Singh B (2021b) Impact of starch storage condition on glycemic index and resistant starch of cooked potato (Solanum tuberosum) tubers. Starch 73(1–2): 1900281. https://doi.org/10.1002/star.201900281

Lal MK, Sharma N, Adavi SB, Sharma E, Altaf MA, Tiwari RK, Kumar R, Kumar A, Dey A, Paul V, Singh B (2022a) From source to sink: mechanistic insight of photoassimilates synthesis and partitioning under high temperature and elevated [CO2]. Plant Mol Biol 110:1–20. https://doi.org/10.1007/s11103-022-01274-9

Lal, M. K., Tiwari, R. K., Gahlaut, V., Mangal, V., Kumar, A., Singh, M. P., Paul, V., Kumar, S., Singh, B., & Zinta, G. (2022b). Physiological and molecular insights on wheat responses to heat stress. In Plant cell reports (Vol. 41, 3, pp. 501–518). Springer. Cham doi:https://doi.org/10.1007/s00299-021-02784-4

Lal MK, Tiwari RK, Kumar R, Naga KC, Kumar A, Singh B, Raigond P, Dutt S, Chourasia KN, Kumar D, Parmar V, Changan SS (2021a) Effect of potato apical leaf curl disease on glycemic index and resistant starch of potato (*Solanum tuberosum* L.) tubers. Food Chem 359:129939. https://doi.org/10.1016/j.foodchem.2021.129939

Lauber JK, Boyd JE, Axelrod J (1968) Enzymatic synthesis of melatonin in avian pineal body: extraretinal response to light. Science 161(840):489–490

Lee K, Zawadzka A, Czarnocki Z, Reiter RJ, Back K (2016) Molecular cloning of melatonin 3-hydroxylase and its production of cyclic 3-hydroxymelatonin in rice (Oryza sativa). J Pineal Res 61:470–478

Lerner AB, Case JD, Mori W, Wright MR (1959) Melatonin in peripheral nerve. Nature 183(4678): 1821

Lerner B, Case JD, Takahashi Y, Lee TH, Mori W (1958a) Isolation of melatonin, the pineal gland factor that lightens melanocytes. J Am Chem Soc 80(10):2587–2592

Lerner AB, Case JD, Takahashi Y, Lee TH, Mori W (1958b) Isolation of melatonin, the pineal gland factor that lightens melanocyteS1. J Am Chem Soc 80:2587. https://doi.org/10.1021/ja01543a060

Liang C, Li A, Yu H, Li W, Liang C, Guo S et al (2017) Melatonin regulates root architecture by modulating auxin response in rice. Front Plant Sci 8:134

Lochner A, Marais E, Huisamen B (2018) Melatonin and cardioprotection against ischaemia/reperfusion injury: what's new? A review. J Pineal Res 65:e12490

Lu J, Lau C, Lee MK, Kai M (2002) Simple and convenient chemiluminescence method for the determination of melatonin. Anal Chim Acta 455(2):193–198

Maharaj DS, Dukie SA (2002) The identification of the UV degradants of melatonin and their ability to scavenge free radicals. J Pineal Res 32:257–261

Manchester LC, Coto-Montes A, Boga JA, Andersen LPH, Zhou Z, Galano A et al (2015) Melatonin: an ancient molecule that makes oxygen metabolically tolerable. J Pineal Res 59:403–419

Manchester LC, Tan DX, Reiter RJ et al (2000) High levels of melatonin in the seeds of edible plants. Possible function in germ tissue protection. Life Sci 67:3023–3029

Mannino G, Gentile C, Ertani A, Serio G, Bertea CM (2021a) Anthocyanins: biosynthesis, distribution, ecological role, and use of biostimulants to increase their content in plant foods—a review. Agriculture 11:212

Mannino G, Pernici C, Serio G, Gentile C, Bertea CM (2021b) Melatonin and phytomelatonin: chemistry, biosynthesis, metabolism, distribution and bioactivity in plants and animals—an overview. Int J Mol Sci 22(18):9996

Margulis L (1975) Symbiotic theory of the origin of eukaryotic organelles; criteria for proof. Symp Soc Exp Biol 29:21–38

Menendez-Menendez J, Martinez-Campa C (2018) Melatonin: an anti-tumor agent in hormone-dependent cancers. Int J Endocrinol 2018:3271948. https://doi.org/10.1155/2018/3271948

Mercolini L, Mandrioli R, Raggi MA (2012) Content of melatonin and other antioxidants in grape-related foodstuffs: measurement using a MEPS-HPLC-F method. J Pineal Res 53:21–28

Milenkovic-Andjelkovic AS, Andjelkovic MZ, Radovanovic AN, Radovanovic BC, Nikolic V (2015) Hem Ind 69:331–337

