Review Article

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Phytomelatonin: a comprehensive literature review and recent advance on medicinal meadow

Abstract

Melatonin (N-acetyl-5-methoxytryptamine), a well-known pineal gland hormone, was discovered in plants in 1995 but till then very little research into it has been carried out in this arena. It is present in different parts of all the plant species studied, including leaves, stems, roots, fruits and seeds. Based on the ubiquitous distribution of melatonin in all kingdoms, melatonin was even suggested as the nature's most versatile biological signal molecule. Since the identification of melatonin in plants by Hattori. Several reports have published and opened up a new area in the field of plant derived melatonin i.e. phytomelatonin. Phytomelatonin is biosynthesized in plants from tryptophan precursor. Majority of the herbs containing high levels of melatonin have been used traditionally to treat neurological disorders associated with the generation of free radicals which might be associated with its potent antioxidant activity. This concise survey will endeavor to provide an overview phytomelatonin along with its distribution, biosynthesis and probable role in plant growth and regulation.

Keywords: phytomelatonin, tryptophan, medicinal plants

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Introduction

Melatonin is old and understood companion in human and creature physiology however novel to plant physiology.[1] Melatonin was first isolated from the bovine pineal gland and identified as N-acetyl-5-methoxy tryptamine by Lerner and co-workers in 1958.[2] It was named melatonin because of its capacity to whiten the skin in certain fish, reptiles and amphibians.[3] In mammals, melatonin plays a key role to regulate circadian rhythm.[4] This molecule is an powerful antioxidant.[4–8] and preserves mitochondrial homeostasis, increases gene expression for antioxidant enzymes and thereby extremely beneficial in neurodegenerative disorders like Alzheimer's, Parkinson's disease whose pathogenesis is associated with the cytotoxic effect of reactive oxygen species.[9–13] The existence of melatonin in plants was independently identified for the first time by Dubbels et al.,[14] & Hattori et al.,[15] in 1995. Since then, search for plant derived melatonin i.e. phytomelatonin has become one of the most emerging field of research in plant physiology. During last two decades, the universal presence of melatonin in plants is supported with numerous scientific evidences. Melatonin was identified in diverse organisms including prokaryotes, eukaryotes, fungi, algae and higher plants.[16] Based on its ubiquitous distribution & multi-directional activity, melatonin is recommended as one of the most versatile biological signal of nature. Indeed, recent research suggests, this classical indole derivative is both synthesized in and taken up by plants.[17] The role of phytomelatonin as antioxidant, free radical scavenger and growth promoter is most vividly supported by the experimental outcomes.[18] Studies suggest production of indole compounds is augmented under high UV radiation and thus provide substantial evidence about the role of phytomelatonin as free radical scavenger and thereby protecting plants against oxidative stress and reducing the damage of macromolecules in a manner similar to that in animals.[19] It plays a key role in regulation of plant reproductive physiology, defense of plant cells against apoptosis induced by unfavorable environmental conditions.[19] Several physiological roles of phytomelatonin, including a possible role in flowering, maintaining circadian rhythms & photoperiodicity and as growth regulator have been identified. Melatonin content varies in different plant organ or tissue and seems to be more profuse in aromatic plants and in leaves than seeds.[20] It shows auxin like activity and thus regulating the growth of roots, shoots, and explants, activating seed germination and rhizogenesis (lateral and adventitious-roots), and delaying induced leaf senescence.[21] Recently, a possible role in rhizogenesis in lupin has also been proposed.[22]

Although presence of melatonin in plants is a universal phenomenon, but still very few information regarding its occurrence outside the angiosperms (exception: micro and macroalgae and other photoautotrophic microorganisms) have been reported. This is majorly attributed to inadequate detection methods and lack of experimental protocol to investigate the biochemical and molecular aspects of phytomelatonin. However, during last few years, certain methodological protocols regarding extraction, isolation and quantification methods had been successfully designed and optimized to certain complexities to obtain quick, reliable results on phytomelatonin content. The complete biosynthetic pathways and enzymatic involvement in phytomelatonin production are yet to be explored; studies with radioisotope tracer techniques revealed tryptophan as common precursor for both serotonin and melatonin as well as for indole-3-acetic acid (IAA).[23–25] It has been reported that plants may be able to absorb melatonin from the soil in which they are grown. Evidence also indicated involvement of melatonin in chlorophyll preservation and thereby promoting photosynthesis.[26–27] Transgenic plants with high level of melatonin may play a significant role to increase crop production and improve the general health of humans.[28] Besides discussing interesting data on phytomelatonin, this article is constructed with objectives to deepen our understandings regarding different physiological roles of melatonin in plants.

