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Melatonin-antioxidant system: what is known in plants, crustaceans and mammals? Perspectives and challenges

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Abstract

Melatonin (N-acetyl-5-methoxytryptamine) is classically known as chemical messenger of darkness. Both plants and animals respond to photoperiodic signals and the harmonization of physiological events with light/dark cues is also well appreciated. It is interesting that plants and invertebrates accumulate melatonin although they are devoid of melatonin producing gland, pineal gland as in vertebrates including mammals. This led to important question related to common cross-kingdom signal molecule. The major goal of this mini-review is to recapitulate biosynthetic aspects and antioxidant property of melatonin in mammals, crustaceans and plants. Based on the available literature, it can be concluded that the synthesis, mode and target sites of melatonin are well documented in vertebrates including mammals and on the other hand, melatonin production pathways are little understood as compared to its antioxidant property in plants whereas, in crustaceans research related to both aspects are not well defined. The overarching point of this review indicates that both edible plants and crustaceans are consumed by humans as their food and obviously benefited from antioxidant, melatonin. Therefore, research towards melanodermic pathways further enhances our understanding into the meaning of melatonin system in edible plants and crustaceans which ultimately fetches human health.

Keywords: Antioxidant enzymes; Crustaceans; Plants; Mammals and melatonin

1. Introduction

Hormones play an important role in the regulation of physiological homeostasis in plants and animals, suggesting endocrine regulation of control and coordination of physiological processes is a common approach across cross-kingdom. Although, hormones of diverse nature and origin exist across plants and animals, many structurally similar molecules are shared between both the kingdoms. For example, oxidation products of fatty acids such as oxylipins and eicosanoids, ecdysteroids and thyroid hormones are cogent examples of molecules with similar structure which are shared by both plants and animals (1-3). Melatonin is another cogent example of this trend which play important roles in plants and animals including vertebrates and invertebrates (4). Moreover, it can able to act as a signal for interaction of plants with herbivores and pests (5). As melatonin coordinates photoperiodic signals to the intrinsic system thereby regulate metabolic events and biological rhythms, it is known as chemical messenger of darkness. According to Arendt (6), if Web citations are a guide (1.9 million citations), it is almost as famous as serotonin (2.3 million) but not quite as well known as DNA (42.5 millions). Pub-med results revealed 14,349 publications related to the term melatonin during 2015-2025. Although, melatonin is an 'old friend' to animals, it is a new molecule to plants and moreover, research related to melatonin induced antioxidant property is little exploited. On the other hand, crustaceans are treated as alternatives to fisheries and now-a-days shell fish industry is gaining popularity. The overarching point of this review indicates that both edible plants and crustaceans are consumed by humans as their food and obviously benefited from

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antioxidant, melatonin. Therefore, research towards melatonergic pathways further enhances our understanding into the meaning of melatonin system in edible plants and crustaceans which ultimately fetches human health.

In view of the importance of melatonin, the present review shed a light on the antioxidant potential of melatonin in plant and animal kingdoms. The topic of melatonin and its antioxidant property is vast; therefore, in the present review I restrict the present topic to specific groups of plants and animals (eg: vertebrate model: mammals and invertebrate model: crustaceans). For additional insights into the pleiotropic effects of melatonin, significant reviews were suggested (7-18).

2. Molecule in focus: Melatonin

Melatonin is a methoxy derivative of serotonin (N-acetyl-5-methoxytryptamine; Fig. 1). Almost fifty years back, Lerner and co-workers (19) identified melatonin in the bovine pineal gland extract. The name of melatonin was derived because of its effects on melanin (mela-: accumulation of melanin in melanocytes of amphibians) and its derivation from serotonin (-tonin). Later studies of Axelrod and Weissbach (20) paved a way regarding its synthetic pathway in the pineal gland.

