



Melatonin Discovery and Divergent Biosynthetic Pathways in Plants

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Thakur Roshan Suresh, Jyostnarani Pradhan, Shailesh Kumar, Hemlata Singh, Killi Prasad, Aman Jaiswal, and Geeta Kumari

Abstract

Despite the fact that we all know that melatonin plays a role and has some profound effects on animals, recent studies have shown that this biochemical can also be found in plants, microorganisms, and algae, and its effects can be seen in these organisms as well. Primarily, melatonin is considered a “sleep hormone”. In animals, it acts as an antioxidant, anti-inflammatory, and anti-carcinogenic agent and is used to treat several diseases. It is available in the market as a supplement. Melatonin has several functional roles in the plants, such as abiotic stress tolerance, as a secondary metabolite, synthesis of several phytohormones, defence mechanism, acts as a phytohormone, seedling growth, fruit development, root development, seed germination, flower development, crop and fruit yield, fruit storage, etc. Melatonin acts differently in different growth phases of the plants, viz., vegetative and reproductive phases. Also, it is found to have nutraceutical value. Here, in this chapter, we are dealing briefly with a historical perspective of this hormone, the isolation of this compound, how this hormone has importance in animals as well as in plants, how it was discovered, its biosynthetic pathways, the precursors and organelles involved in synthesis; altogether. Also, we are dealing with the comparative study of the mechanism

T. R. Suresh · J. Pradhan (✉) · S. Kumar · H. Singh

Department of Botany, Plant Physiology and Biochemistry, College of Basic Sciences and Humanities, Dr. Rajendra Prasad Central Agriculture University, Pusa, Samastipur, Bihar, India
e-mail: [jyotsna.pradhan@rpcau.ac.in](mailto: jyotsna.pradhan@rpcau.ac.in)

K. Prasad

Department of Horticulture, Tirhut College of Agriculture, Dr. Rajendra Prasad Central Agriculture University, Pusa, Samastipur, Bihar, India

A. Jaiswal · G. Kumari

Department of Microbiology, College of Basic Sciences and Humanities, Dr. Rajendra Prasad Central Agriculture University, Pusa, Samastipur, Bihar, India

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of this newly discovered chemical in plants as well as animals, along with its current use in our day-to-day lives. Various studies have shown the abundance of this molecule and its benefits for humankind and plants.

Keywords

Melatonin · Plants · Animals · Biosynthetic pathways · Nutraceutical value

1.1 Introduction

Melatonin has also been studied for use in treating sleep disorders in addition to jet lag. Generally speaking, it decreases sleep latency and enhances sleep, particularly when circadian phasing is disrupted. Patients with neurological illnesses benefited the most from this in the latter situation (Hardeland 2005; Altaf et al. 2023). Several initiatives designed to lessen the effects of neurodegenerative illnesses such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis have been created or are being investigated to deal with these conditions (Altaf et al. 2022a, b). The effectiveness of this compound as a cancer-fighting agent has been extensively studied. More research should be focused on the potential anti-inflammatory effects of *N*¹-acetyl-5-methoxykynuramine (AMK), particularly given that AMK is a natural downregulation and inhibitor of COX-2 (cyclooxygenase-2) (Hardeland 2005). The regulation of melatonin in the sleep/wake cycle, seasonal rhythms, and other circadian rhythms has already been observed, as well as its effect as an immunostimulator and cytoprotective agent. It has been observed that the substance is capable of safeguarding mitochondrial electron flux, antioxidant protection, and neuroprotection in various experimental systems. At night, melatonin levels are more significantly elevated, then information about "darkness" is passed on to the brain and light suppresses the mechanism by which it increases (Hardeland et al. 2006).

The chemical compound N-acetyl-5-methoxytryptamine, also referred to as melatonin, has been extensively researched in other parts of the world, and it is found in all living organisms, i.e., it is everywhere (Lerner et al. 1958; Zhang et al. 2023). In addition, it has been identified as a plant hormone that plays an important role in facilitating the regulation and development of plants (Arnao and Hernández-Ruiz 2019). A number of studies have shown that melatonin plays an essential role in maintaining a healthy circadian rhythm, sleep, mood, body temperature, appetite, and immune response in humans (Socaciu et al. 2020). Melatonin is a common indolamine that has received much research because the substance plays an essential role in controlling a wide range of physiological processes in animals and plants (Fig. 1.1). During the twentieth century, scientists discovered that certain plant species can synthesize large quantities of this chemical and store it in specialized tissues throughout the plant. As a result, it has been considered a ubiquitous molecule (Mannino et al. 2021).