Biosynthesis of melatonin in plants

As mentioned, melatonin is derived from amino acid precursor tryptophan with a phylogenetic ubiquitous distribution. For a long time, it was portrayed that this neuro-hormone was synthesized only in the pineal gland of vertebrates.[29] Later, the identification of melatonin in photosynthesizing organisms opened a new meadow of research on this compound. Tryptophan is an essential amino acid and hence, animals lack the ability to synthesize it; they must obtain it from other natural sources.[30] In plants, tryptophan provides precursors for melatonin along with hormone auxin, phytoalexins, glucosinolates, alkaloids and indoleamines.[31] The rate of melatonin formation in higher plants follows a rhythmic variation with nocturnal maximum and seasonal fluctuation with maximum in flowering stage.[32] Tryptophan is biosynthesized through shikimic acid pathway via chorismate and anthranilate. Tryptophan is converted to 5-hydroxy tryptophan by tryptophan hydroxylase and subsequently to serotonin. Serotonin is converted to N-acetyl serotonin by arylalkylamine N-acetyl transferase (AANAT) from which melatonin is synthesized by hydroxyindole-O-methyltransferase (HIOMT). It should be noted that melatonin is synthesized by plants themselves even though arylalkylamine N-acetyltransferase (AANAT) has not been detected yet. Thus, the genetic characteristics of serotonin N-acetylating enzyme in plants may differ greatly with regard to its sequence and structure from the animal AANAT. Indole-3-acetic acid (IAA) is synthesized exclusively in plants from tryptophan by tryptophan decarboxylase (Figure 1).[33–35]