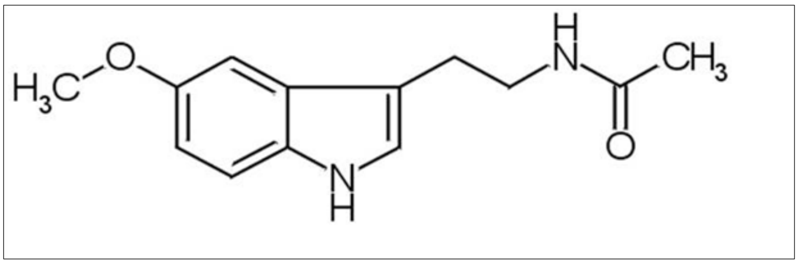

Figure 1 Chemical structure of melatonin (N-acetyl-5-methoxy tryptamine

The fundamental point about production of melatonin is that it is synthesized and secreted at night and that the circadian rhythm of melatonin is dictated by photoperiodic signal (21). This finding clearly showed why nocturnal circulating melatonin levels are higher at night than during the day in all species examined. As a consequence, this molecule is classically named as 'chemical of darkness'. This discovery, in fact fueled the research into melatonergic system and several researchers focused on its biosynthesis, metabolism, physiological and pathophysiological functions. Surprisingly, melatonin is not confined to vertebrates, but its role in the biochemistry of plants and invertebrates is also well acknowledged. In vertebrates, pineal gland is the organ that produces melatonin, whereas in invertebrates and plants such type of glands or its equivalent glands are absent. This eventually led to important question regarding the existence of common signaling mechanism across plants and animals. This also led to another important point that melatonin is not a vertebrate *bona fide* molecule. Thus, it seems apparent that melatonin is an almost ubiquitous molecule in the animal and plant kingdom (11-18).

It is evident that many physiological events depend on photo-periodic signals. Melatonin acts as a channel to convey the photic information to the organism link photoperiodic signals and the internal milieu and play a vital role in synchronization of regulation of diverse physiological functions to light/dark cycle (22, 23). This linking mechanism is one of the characteristic conserved natures of melatonin indicating its potential impact in the framework of both plants and animals. Moreover, in plants and animal kingdoms, melatonin is putatively mediate a range of physiological and metabolic events. In vertebrates including mammals, it almost influences all processes such as reproduction, sleep, aging, thermoregulation, circadian rhythms and most significantly scavenging of free radicals (24-30), whereas in crustaceans, it plays important role in molting, reproduction, glucose metabolism and detoxifying mechanisms by neutralizing free radicals (23). On the hand, in plants melatonin intervenes with synchronization of reproduction to photoperiod, cell protection and vegetative development (5, 22).

Thus, based on the melatonin actions it is very clear that it has ability to mediate both hormonal and non-hormonal processes. One of the non-hormonal actions of melatonin that commonly occurs in plants and animals is antioxidant property. Before, addressing antioxidant potential of melatonin, it is appropriate to know the biosynthetic machinery related to melatonin in plants, mammals and crustaceans which is very important to understand melatonin actions including antioxidant property.

3. Biosynthesis

3.1. Mammals

The biosynthetic aspects related to melatonin are well documented in vertebrates including mammals. Therefore, it is appropriate to consider biosynthesis of melatonin in plants and crustaceans on mammalian background. Hardeland et al. (31) indicated that biosynthesis of melatonin seems to be identical across the phyla. Melatonin biosynthesis includes different steps: Tryptophan hydroxylase (EC 1.14.16.4) converts tryptophan into 5-hydroxytryptophan by hydroxylation. This hydroxylation product in the presence of aromatic amino acid decarboxylase (EC 4.1.1.28) undergoes decarboxylation to form serotonin which further undergoes N-acetylation catalyzed by *N*-acetyl transferase (EC 2.3.1.37) leading to the synthesis of *N*-acetyl-serotonin. Finally, hydroxyindole-*O*-methyl transferase (EC 2.1.1.4) through *O*-methylation converts N-acetyl serotonin into melatonin. In the melatonin pathway, hydroxylation and N-acetylation reactions are considered rate limiting steps.

It has also been shown that besides classical pathway of melatonin synthesis, it can be formed via *O*-methylation of serotonin and subsequent *N*-acetylation of 5-methoxytryptamine, or by *O*-methylation of tryptophan followed by decarboxylation and *N*-acetylation in vertebrates (32).