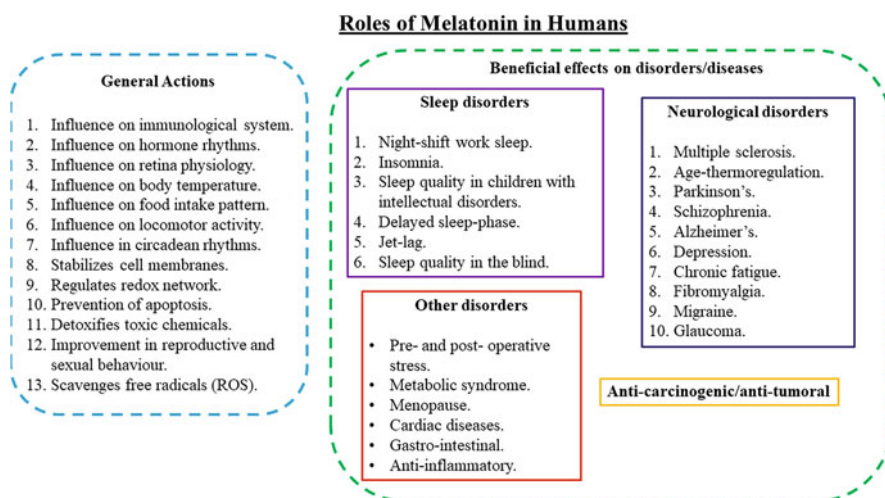


Fig. 1.1 Roles of melatonin in human physiology. Melatonin serves as a beneficial molecule/chemical in humans. Several functions of this hormone are depicted here entitled general actions, beneficial effects on sleep disorders, neurological disorders, other disorders, and anti-carcinogenic/anti-tumoral effects. *ROS* reactive oxygen species

It was originally thought that, when the substance was discovered, it was an antioxidant that had a wide range of positive effects on the various phases of plant growth and development, such as germination, root extension, photosynthesis, and leaf senescence (Arnao and Hernández-Ruiz 2019), as well as photosynthesis and leaf senescence (Wang et al. 2022). Among the many bioactive compounds present in vascular plants, it has been observed to be one of the most important (Ahmad et al. 2023) The compound can be found in a wide range of plant tissues, including those of seeds, roots, leaves, and fruits (Ahmad et al. 2023) Melatonin has been used extensively for disease pathogenesis and therapeutic development since it has been shown to modulate antioxidant, anti-inflammatory, and other biological properties (Zhang et al. 2023).

Melatonin is an artificially manufactured form of hormone present in animals, bacteria, plants, and fungi; apart from its antioxidant properties, melatonin has applications in beverages and food, dietary supplements, and pharmaceuticals. Bio-based “SPF” (spray polyurethane foam) is also synthesized from melatonin and having a role in generating insulation (Market analysis report 2019–2025). It is suggested by APA (American Psychiatric Association) reports that, throughout their lives, about one-third of adults experience sleep problems i.e., insomnia. Symptoms of this are persistent difficulties falling and persist in being asleep. Hence, it is obvious to observe the increased use of artificially synthesized melatonin (Lal et al. 2022; Mishra et al. 2022; Naz et al. 2022). It is expected that over the next 5 years, according to calculations, the Compound Annual Growth Rate (CAGR) for the melatonin market will be greater than 10%. The major companies which are functional in Melatonin Market are, viz., LLC, Natrol, Aspen Holdings, Pfizer

Incorporation, Biotics Research Corporation, Nature's Bounty (Market analysis report 2019–2025; Mordor Intelligence 2023–2028).

1.2 Melatonin Discovery in Animals and Plants

Up until 1995, “melatonin” had been one of the compounds that had received the most attention in the scientific literature as well as specialized journals, such as the *Melatonin Research* and *Journal of Pineal Research* (founded in 1984), which was founded in 1985. There was a belief that an animal hormone might be the cause of this problem in particular. However, after that, the undeniable discovery of plant-based melatonin was eventually made available to the scientific community back in 1995 by a trio of different research groups (Hattori et al. 1995; Dubbels et al. 1995). Similarly, Dr. Saxena's group in Canada has been developing and carrying out a line of research that is of particular interest. Various studies have suggested that melatonin may function as an auxin in in vitro cell cultures as a result of the structural similarities between IAA (indole-3-acetic acid) and melatonin. The researchers discovered phases of the phytomelatonin production pathway that were identical to the pathways already present in mammals (Murch et al. 2000, 2001; Murch and Saxena 2002) while they were studying the cells of St. John's wort (*Hypericum perforatum* L.) culture.