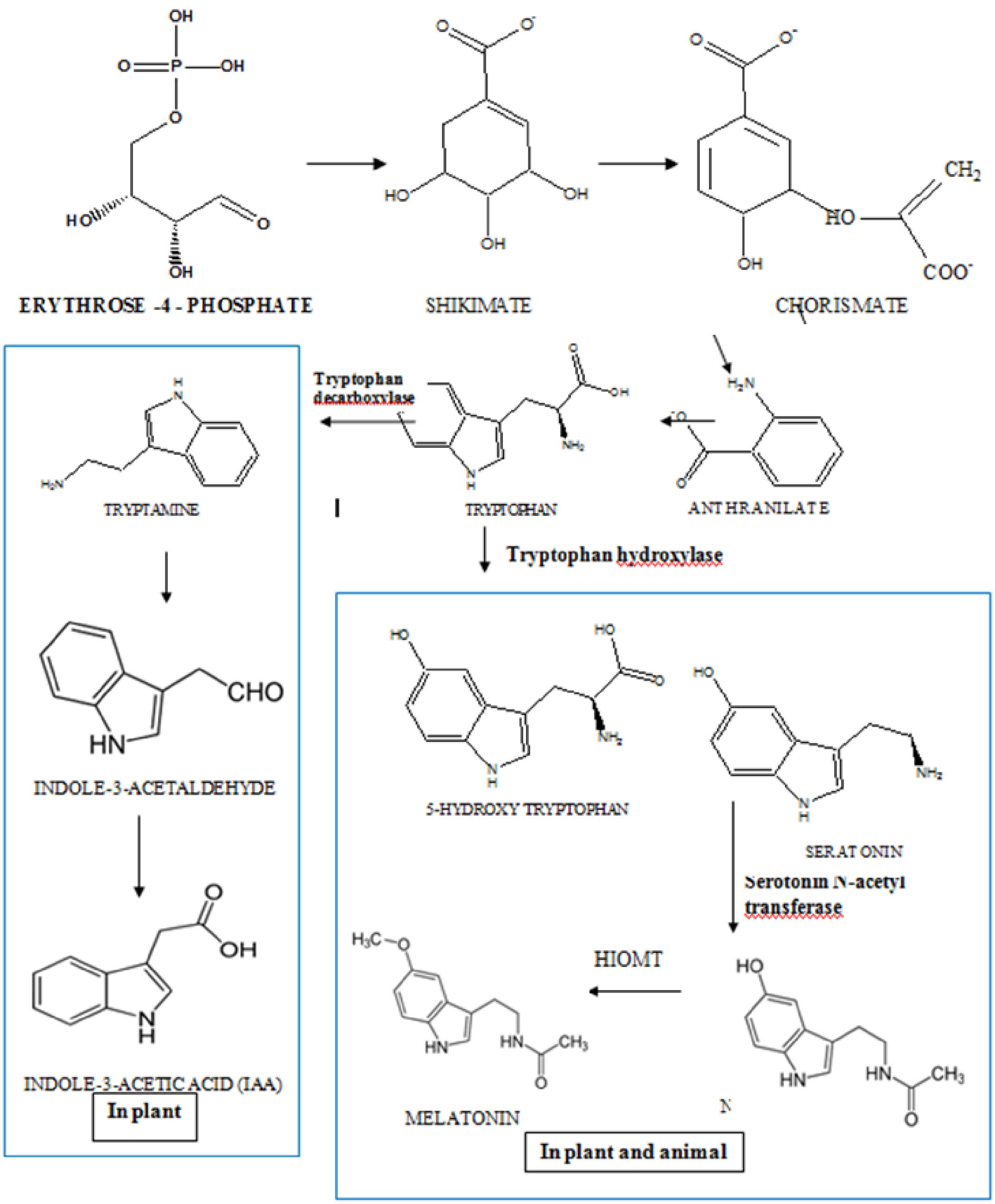

Figure 1 Biosynthesis of melatonin and its precursors in plants (Based on Marcello I et al.[35]).

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Occurrence of phytomelatonin in edible plants

The occurrences of melatonin have been identified in more than 140 different aromatic & medicinal plants and edible plants by humans.[36] Several sophisticated analytical techniques were developed to detect the presence of melatonin in plant tissues. Among them radioimmuno assays (RIA), enzyme linked immunoadsorbant assay (ELISA), high-performance liquid chromatography (HPLC) and gas chromatography-mass spectrophotometry (GC-MS) have been considered as most reliable sources.[37–39] The ubiquitous distribution of melatonin is observed in different parts of plants viz. leaves, roots, fruits, and seeds. It has been reported that crops belonging to family Graminae (ex: rice, barley, sweet corn, oat) contains high amount of melatonin.[40] GC-MS analysis showed banana contains melatonin at a concentration of 0.655ng/g, but HPLC-MS suggested significant higher level of melatonin (1ng/g of plant tissue).[41] Melatonin was found also in fruits such as strawberries, kiwis, pineapples, apples and in grapes as well as tart cherries and tomatoes.[41] RIA showed presence of melatonin in both white and black mustard seeds (189ng/g of plant tissue & 123ng/g of plant tissue respectively).[42–43] Presence of melatonin was also identified in both green and roasted beans of *Coffea canephora* and *Coffea arabica* at a concentration of 5.8±0.8μg/g dry weight and 8.0±0.9μg/g dry weight respectively.[44] A brief information regarding the distribution of melatonin in plants according to the families is summarized in Table 1.