3.2. Crustaceans

Although functional aspects related to the enzymes involved in melatonin synthesis is not clarified, in several invertebrates including crustaceans, components of melatonin pathway such as tryptophan hydroxylase, aromatic amino acid decarboxylase, arylalkylamine N-acetyltransferase (AANAT), hydroxyindole-*O*-methyltransferase (HIOMT) and N-acetylserotonin (NAS) have been detected (32-36). Studies of Withyachumnarnkul et al. (37) and Tilden et al. (38) showed the activity levels of NAS in giant freshwater prawn *Macrobrachium rosenbergii de Man* and in fiddler crab, *Uca pugilator*, respectively. Mendoza-Vargas et al. (39) showed that melatonin synthesis occurs in the eyestalk of crayfish. Further, the occurrence of melatonin type receptor2 has been demonstrated in crayfish (39). Recently, studies of Strauss and Dricksen (40) suggested the expression of AANAT and HIOMT by the serotonin neurons and also demonstrated the production of NAS and melatonin. With the advancement of molecular approaches, identification of particular genes in the genome sequence is possible. For example, gene mining studies into the genome sequence of *Daphnia pulex* showed enzymes of melatonin pathway (41). Thus, crustaceans also possess melatonin machinery pointing towards biosynthesis aspects; however, further research is needed to clarify mechanistic actions of enzymes in melatonin pathway.

3.3. Plants

As understood from mammalian background, tryptophan undergoes hydroxylation and decarboxylation to form serotonin further undergoes *N*-acetylation and O-methylation thereby melatonin, whereas in plants such classical mechanistic pathway have yet to be clarified. It has been indicated that melatonin pathway and indole aceticacid (IAA) pathway uses the same precursors, tryptophan and tryptamine. While the pathway IAA has been extensively investigated, studies related to melatonin in plants is almost practically nil (22, 42). All most two decades back, studies of Murch et al. (43) demonstrated the evidences for melatonin biosynthesis *in vitro* in St John's wort (*Hypericum perforatum* L. cv. Anthos) like in animals. Murch and co-workers (43) through radio-labeled tryptophan ^{14}C-Trp monitored the accumulation of indole compounds including melatonin and serotonin in the plant tissue. This experiment forms the bases for melatonin biosynthesis suggesting major backbone of the synthetic pathway may be similar both in plants and animals. Studies of Facchini et al. (44) and Fujiwara et al. (45) showed the existence of enzymes required for hydroxylation and decarboxylation of melatonin pathway. Some studies also identified serotonin in plants (47,47). Recently, studies of Park et al. (48) indicated that serotonin formation occurs in a reverse process in rice plant as compared to animals. Park and co-workers (48) showed that the first product of hydroxylation is tryptamine but not 5-hydroxytryptophan, which is catalysed by tryptophan decarboxylase, and secondly, tryptamine is catalysed to serotonin by tryptamine 5-hydroxylase. On the other hand, so far, no studies are available to show whether the activity or the AANAT is present in plants. Although biosynthetic melatonin pathways exist in plants, some steps might at least in part differ from animals.

3.4. What evolution tells us about melatonin enzymes?

Evolution is an event which is crucial for wide range of gene changes across plants, bacteria, fungi and animals (49). There are two observations: AANAT is encoded in bacteria, yeast and vertebrates, but not in plants, worms or flies (50) and secondly, HIOMT enzyme is present only bacteria and vertebrates (49) predominantly indicated that melatonin enzymes might undergo evolutionary changes. Further, it has been hypothesized that horizontal gene transfer is preferred over vertical inheritance during evolution of cell-cell signaling (51). In accordance with this statement, it has been shown that bacteria produce tiny molecules which acts as cues for bacteria–bacteria communication and also function directly in bacteria–host communication. Recently, in plants HIOMT (also called as acetylserotonin N-methyltransferase) gene was also cloned and expressed in rice (52) and in crustaceans the expression of HIOMT in the serotonin producing neurons was reported (40). In addition, in mammals, N-acetylation of serotonin was performed by paralogues of NAT enzymes (53). In plants, although N-acetylation has not been demonstrated, accumulation of data indicates the existence of melatonin (54). At this level of observation, like in mammals, AANAT paralogues might play important roles in N-acetylation reactions and these paralogues might be inherited from chlorophyceans because plants share same clade with them or via horizontal gene transfer. However, this speculation warrants further authentication studies.