There was an initial confirmation in 2004 that melatonin had a growth-stimulating effect in the hypocotyls of etiolated lupin (*Lupinus albus* L.), with an estimated stimulatory potential up to 63% when compared to IAA's effects on lupin (Hernández-Ruiz et al. 2004). As previously mentioned, melatonin is the scientific name given to a hormone that is able to contract melanophores, which is implicated in the lightening of skin in frogs and fish melanocytes (skin-lightening molecule) (Hardeland et al. 2006). As a matter of fact, melatonin is now well known to exist in all kingdoms of life, from prokaryotes to eukaryotes, and even in plants (Lal et al. 2023; Kumar et al. 2023a, b). Phytomelatonin is the name given to a molecule that can be found in plants, known as melatonin (Arnao 2014). There is a distinction between phytomelatonin, which is derived from algae and plants, and animal or synthetic melatonin, which is derived from animals or synthetic materials. There are a number of studies that deal with plant-derived melatonin, such as those in food chemistry, plant physiology, phytochemistry, botany, and so on, but this term is often used in these studies. A pleiotropic chemical that has many roles in a variety of physiological reactions in plants is phytomelatonin (Arnao and Hernández-Ruiz 2018, 2020a, 2022; Aghdam et al. 2022).

This hormone, originally discovered as a hormone produced by the pineal gland of a cow (Lerner et al. 1958; Arnao and Hernández-Ruiz 2020b), is now produced by fungi, invertebrates, protozoa, bacteria, plants, the Harderian gland, skin, gut, leukocytes, and a number of extrapineal sites in vertebrates. As a result of the accumulation of melanin granules in the melanocytes, this active factor plays a crucial role in illuminating the skin colour of tadpoles, frogs, toads, and some fish, but does not affect animals (Fig. 1.2). Melatonin is the name of the compound, and it



Fig. 1.2 This figure illustrates the effects of melatonin on plant growth and development, including seed germination, root development, seedling growth, flower development, crop and fruit yield, and fruit storage, which are all important in the development and growth of plants. (Modified from Zhang et al. 2023)

was scientifically identified as a N-acetylserotonin derivative in 1959 by Arnao and Hernández-Ruiz (Arnao and Hernández-Ruiz 2020a).

In 1960, Lerner isolated and identified this compound as a small molecule with a molecular weight of 232 Daltons. It was discovered that this molecule aggregated pigment granules in both fish and frog skin; hence, it was named. Melatonin is an extensively dispersed chemical found in all kingdoms of life (Mannino et al. 2021; Arnao et al. 2022). There are several physiological properties of melatonin that contribute to its ability to combat oxidative stress, promote reproduction, and promote plant growth. Plant NPs (natural products) are considered to be hormones as well as plant hormones (Mangal et al. 2023; Watpade et al. 2023). In an indirect manner, melatonin is synthesized through the shikimate pathway, as it is a by-product of the shikimate pathway (Elshafie et al. 2023). Including its pleiotropic properties, melatonin is an important abiotic stress signalling molecule for plants as it makes them more resilient to both mild and severe conditions, and it affects many aspects of their development and function (Ahmad et al. 2023).

1.3 Melatonin Precursors and Organelle Involved

Melatonin was discovered to be a component of all vertebrates, to be rhythmically modulated by the pineal gland's secretion, and to have a role in the circadian control and, occasionally, in the seasonal patterns (Hardeland et al. 2006). Several subcellular compartments, including the cytoplasm, endoplasmic reticulum, mitochondria, and chloroplasts, synthesize melatonin intermediates that control the following enzymatic pathways (Zhao et al. 2019; Arnao et al. 2023). It has been shown that rice plants contain up to four genes for histone DAC (deacetylases), enzymes that may reverse the conversions of 5-methoxytryptamine and serotonin into N-acetylserotonin and melatonin, respectively. Deacetylase activity of DAC is maximum for N-acetyltryptamine. Also, the chloroplast-expressed DAC displayed enzyme activity towards melatonin, N-acetyltryptamine, and N-acetylserotonin (Lee et al. 2018; Arnao et al. 2023).

The PMTR1, phyto melatonin receptor facilitates ROS signalling, controls homeostasis, and transmits a dark signal that stimulates night stomatal closure (preventing water loss during the night), which aids plant adaptation to dryland environments (Li et al. 2020). Melatonin is a multiregulatory molecule that controls the expression of genes related to abiotic stress resistance, the redox reactions and plant growth and development, sucrose metabolism {CWIN [cell wall invertase] and SUSY [sucrose synthase]}, and specialized metabolism {phenylpropanoid metabolism: DFR [dihydroflavonol reductase], CHI [chalcone isomerase] (Fig. 1.3). PAL [phenylalanine ammonia lyase], F3H [flavanone 3-hydroxylase], CHS [chalcone synthase], and ANS [anthocyanidin synthase]} (Weeda et al. 2014; Ahmad et al. 2023).