Table 1 Occurrence of melatonin in edible and medicinally important plants

Family	Common name	Scientific name	Method of detection	Amount of melatonin (pg/g)	Reference
Actinidiaceae	Kiwi fruit	Actinidia deliciosa Liang-Ferg.	ELISA	24.4	15
Amaranthaceae	Beet root	Beta vulgaris L.	RIA	2	14
Araceae	Taro	Colocasia esculenta L.	ELISA	54.6	15
Asparagaceae	Asparagus	Asparagus officinalis L.	ELISA	9.5	15
		Asparagus racemosus L.	ELISA	10	15
Asteraceae	Feverfew	Tanacetum parthenium L.	HPLC-UV	1300-7000ng/g	95
		Tripleurospermum disciforme Schultz. Bip	HPLC-UV	1305.8ng/g (in hot water extract)	95
			ELISA	3073.3ng/g (in 50% methanol extract)	
				1112.0ng/g (in hot water extract)	
				2096.2ng/g (in 50% methanol extract)	
	Shungiku	Chrysanthemum coronarium L.	ELISA	416.8	15
	Butterbur (fuki)	Petasites japonicus Maxim	ELISA	49.5	15
	Milk thistle seed	Silybum marianum L.	ELISA	2,000	43
Berberidaceae	Barren wort	Epimedium brevicornum M.	ELISA	1105ng/g	71
Basellaceae	Indian spinach	Basella alba L.	ELISA	38.7	15
Brassicaceae	Cabbage	Brassica oleracea L.	ELISA	107.4	15
	white radish	Raphanus sativus L.	ELISA	657.2	15
	Chinese cabbage	Brassica rapa L.	ELISA	485,000	15
	Black, white mustard seed	Brassica nigra L., Brassica hirta L.	ELISA	112.5, 129,000	43
Bromeliaceae	Pineapple	Ananas comosus L.	ELISA	36.2	15
Cucurbitaceae	Cucumber fruit	Cucumis sativus L.	HPLC	24.6	15
Fabaceae	Alfalfa seed	Medicago sativa L.	HPLC-UV	16,000	43
	Fenugreek seed	Trigonella foenum-graecum L.	HPLC-UV	43,000	43
	Lupin seed	Lupinus albus L.	HPLC-UV	3,830	23
	Tora	Senna tora	ELISA	-	90
			HPLC-UV	10.5	
	Hummingbird tree	Sesbania glandiflora L.	ELISA	43.7	90
			HPLC-UV	26.3	
Hypericaceae	Saint John's wort	Hypericum perforatum L.	Leaf	1750ng/g	79
			Flower	2400-4000ng/g	

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Table Continued...

Family	Common name	Scientific name	Method of detection	Amount of melatonin (pg/g)	Reference
Juglandaceae	Walnut	Juglans regia L.	ELISA	3,500	59
Papaveraceae	Poppy seed	Papaver somniferum L.	RIA	6,000	43
Phyllanthaceae	Burmese grape	Baccaurea ramiflora L.	ELISA	76.7	90
			HPLC-UV	43.2	
Poaceae	Rice seed	Oryza sativa L.	ELISA	1,006	15
	Barley seed	Hordeum vulgare L.	ELISA	378.1	15
	Sweet corn	Zea mays L.	ELISA	580	15
	Oat seed	Avena sativa L.	ELISA	1,366	15
Lamiaceae	-	Scutellaria baicalensis L.	ELISA	2000-7000ng/g	26
Liliaceae	Onion	Allium cepa L.	RIA	31.5	15
	Welsh onion	Allium fistulosum L.	RIA	85.7	15
Lythraceae	Pomegranate	Punica granatum L.	HPLC-MS	540–5,500	91
Moraceae	White mulberry	Morus alba M.		151ng/g	92
Musacea	Banana	Musa acuminata Colla	GC-MS	0.46	24
Oleracea	Olive oil	Olea europaea L.	ELISA	50–119pg/mL	93
Polygonaceae	Chinese rhubarb	Rheum palmatum L.	ELISA	1078ng/g	24
Ranunculaceae	Chinese goldthread	Coptis chinensis F.	ELISA	1008ng/g	24
Rosaceae	Apple	Malus domestica Borkh.	ELISA	47.6	15
	Strawberry	Fragaria ananassa Duch.	ELISA	12.4	15
	Almond seed	Prunus amygdalus Batsch.	ELISA	1,400–11,260	24
Rubiaceae	Coffee beans	Coffea arabica L.	ELISA	5.8μg/g	15
	Gambir Vine	Uncaria rhynchophylla	ELISA	2460ng/g	15
Rutaceae	Orange juice	Citrus sinensis L.	HPLC-UV	150	94
	Amur cork tree	Phellodendron amurense	ELISA	1235ng/g	15
Solanaceae	Tomato fruit	Solanum lycopersicum L.	HPLC-UV	32.2	24
	Silver leaf nightshade fruit	Solanum elaeagnifolium Cav.	HPLC	7,895	24
	Black nightshade fruit	Solanum nigrum L.	HPLC	323	24
	Tobacco leaf	Nicotiana tabacum L.	HPLC	50	24
	Devil's trumpet flower	Datura metel L.	HPLC	1,500	24
Umbelliferae	Carrot	Daucus carota Hoffm.	ELISA	55.3	15
	Anise seed	Pimpinella anisum L.	ELISA	7,000	15
	Coriander seed	Coriandrum sativum L.	ELISA	7,000	43
	Fennel seed	Foeniculum vulgare L.	ELISA	28,000	43
	Sunflower seed	Helianthus annuus L.	ELISA	29,000	43
Violaceae	-	Viola philipica Cav.	ELISA	2368ng/g	95
Vitaceae	Grapevine	Vitis vinifera L.	ELISA	5-965	43
Zingiberaceae	Cardamom seed	Elettaria cardamomum L.	HPLC-MS	15,000	24
	Curcuma	Curcuma aeruginosa Roxb.	GC-MS	120,000	24

Table Continued...