Muxel SM, Laranjeira-Silva MF, Carvalho-Sousa CE, Floeter-Winter LM, Markus RP (2016) The RelA/cRel nuclear factor-κB (NF-κB) dimer, crucial for inflammation resolution, mediates the transcription of the key enzyme in melatonin synthesis in RAW 264.7 macrophages. J Pineal Res 60:394–404

Onaolapo AY, Onaolapo OJ (2018) Circadian dysrhythmia-linked diabetes mellitus: examining melatonin's roles in prophylaxis and management. World J Diabetes 9:99–114

Park M, Kang K, Park S, Back K (2008) Conversion of 5-hydroxytryptophan into serotonin by tryptophan decarboxylase in plants, Escherichia coli, and yeast. Biosci Biotech Bioch 72:2456–2458

Pieri C, Marra M, Moroni F, Recchioni R, Marcheselli F (1994) Melatonin: A peroxyl radical scavenger more effective than vitamin E. Life Sci 55:PL271–PL276. https://doi.org/10.1016/0024-3205(94)00666-0

Poeggeler B, Hardeland R (1994) Detection and quantification of melatonin in a dinoflagellate, *Gonyaulax polyedra*: solutions to the problem of methoxyindole destruction in non-vertebrate material. J Pineal Res 17:1–10

Pshenichnyuk SA, Modelli A, Jones D, Lazneva EF, Komolov AS (2017) Low-energy electron interaction with melatonin and related compounds. J Phys Chem B 121:3965–3974

Radi A, Bekhiet GE (1998) Voltammetry of melatonin at carbon electrodes and determination in capsules. Bioelectrochem Bioenerg 45(2):275–279

Reiter RJ, Rosales-Corral S, Tan DX, Jou MJ, Galano A, Xu B (2017a) Melatonin as a mitochondria-targeted antioxidant: one of evolution's best ideas. Cell Mol Life Sci 74:3863–3881

Reiter RJ, Rosales-Corral S, Zhou X, Tan DX (2017b) Role of SIRT3/SOD2 signaling in mediating the antioxidant actions of melatonin in mitochondria. Curr Trends Endocrinol 9:45–49
Reiter RJ, Tan DX, Manchester LC, Pilar TM, Terron PM, Koppisepi S (2007) Medical implications of melatonin: receptor-mediated and receptor independent actions. Adv Med Sci 52:11–28
Reiter R, Tan DX, Rosales-Corral S, Manchester C (2013) The universal nature, unequal distribution and antioxidant functions of melatonin and its derivatives. Mini Rev Med Chem 13(3): 373–384
Reiter JR, Tan DX, Zhou Z, Cruz HM, Fuentes-Broto L, Galano A (2015) Phytomelatonin: assisting plants to survive and thrive. Molecules 20:7396–7437
Reybier K, Perio P, Ferry G, Bouajila J, Delagrange P, Boutin JA et al (2011) Insights into the redox cycle of human quinone reductase 2. Free Radic Res 45:1184–1195
Riga P, Medina S, García-Flores LA, Gil-Izquierdo Á (2014) Food Chem 156:347–352
Rizzo V, Porta C, Moroni M, Scoglio E, Moratti R (2002) Determination of free and total (free plus protein-bound) melatonin in plasma and cerebrospinal fluid by high-performance liquid chromatography with fluorescence detection. J Chromatogr B 774(1):17–24
Rodriguez IR, Mazuruk K, Schoen TJ, Chader GJ (1994) Structural analysis of the human hydroxyindole-O-methyltransferase gene. Presence of two distinct promoters. J Biol Chem 269:31969–31977
Setyaningsih W, Palma M, Barroso CG (2012) A new microwave-assisted extraction method for melatonin determination in rice grains. J Cereal Sci 56:340–346
Setyaningsih W, Saputro IE, Barbero GF, Palma M, Garcia-Barroso C (2015) J Agric Food Chem 63:1107–1115
Shi H, Chen K, Wei Y, He C (2016) Fundamental issues of melatonin mediated stress signaling in plants. Front Plant Sci 7:1124
Shi H, Jiang C, Ye T, Tan DX, Reiter RJ, Zhang H et al (2015) Comparative physiological, metabolomic, and transcriptomic analyses reveal mechanisms of improved abiotic stress resistance in bermudagrass [Cynodon dactylon (L). Pers] by exogenous melatonin. J Exp Bot 66: 681–694
Slominski RM, Reiter RJ, Schlabritz-Loutsevitch N, Ostrom RS, Slominski AT (2012) Melatonin membrane receptors in peripheral tissues: distribution and functions. Mol Cell Endocrinol 351: 152–166
Stege PW, Sombra LL, Messina G, Martinez LD, Silva MF (2010) Determination of melatonin in wine and plant extracts by capillary electrochromatography with immobilized carboxylic multiwalled carbon nanotubes as stationary phase. Electrophoresis 31(13):2242–2248
Sturtz M, Cerezo AB, Cantos-Villar E, Garcia-Parrilla MC (2011) Determination of the melatonin content of different varieties of tomatoes (Lycopersicon esculentum) and strawberries (Fragaria ananassa). Food Chem 127:1329–1334
Sun Q, Zhang N, Wang J, Zhang H, Li D, Shi J, Guo YD et al (2015) Melatonin promotes ripening and improves quality of tomato fruit during postharvest life. J Exp Bot 66(3):657–668
Suofu V, Li W, Jean-Alphonse FG, Jia J, Khattar NK, Li J et al (2017) Dual role of mitochondria in producing melatonin and driving GPCR signaling to block cytochrome c release. Proc Natl Acad Sci USA 114:E7997–E8006. https://doi.org/10.1073/pnas.1705768114
Tamtaji OR, Mobini M, Reiter RJ, Azami A, Gholami MS, Asemi Z (2018) Melatonin, a toll-like receptor inhibitor: current status and future perspectives. J Cell Physiol 2018:27698
Tan DX, Chen LD, Poeggeler B, Manchester LC, Reiter RJ (1993) Melatonin: a potent, endogenous hydroxyl radical scavenger. Endocr J 1:57–60
Tan DX, Hardeland R, Manchester LC, Paredes SD, Korkmaz A, Sainz RM et al (2010) The changing biological roles of melatonin during evolution: from an antioxidant to signals of darkness, sexual selection and fitness. Biol Rev 85:607–623
Tan DX, Manchester LC, Esteban-Zubero E, Zhou Z, Reiter R (2015) Melatonin as a potent and inducible endogenous antioxidant: synthesis and metabolism. Molecules 20:18886