In plant cells, the location of the enzymes involved in the production of melatonin from tryptophan is varied. TDC is contained in the cytoplasm (Zhou et al. 2020). In chloroplasts, SNAT is expressed; in the endoplasmic reticulum, T5H is expressed

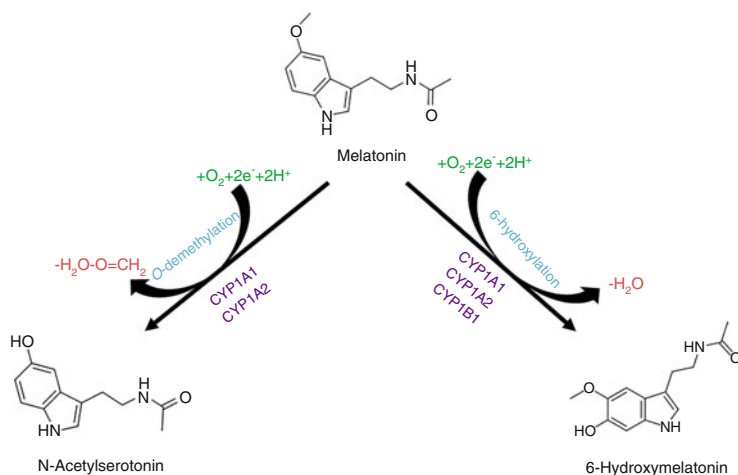


Fig. 1.3 The different P450 isozymes react with melatonin in different ways. For example, CYP1A1, CYP1A2, and CYP1B1 cause dominant 6-hydroxylation, but CYP2C19 creates products of the *O*-demethylation only in certain circumstances. However, some products of the *O*-demethylation are also seen with CYP1A2

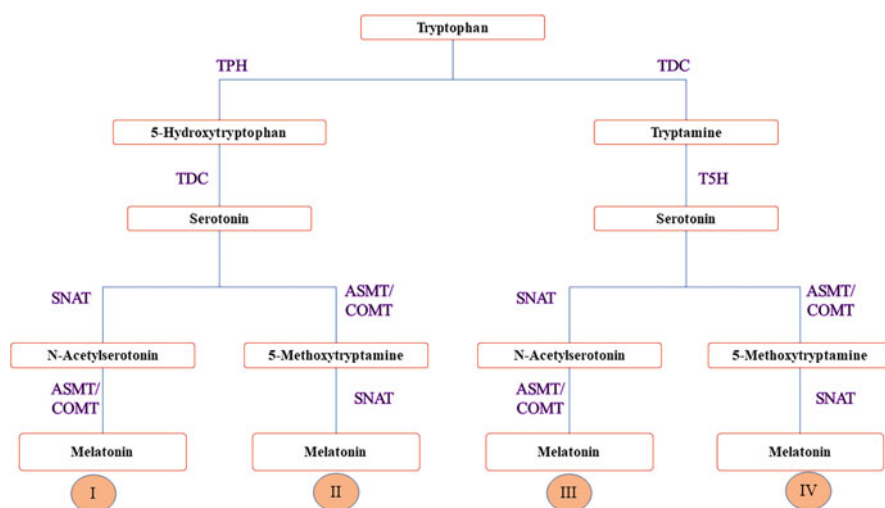


Fig. 1.4 Simplified representation of the melatonin biosynthesis via four different pathways. *TPH* tryptophan hydroxylase, *TDC* L-tryptophan decarboxylase, *T5H* tryptamine-5-hydroxylase, *SNAT* serotonin *N*-acetyltransferase, *ASMT* acetylserotonin *O*-methyltransferase, *COMT* caffeic acid 3-*O*-methyltransferase

(Back 2021; Rather et al. 2022), ASMT and COMT, however, are found in the cytoplasm (Mannino et al. 2021). The first and second of the four probable biosynthetic pathways of melatonin shown in Fig. 1.4 occur in the cytoplasm, while the

third and fourth pathways lead to serotonin production in the endoplasmic reticulum (Back et al. 2016). Melatonin synthesis and accumulation can occur at a variety of ultimate subcellular sites; however, SNATs are exclusively found in the chloroplast and ASMTs/COMT in the cytoplasm. For instance, the serotonin SHT (N-hydroxycinnamoyl transferase) rapidly converts serotonin into phenylpropanoid amides in the cytoplasm, such as feruloylserotonin (Byeon and Back 2015). 2-OHM (2-hydroxymelatonin) is a product of the melatonin metabolism in chloroplasts; this reaction is catalysed by M2H (melatonin-2-hydroxylase). Conversely, melatonin is quickly transformed into cyclic 3-OHM (3-hydroxymelatonin) by M3H (melatonin-3-hydroxylase) (Lee et al. 2016; Ye et al. 2019).