Family	Common name	Scientific name	Method of detection	Amount of melatonin (pg/g)	Reference
	Ginger	Zingiber officinale Rose	HPLC-MS	583.7	24
	Piper	Piper nigrum L.	ELISA	865ng/g	24
			HPLC-UV	1092.7ng/g	

Role of melatonin in plants

Regulation of circadian rhythm

In mammals, melatonin plays a key role to regulate circadian rhythm with highest level during scotophase and baseline level during the photoperiod.[45] Hence, it was hypothesized to have similar function of melatonin in plants. Melatonin causes a diurnal oscillation with augmentation in night and decline during day period.[46] This depicted the role of melatonin in regulation of circadian rhythm is photoperiod dependent. Not only in higher plants but also in algae and dinoflagellates, circadian changes of melatonin contents were reported.[47–49] Recently effects of the exogenous application of melatonin on flowering of *Chenopodium rubrum* were studied. Data suggested neither toxic effects nor changes in the shape, color or number of leaves compared with the control plants. In addition, it should be noted that the concentrations of melatonin that induces plant responses are higher than the concentrations found in nature. Thus, the role of melatonin in flowering remains unclear.[50–51]

Antioxidant and free radical scavenger

In animals, melatonin is a proven free radical scavenger and broad spectrum antioxidant.[52] This led researchers to hypothesize that the indole molecule might act presumably in a similar manner in plants. It has been reported that *Lycopersicon esculentum* Mill. (cultivated tomato) contains about 5-fold more melatonin content than *Lycopersicon pimpinellifolium* Mill. (wild tomato) due to which the cultivated species is more tolerant of higher ozone levels than the ozone susceptible wild strain.[54] Melatonin acts as photo-protector.[55] During photosynthesis, large quantities of free radicals or reactive oxygen species (ROS), H_2O_2, singlet oxygen and reactive nitrogen species (RNS) are generated. In addition, violaxanthin cycle gets impaired with increasing exposure to light during the photophase resulting diminished plastidial photo-protection. Tan observed that *Eichhornia crassipes* (Mart.) Solms showed optimum diurnal rhythm with melatonin and its metabolites level peak during late night phase of the light-dark cycle. From this, they postulated that melatonin and its metabolites observed during the late night phase may act as protector against free radical damage from toxic ROS and RNS.[56] In addition, melatonin has also been proposed to exert its photo-protective effects against UV radiation in algae and higher plants.[57] This possibility is supported by Tettamanti et al.,[58] who showed that Alpine and Mediterranean plants exposed to high UV in their natural habitat contain more melatonin than the same species living under lower UV exposure.[58]

Growth promoter

Structurally melatonin is related with IAA, a potent growth promoter of plants. Hence, melatonin is recommended to act like auxin to support vegetative growth various plant species.[59] Studies suggested that auxin induced root and cytokinin induced shoot organogenesis were inhibited by the alterations in endogenous melatonin concentration. This illustrates the role of melatonin as a potential plant growth regulator.[60] Later, to find the role of melatonin more elaborately, Hernandez-Ruiz et al.,[61] incubated etiolated hypocotyls from *Lupinus albus* L. with different concentrations of melatonin and IAA. Both compounds were seen to be distributed in plant tissues in a similar concentration gradient and promote growth at lower concentration while growth inhibitory effect in intact and de-rooted plant tissues was observed at high concentrations.[61] Furthermore, both indoles induced the appearance of root primordial from pericycle cells, modifying the pattern of distribution of adventitious or lateral roots, the time-course, the number and length of adventitious roots, and the number of lateral roots. In this study, melatonin produced the maximum number of roots/hypocotyls with similar values to IAA for root length in practically the entire range of concentrations tested.[62]

Moreover, in some monocots viz. *Triticum aestivum* L. (oat), *Avena sativa* L. (wheat), *Hordeum vulgare* L. (canary grass) and *Phalaris canariensis* L. (barley) growth-promoting action of melatonin was established through coleoptiles longitudinal-growth assays. Studies revealed, melatonin promoted growth in coleoptiles of around 10, 20, 31 and 55% respectively compared with IAA.[63]