Piecing the results, melatonin synthetic pathway varies between plants, mammals and crustaceans, although, tryptophan is fundamental precursor of melatonin in all taxa. With regard to animals, hydroxylation of tryptophan to 5-hydroxytryptophan followed by decarboxylation leads to serotonin, which eventually either undergoes acetylation to form *N*-acetylserotonin or methylation to form 5-methoxytryptamine. Further, methylation of *N*-acetylserotonin or acetylation of 5-methoxytryptamine produce melatonin. Whereas in plants, decarboxylation of tryptophan to tryptamine followed by its hydroxylation to form serotonin are the crucial steps for the biosynthesis of melatonin (55,56). In summary, although, there are evidences for biosynthesis of melatonin, due to consideration of few species from both plants and crustaceans the functional and mechanistic actions of melatonin are hampered. Therefore, research related to melatonin synthesis awaits further research with respect to both plants and crustaceans.

4. Antioxidant efficacy of melatonin

It is well established that oxygen is crucial for all most all physiological processes in plants and animals. The major paradox is that, the chemical reduction of oxygen often led to generation of toxic particles, known as free radicals. These oxygen by-products are generally known as reactive oxygen species (ROS) and reactive nitrogen species (RNS) (57). One of the major characteristic features of ROS and RNS indicates that they contain unpaired electrons in their valance orbital which makes them highly reactive (58). To mitigate toxic effects of free radicals, cells often equipped with protective machinery. The components of protective machinery are known as free radical scavengers and antioxidant enzymes (57). In general, during stressed conditions, the levels of free radicals overwhelm intrinsic antioxidant defense system thereby leads to oxidative stress. It has been shown that overwhelming levels of ROS and RNS have ability to trigger apoptosis or necrosis cascades thereby causes cellular death (59,60). Thus, maintaining a balance of pro- and anti-oxidant levels in living cell is considered crucial.

Melatonin is a natural antioxidant and play pivotal roles to neutralize toxic effects of ROS/RNS (57). It has been shown that melatonin has ability to directly counterattack free radicals and/or indirectly provoke antioxidant enzyme system to neutralize the same (61). This led to important question regarding its chemical nature. It has been indicated that structural analysis of melatonin comprises of two functional groups viz., *O*-methyl and *N*-acetyl residues which are considered for its biological actions and also for its oxidation chemistry. These functional groups are attached to indole nucleus to adopt specific orientation with the receptor binding pocket. Further, the functional groups and specific confirmation provided melatonin feasible to adapt amphiphilic nature which is very important to enter cells directly (62).

The subject of melatonin-induced antioxidant effects is vast. Moreover, the major goal of this review is to show melatonin as a crosskingdom molecule with antioxidant property. Therefore, in this review, some of the potential aspects related to antioxidant property of melatonin. So, obviously full-picture of melatonin-induced antioxidant property has been not covered and the reader is urged to refer other reviews for additional details (5-18, 63,64).

4.1. Vertebrates including mammals

The putative roles of melatonin in inducing protection against free radicals have been extensively reviewed (57,61). Due to amphiphilic nature, melatonin has ability to neutralize free radicals (ROS/RNS) directly and/or indirectly. Melatonin has ability directly mitigate the effect of hydroxyl radicals. It has been shown that the second carbon of indole ring of melatonin has capacity to react with hydroxyl radical (65). Many studies also indicated that during melatonin-induced neutralizing effect of hydroxyl radicals, a product known as 3-hydroxymelatonin has been observed as by-product (61). In fact, hydroxyl radicals are formed from hydrogen peroxide (H_2O_2) which in turn produced intracellularly due to dismutation of superoxide radicals. H_2O_2 is not electrically charged and easily traverse cell membranes, therefore, there is a possibility for its removal from its generation site; however, due to Fenton or Haber Weiss reactions H_2O_2 is converted into highly toxic hydroxyl radicals (57). Melatonin has ability to neutralize not only