1.4 Melatonin Biosynthetic Pathway in Animals and Plants

All vertebrates now have an enlarged mechanism for melatonin production, and other creatures, like insects, can also use this system (Herbert et al. 1960; Rahman et al. 2023; Thakur et al. 2023; Bairwa et al. 2023). The availability of the precursor, tryptophan, is a glaring variation in melatonin synthesis between animals and plants. Animals must consume tryptophan through diet because they cannot synthesize it on their own, unlike plants (Naz et al. 2023). The main melatonin-producing organelles and concentration centres are found to be animal mitochondria, similar to plants (Reiter 1991). In an isotope tracer investigation, the idea of melatonin produced by plants was initially suggested (Murch et al. 2000). Although there is a great deal of controversy surrounding this, it is believed that the biosynthetic pathway for phytomelatonin in vascular plants is comparable to that in animals (Murch et al. 2000; Tan et al. 2013; Zhao et al. 2019). Axelrod's team first identified the mammalian melatonin biosynthesis route in 1960, and it is now well understood (Hardeland and Poeggeler 2003). The two functional groups of an indoleamine N-acetyl-5-methoxytryptamine (melatonin) have significance for the specificity of receptor binding, as well as for the molecule's amphiphilicity, which allows it to enter any cell, compartment, or bodily fluid, and, intriguingly, for its oxidation chemistry (Hardeland et al. 2006).

Pathways for biosynthesis appear to be the same. Membrane and nuclear receptors, additional chemical interactions, or binding sites mediate these pleiotropic activities. Hepatic P₄₅₀ monooxygenases mostly convert circulating melatonin to 6-hydroxyl and excrete it as 6-sulfatoxymelatonin. The relevance of pyrrole-ring cleavage is of the greater importance in other tissues, notably the brain. Photocatalytic, enzymatic, pseudoenzymatic, and multiple free-radical processes combine to produce the end product, *N*¹-acetyl-*N*²-formyl-5-methoxykynuramine. Hydroxylation and nitrosation lead to the production of additional metabolites. *N*¹-acetyl-5-methoxykynuramine, a secondary metabolite, promotes mitochondrial activity and suppresses cyclooxygenase-2 (Hardeland et al. 2006).

Tryptophan is assumed as the first substrate of the biosynthesis of melatonin and is engaged in four enzymatic steps that are catalysed by at least six enzymes, according to a number of research: including COMT (caffeic acid-*O*-

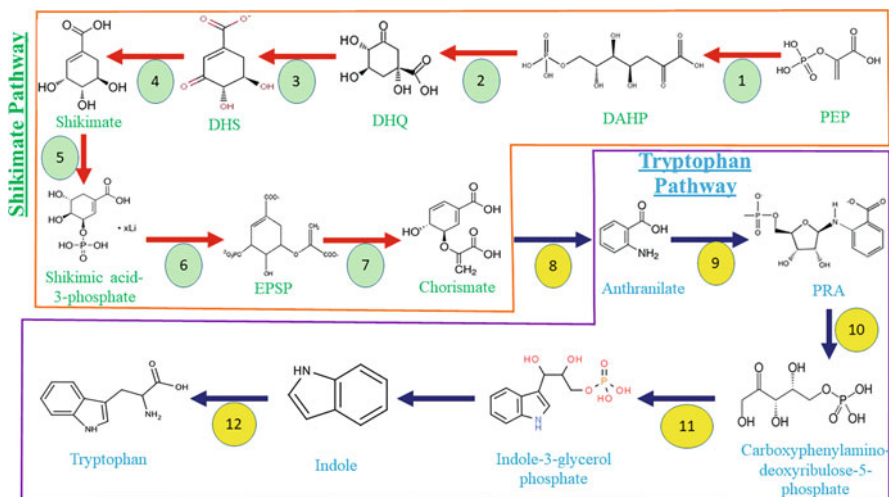


Fig. 1.5 Tryptophan, a major ingredient in the production of melatonin in plants, is produced by a biosynthetic process. (1) DAHP synthase; (2) DHQ synthase; (3) DHQ dehydratase; (4) Shikimate dehydrogenase; (5) Shikimate kinase; (6) EPSP synthase; (7) Chorismate synthase; (8) Anthranilate synthase; (9) PRPP (phosphoribosyl pyrophosphate) transferase; (10) PRAI (PRA isomerase); (11) IGP synthase; (12) Tryptophan synthase. *PEP* 2-phosphoenolpyruvate, *DAHP* 3-deoxy-D-arabinoheptulosonate-7-phosphate, *DHQ* 3-dehydroquinic acid, *DHS* 3-dehydroshikimate, *EPSP* 5-enolpyruvylshikimate-3-phosphate, *PRA* Phosphoribosyl antranilate