Defense against herbivores

Melatonin being an alkaloid bitter and unpleasant in taste; hence, provides protection against herbivores.[64] Moreover, consumption of plants containing high level of melatonin like walnut (3.5±1.0ng/g) can disturb the physiology of herbivores as melatonin tends to be accumulated in the animal body. Studies suggest feeding with high melatonin content diet increased blood melatonin level from 11.5±1.9 pg/ml to 38.0±4.3pg/ml in rats.[65] This fact could be correlated with plant defense against herbivores. Over expression of tryptophan decarboxylase, (converting enzyme for 5-hydroxytryptophan to 5-hydroxytryptamine) in tobacco leads to minimize the reproduction of white fly.[66] However, the mechanism by which melatonin exert inhibitory effect on white fly reproduction is yet to be established.

Miscellaneous

Melatonin posses a significant role in the regulation of reproductive physiology and flower development of *Hypericum perforatum* L. (St. John's wort).[67] The indole was detected in highest concentrations during uninucleate microsporogenesis. Moreover, elevated melatonin level improved regenerative potential of isolated anthers. Melatonin supplementation attenuates cold-induced apoptosis in *Daucus carota* L. (carrot) root cell suspensions.[68] Melatonin also helps to maintain the dormancy stage of germs or to a differentiated state in fruit tissue.[69] Studies revealed that melatonin slowed down the senescence process in concentration dependent manner in the leaves of *Hordeum vulgare* L.; this activity may be associated with a specific action of melatonin on the chrorophyll-degrading enzymes chlorophyllase, pheophorbide a oxygenase or red-chlorophyll catabolite reductase.[70–72] The summary of multi directional actions of melatonin in plants is shown in Figure 2.

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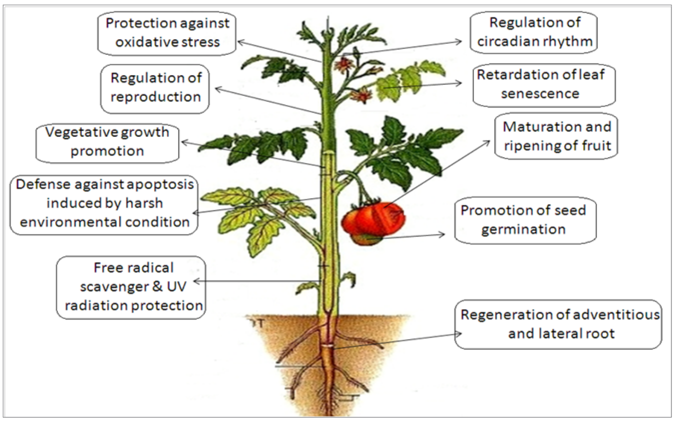

Figure 2 Multi-directional function of phytomelatonin in higher plants (Based on Sergio et al.[72]).

Conclusion & future aspects

Melatonin plays an important aspect to regulate several physiological role of plants viz. circadian regulator, cytoprotector and growth promoter, antioxidant and free radical scavenger.[73] It also promotes rhizogenesis, cellular expansion and provide defense against environmental stress condition.[74] At present, two diverse aspects of phytomelatonin gained the utmost importance:

(i) its application in agriculture and

(ii) Its use to improve human health condition. In the first aspect, exogenous application of melatonin to plants improves their growth & development and better adaptation to environmental stress situations such as drought, cold, heat, and radiation, among others.

Melatonin also enhances the rate of germination and growth and plant productivity. It acts as a retardant in stress-induced leaf senescence. These cumulative observations bring forward the idea that exogenous melatonin treatment of cultivated plants or overproducing higher melatonin containing plants might help crops resist more easily against many adverse environmental conditions from which they normally suffer throughout their development.[75] The later aspects refer to the possibility of introducing melatonin-rich plants foods or food supplements due to its immense health benefits particularly against neurodegenerative disorders like Alzheimer's. Studies revealed that oral dose of melatonin of up to 1 gram/day produce no adverse effects in humans. In addition, melatonin is easily absorbed via the gastrointestinal tract. So, the utility of melatonin as a nutraceutical seems to have a promising future to promote healthier life.[76,77]

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Conflict of interest

The author declares there is no conflict of interest

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