Tan DX, Manchester LC, Liu X, Rosales-Corral SA, Acuna-Castroviejo D, Reiter RJ (2013) Mitochondria and chloroplasts as the original sites of melatonin synthesis: a hypothesis related to melatonin's primary function and evolution in eukaryotes. J Pineal Res 54:127–138

Treberg JR, Braun K, Zacharias P, Kroeker K (2018) Multidimensional mitochondrial energetics: applications to the study of electron leak and hydrogen peroxide metabolism. Comp Biochem Physiol B Biochem Mol Biol 224:121–128

Van Tassel DL, Roberts N, Lewy A et al (2001) Melatonin in plant organs. J Pineal Res 31:8–15

Wang L, Feng C, Zheng X, Guo Y, Zhou F, Shan D, Liu X, Kong J (2017) Plant mitochondria synthesize melatonin and enhance the tolerance of plants to drought stress. J Pineal Res 63: e12429

Wang RX, Liu H, Xu L, Zhang H, Zhou RX (2015) Involvement of nuclear receptor RZR/RORgamma in melatonin-induced HIF-1alpha inactivation in SGC-7901 human gastric cancer cells. Oncol Rep 34:2541–2546. https://doi.org/10.3892/or.2015.4238

Wei Y, Chang Y, Zeng H, Liu G, He C, Shi H (2018) RAV transcription factors are essential for disease resistance against cassava bacterial blight via activation of melatonin biosynthesis genes. J Pineal Res 64:e12454

Yu Y, Bian L, Jiao Z, Yu K, Wan Y, Zhang G, Guo D (2019) Molecular cloning and characterization of a grapevine (Vitis vinifera L.) serotonin N-acetyltransferase (VvSNAT2) gene involved in plant defense. BMC Genomics 20:880

Yu Y, Lv Y, Shi Y, Li T, Chen Y, Zhao D et al (2018) The role of phyto-melatonin and related metabolites in response to stress. Molecules 23:1887. https://doi.org/10.3390/molecules23081887

Zhang J, Qiu J, Zhou Y, Wang Y, Li H, Zhang T et al (2018) LIM homeobox transcription factor Isl1 is required for melatonin synthesis in the pig pineal gland. J Pineal Res 65:e12481

Zhao Y, Xu L, Ding S, Lin N, Ji Q, Gao L et al (2017) Novel protective role of the circadian nuclear receptor retinoic acid-related orphan receptor-alpha in diabetic cardiomyopathy. J Pineal Res 62:e12378. https://doi.org/10.1111/jpi.12378

Zhao D, Yu Y, Shen Y, Liu Q, Zhao Z, Sharma R, Reiter RJ (2019) Melatonin synthesis and function: evolutionary history in animals and plants. Front Endocrinol 10:249