methyltransferase), ASMT (*N*-acetylserotonin methyltransferase), SNAT (serotonin-*N*-acetyltransferase), T5H (tryptamine-5-hydroxylase), TPH (tryptophan hydroxylase), and TDC (tryptophan decarboxylase) (Back et al. 2016; Sun et al. 2021). For the synthesis of melatonin, the two reactions that contribute to tryptophan are hydroxylation and decarboxylation. They have been found in plants that are classified as herbivorous (Ahmad et al. 2023). There are four potential pathways for the biosynthesis of auxin, or IAA (indole-3-acetic acid), which is produced naturally in plants, that is, IAM (indole-3-acetamide), TAM (tryptamine), IAOx (indole-3-acetaldoxime), and IPyA (indole-3-pyruvic acid) (Fig. 1.5). There is still a need for more research into the synthesis of auxin from tryptophan in various crops under abiotic stress. *N*-acetylserotonin is produced by the catalysis of serotonin by SNATs, which is then methoxylated by ASMTs to produce melatonin (Ahmad et al. 2023).

Tryptophan is the precursor of melatonin production and is an amino acid that plants can synthesize *de novo* through the shikimate pathway. All aromatic amino acids, including tryptophan, can be biosynthesized in plants using this process, which entails seven distinct stages. Briefly,

1. The enzyme DAHP synthase (EC 2.5.1.54) is responsible for converting PEP (phosphoenol pyruvate) and erythrose-4-phosphate into DAHP (3-Deoxy-D-arabinoheptulosonate-7-phosphate). DHQ synthase (EC 4.2.3.4) is an enzyme

that cyclizes DAHP into the 3-dehydroquinone form of DHQ by cyclizing DAHP into DHQ.

2. DHQ dehydratase (EC 4.2.1.10) catalyses the dehydration which converts DHQ (3-dehydroquinic acid) into DHS (3-dehydroshikimate). Shikimate dehydrogenase (EC 1.1.1.25) further catalyses the dehydrogenation reaction, which converts DHS (3-dehydroshikimate) into Shikimate.
3. The enzyme EPSP synthase (EC 2.5.1.19) transforms shikimate into EPSP (5-enolpyruvylshikimate-3-phosphate) after shikimate has been phosphorylated by the enzyme shikimate kinase (EC 2.7.1.71).
4. The enzyme chorismate synthase (EC 4.2.3.5), the crucial stage in tryptophan biosynthesis, which transforms EPSP into chorismate, produces chorismite.
5. Anthranilate synthase (EC 4.1.3.27) converts chorismate into anthranilate, which is then combined with PRPP (phosphoribosyl pyrophosphate) to produce PRA (phosphoribosyl anthranilate).
6. To create indole-3-glycerol phosphate, which is then spontaneously transformed into the indole scaffold, the ribose ring added in this final process is first opened by PRAI (PRA isomerase; EC 5.3.1.24).
7. The final step in the production of tryptophan is the action of TPS (tryptophan synthase; EC 4.2.1.20), which is responsible for the interaction of indole with serine (Mannino et al. 2021).

COMT, ASMT, and SNAT are three different enzymes, each of which may have several isoforms, which are required for two-step processes that produce melatonin from serotonin (Back et al. 2016). While the other two enzymes are methyltransferases, the first enzyme catalyses acetylation. Since serotonin, N-acetylserotonin, and 5-methoxytryptamine are substrates for all three enzymes, the order in which they function can also change in this situation (Park et al. 2013; Byeon et al. 2014; Lee et al. 2014). The conditions of plant growth determine which pathway is used for melatonin production (Fig. 1.6). In fact, the metabolic pathway from tryptophan to melatonin passes through the “tryptamine/serotonin/N-acetylserotonin intermediate” before arriving at melatonin under stressful or normal circumstances that do not create a substantial accumulation of serotonin (Byeon et al. 2015).

The initial step in the biosynthesis of melatonin in plants corresponds to the generation of serotonin from tryptophan. Two distinct routes might be implicated.

- (a) In the first route, tryptophan is first decarboxylated by TPH into tryptamine, which TDC subsequently hydroxylates into serotonin.
- (b) “TDC converts 5-hydroxytryptophan into serotonin by decarboxylation” follows the “TPH-mediated hydroxylation of tryptophan into 5-hydroxytryptophan, “ another alternative.