H_2O_2 but also neutralizes superoxide radicals. During neutralization process the by-products such as degradation products of melatonin, 6-hydroxymelatonin, N^1-acetyl-N^2-formyl-5-methoxykynuramine (AFMK), and N-acetyl-5-methoxykynuramine formed which are also well known antioxidants (57,61). Melatonin-induced direct effects on RNS indicated that melatonin reacts with peroxynitrite (a product formed due to reaction of nitrogen monoxide and superoxide radicals) and led to reduce the effect of nitrogen monoxide (57).

On the other hand, melatonin induced indirect effects is through triggering of antioxidant enzymes. Antioxidant enzymes are broadly classified into enzymes with or without participation directly in glutathione metabolism. First group of enzymes comporises of superoxide dismutase and catalase which participate in first line of defense against free radicals and second group of enzymes comprises of Glutathione-*S*-transferase (GST), glutathione reductase (GR) and glutathione peroxidase (GPx). The antioxidant SOD converts the superoxide anions into H_2O_2 which easily enters cell membranes and are acted upon by two enzymes namely catalase and GPx. On the other hand, GST mediates the conjugation of reduced glutathione (GSH) toxic free radicals thereby mitigates free radical induced toxicity. GR is an enzyme which replenishes the GSH from its oxidized form (GSSG) in the presence of NADPH as co-factor thereby sustains functions of GST and GPx and also maintains GSH/GSSG ratio which is crucial for glutathione metabolism. It has been shown that melatonin has ability to activate all most all enzymes of antioxidant defense mechanism and at the same it ahs ability to maintain GSH/GSSG ratios (57). It has also been shown that melatonin plays a key role in recycling of GSH which appears to be a major action in curtailing toxicity of free radicals. Other studies also indicated that melatonin activates glucose-6-phosphate dehydrogenase thereby maintains the levels of NADPH to accomplish GR actions (66).

Mitochondrion is popularly known as energy currency of cell. The inner mitochondrial membrane is involved in electron transport chain and in aerobic cells oxidative phosphorylation leads to generation of ATP. During energy production mechanisms, free radicals are generated and thus mitochondria are exposed to oxidative stress. Moreover, leakage of such frees radicals from electron transport chain damages mitochondria and may lead to mitochondrial-related diseases. Many studies indicated that melatonin has ability to protect mitochondria and this efficacy might be attributed to its direct actions and or indirectly by activating GPx and GR (67).

In summary, melatonin has ability to protect cells at many levels indicating its versatile nature as an antioxidant.

4.2. Crustaceans

Although research related to melatonin-induced antioxidant effects is little exploited, the putative role of melatonin in antioxidant system has been demonstrated in crustaceans. It is well established that photoperiod harmonization of oxygen consumption is an important aspect which reflects aerobic respiration and in turn might alter antioxidant defense system in crustaceans (23). In accordance with this view, it has been shown that antioxidant enzymes such as glutathione based enzymes show daily fluctuations with respect to photoperiod in the hemolymph and hepatopancreas of crayfishes, *Procambarus clarkii* and *P. digueti* (68). In addition, studies of Geihs et al. (69) and Maciel et al. (70) provided a direct evidence for melatonin and pro- and anti-oxidant balance in the locomotor muscle and gills of the estuarine crab, *Neohelice granulata*. Recently, studies of Cary and co-workers (71) indicated that melatonin (1 µM) significantly mitigate the H_2O_2-induced neurite-inhibiting effects in the XO cells of fiddler crab *Uca pugilator*.

In summary, melatonin plays an important role in the regulation of oxidant homeostasis in crustaceans. However, additional studies are warranted to get a full-picture of melatonin-induced antioxidant effects which in turn also provide insights into the synchronization mechanisms mediated by melatonin with intrinsic antioxidant status in crustaceans.