Both of these approaches are feasible since TDC exhibits strong *in vitro* affinities for tryptophan and 5-hydroxytryptophan. Decarboxylation has been shown to occur more frequently in plants than hydroxylation as a preliminary step, though (Back

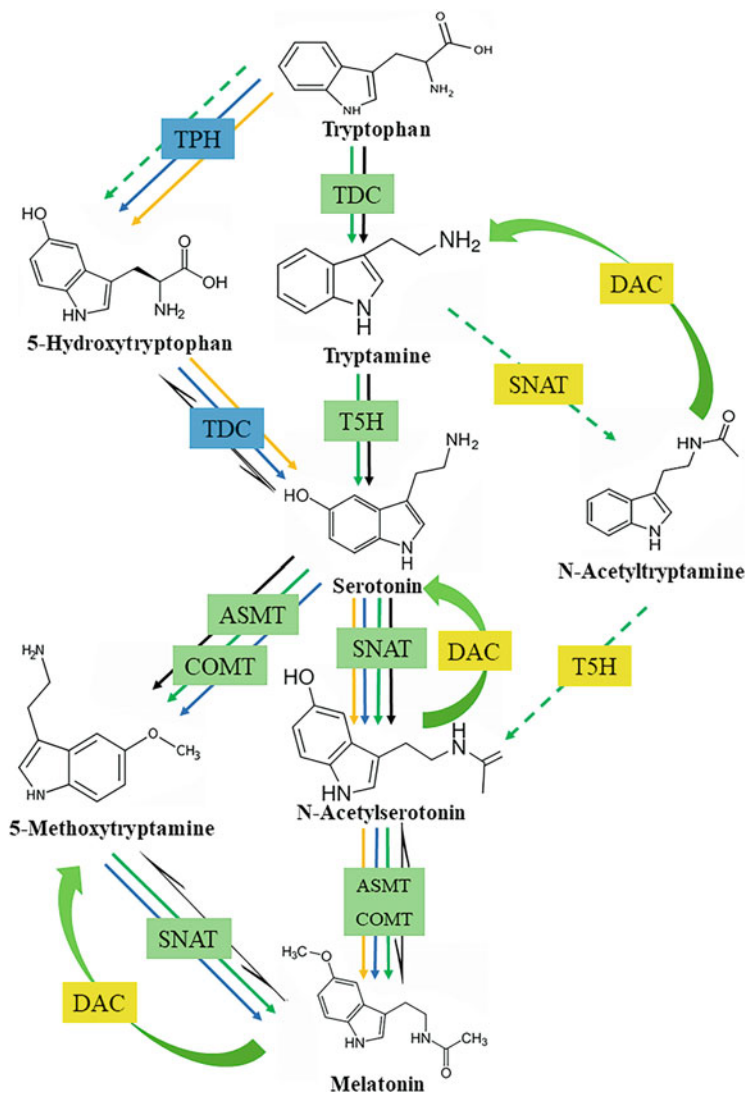


Fig. 1.6 Melatonin biosynthesis mechanisms in microbes, humans, and plants. Green (plants), blue (animals), yellow (bacteria), and black (yeasts) are represented by various arrow colours. Unproven reactions are indicated by dashed lines. *TPH* tryptophan hydroxylase, *TDC* L-tryptophan decarboxylase, *T5H* tryptamine-5-hydroxylase, *SNAT* serotonin *N*-acetyltransferase, *ASMT* acetylserotonin *O*-methyltransferase, *COMT* caffeic acid 3-*O*-methyltransferase, *DAC* deacetylases

et al. 2016). An acetylated substance produced from serotonin is melatonin. The biosynthetic process in which the amino acid tryptophan produces indolic amines has been effectively examined in plants and mammals (Tan et al. 2015; Back et al. 2016).

In plants,

1. The enzyme TDC (tryptophan decarboxylase) transforms tryptophan into tryptamine (Fig. 1.6).
2. The enzyme T5H (tryptamine-5-hydroxylase), which has been widely researched in rice, converts tryptamine into serotonin (5-hydroxytryptamine) but has not been well investigated.
3. SNAT (serotonin *N*-acetyltransferase) is *N*-acetylated serotonin. The hydroxyindole-*O*-methyltransferase i.e., ASMT (acetylserotonin methyltransferase) then methylates *N*-acetylserotonin to produce melatonin. COMT (caffeic acid-*O*-methyltransferase), an enzyme with a broad range of potential substrates, such as quercetin and caffeic acid, can methylate *N*-acetylserotonin in plants, as well (Byeon et al. 2014).
4. After SNAT takes effect, serotonin may also be converted by ASMT/COMT into 5-methoxytryptamine to produce melatonin. In times of stress or senescence, this approach would take place (Back et al. 2016; Tan et al. 2016).

TPH (tryptophan hydroxylase) and TDC (tryptophan decarboxylase) operate in sequence to convert 5-hydroxytryptophan into serotonin in mammalian cells. The occurrence of 5-hydroxytryptophan revealed that certain enzymatic activities, including the action of TPH, operate with a reduced degree in the plant cells even though TPH was not identified in plants. Furthermore, according to several authors, 5-methoxytryptamine can be converted into melatonin under stress, suggesting that plant cells have greater potential for metabolic adaptation than animal cells do. This suggests that the melatonin biosynthesis pathway may take many different kinds of alternative routes (Arnao and Hernández-Ruiz 2014; Tan et al. 2016).

There are five enzymatic stages in the process (Fig. 1.7). Tryptophan is first hydroxylated by TPH to 5-hydroxytryptophan, which is then decarboxylated by the AADC (aromatic amino acid decarboxylase) to serotonin (5-hydroxytryptamine). For many years, the two last phases were ambiguous. In fact, neither the site of melatonin's biosynthesis process nor the specific enzymes required for it were acknowledged to participate in the synthesis. When the mammalian melatonin biosynthetic route was found in 1960, it had been anticipated that only the pineal gland and liver are capable of acetylating serotonin to produce *N*-acetylserotonin (Pevet et al. 2017). It was incorrectly assumed that melatonin synthesis was not specialized in the liver, because ASMT was the first to be discovered in the pineal gland. Melatonin was first distinguished as a pineal-related neurohormone because of this. The production of melatonin by several organs and tissues in the periphery, including the skin, gut, hepatic cholangiocytes, lymphocytes, bone marrow, testis, ovary, Harderian gland, and retina, is currently well understood (Hardeland et al. 2011).

Because of the enzyme activity of ASMT for *N*-acetylserotonin was found to be around 14 times more potent, it was determined that this compound was the most suitable substrate of ASMT, as compared with the serotonin (Skene 2003). Based on these findings, it was hypothesized that firstly, AANAT acetylates serotonin in order

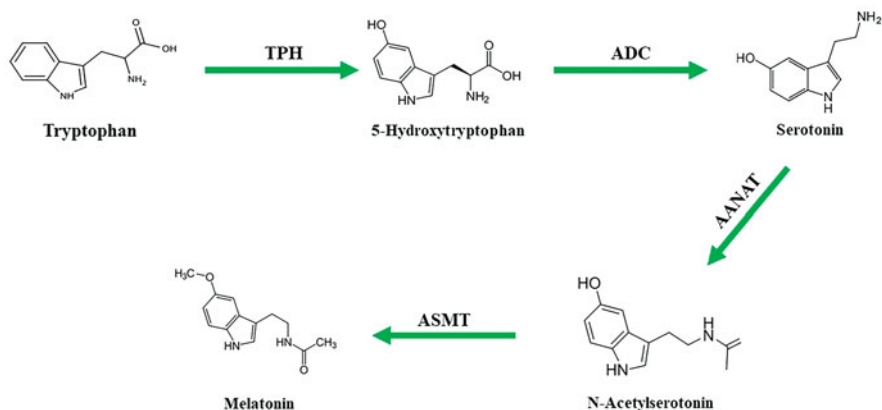


Fig. 1.7 The conventional melatonin synthesis pathway in mammals. TPH Tryptophan hydroxylase, AADC aromatic amino acid decarboxylase, AANAT aralkylamine *N*-acetyltransferase, ASMT acetylserotonin *O*-methyltransferase

to generate N-acetylserotonin, and that ASMT then converts the subsequent N-acetylserotonin into melatonin. It is generally acknowledged that AANAT is the enzyme that limits melatonin synthesis, i.e., a limiting factor. In fact, blue light (420–480 nm) is the primary regulating component in the melatonin synthesis process in animals (Ganguly et al. 2005). This type of daytime irradiation reduces the production of melatonin instantaneously by impairing AANAT's ability to function both through protein dephosphorylation and downregulation of gene expression (Tan et al. 2011; Venegas et al. 2012). Other variables that could interfere with an animal's ability to produce melatonin include fluctuations in temperature, food consumption, and various kinds of health conditions (Mannino et al. 2021). N-acetyltryptamine, which is produced by SNAT, may be transformed by T5H into N-acetylserotonin, which is subsequently manufactured as melatonin (Arnao et al. 2023).

1.5 Conclusion/Future Directions

Several recent studies have established the critical significance of melatonin in plant processes, notably its control of crop development and productivity. However, a full knowledge of melatonin, which affects crop development and production under abiotic stress conditions, is still inadequate. Other melatonin biosynthetic pathways, including ones independent of serotonin synthesis, may exist. The enzymes involved have yet to be discovered, and those that are known do not appear to be participating in this process. Aromatic and therapeutic plants have greater phytomelatonin levels than conventional veggies. Such botanical medicinal plants are perfect choices for future melatonin supplements. Controlling growing conditions might aid in the

production of phytemelatonin-rich plants. Additional investigation on other species and varieties is required. The existence of phytemelatonin in all plant species studied so far suggests that it might be used as a nutraceutical ingredient. The discovery and research of phytemelatonin-rich species and variants should be prioritized. In terms of melatonin intake, we should focus on alternatives to synthetic melatonin and boost organically generated melatonin.

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