4.3. Plants

Recently, Gill and Tuteja (64) in their proactive review indicated that various abiotic stresses extrinsically and endogenously, due to the activities of chloroplast (phtosystems) and mitochondria (electron transport chain) lead to generation of accumulation of ROS. Like animals, plants also counterattack the ROS with its intrinsic antioxidant defense system comprising of SOD, CAT, GR, GPx, GST, ascorbate peroxidase, mono- and de- dehydroascorbate reducatses and also gluaicol peroxidase. Further non-enzymatic antioxidants such as GSH, phenolic compounds, alkaloids and tocopherols also play vital roles in neutralizing oxidative stress (64). Several reports indicated that photoperiodism palys a vital role in the regulation of a range of physiological events including energy metabolism where free radical generation is unavoidable (63). This fueled the idea to address the role of melatonin as antioxidant in plants. Many studies indicated the protective function of melatonin against oxidative stress (43). In plants, melatonin might act as first line of defense against abiotic factors such as cold, heat, drought and environmental pollution (72). In accordance with statement, elevated melatonin levels has been shown that in plants grown in alpine and Mediterranean environments exposed to intense UV radiation , melatonin levels (73,74). Several exogenous studies also indicated that melatonin protect plants against oxidative stress induced by cold or hot environments, UV irradiation, metals such as copper, and also hydrogen peroxide (54,63). It has also been documented that melatonin showed protective effects against irradiation of UV-B thereby directly scavenges ROS and reduces the malondialdhyde levels in the leaves of mung bean plant (*Vigna radiata*) (75) and protects DNA and enhances DNA repair in protoplasts of *Gentiana macrophylla* (76). Most significantly, exogenous application of melatonin protected seedlings of cucumbers against heat stress triggered MDA, superoxide anion, and hydrogen peroxide (77). Therefore melatonin-induced protective effects against these stressors might be attributed to free radical scavenging efficacy. On the other hand, it has also been indicated that melatonin also triggers the intrinsic antioxidant enzymes such as SOD, CAT, APX, GR and monodehydroascorbate reductase in plants which eventually protect cells against oxidative stress (78). In addition, melatonin also protects chloroplast against oxidative stress (54). Studies related to chlorophyll indicated melatonin has ability to protect structural and functional integrity of chlorophyll by protecting its photosystem (78,79).

In summary, melatonin in plants has ability to exert effects directly and indirectly to neutralize free radical induced damage. Moreover, it elevates chlorophyll functions against oxidative stress which is considered crucial for survival and growth of plants. In addition, the antioxidant role of melatonin against abiotic and biotic stress has been demonstrated (80,81).

5. Conclusion

Melatonin thus, fits well as a molecule with antioxidant property across plants and animals. The review is mainly divided into two areas. Firstly, although melatonin has fifty years of background, as compared with vertebrates including mammals, the biosynthetic aspects in invertebrates (eg: crustaceans) and plants is still with many gaps. Secondly, melatonin induced antioxidant property is a conserved in plants and animals. The other major goal of this review is to pose a question regarding why do we (need) to know about melatonin in plants and animals. The plausible answer might be energy transfer across tropic levels (plants to humans or crustaceans to humans). All over the world, billions of people depend on plants and crustaceans as food sources and therefore, obviously led to exogenous accumulation of melatonin thereby health benefits in humans. For example, consumption of edible plants led to improve antioxidant potential thereby improves human health and also recommended to treat a wide array of health problems including neurological diseases such as Alzhemer's and parkinson's disease), cardiac diseases, metabolic abnormalities and also against cancer Many experimental studies using animal models also indicated that exogenous treatment of melatonin accumulated plants (eg: coffee) protected animals from hepatic problems and also chemical induced liver cirrhosis. Studies related to crustaceans indicated that shell fish culture is growing day-by-day and throughout the world people consume them as routine food. To sustain shell fish culture, quality of brood stock is crucial and recently exogenous melatonin has been used as an alternative to eyestalk ablation method. However, due to lack of sound knowledge regarding the biosynthetic pathways, melatonin actions are not fully understood and research in this direction might fetch not only plants and crustaceans but finally human beings can be benefitted.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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