

Review

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Posted Date: 23 April 2024

doi: 10.20944/preprints202404.1408.v1

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Review

Effects of Melatonin on Human, Animal and Plant Metabolisms

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Abstract: Melatonin is an important hormone with a methoxy-indole structure. It is secreted regularly by the pineal gland of mammals. It functions in many chemical, biological and physiological activities of the body. Melatonin acts as a basic hormone and is responsible for maintaining the circadian rhythm and sleep control. It has been shown to occur in the highest concentration in organisms during the night times. In living organisms, many activities that have physiological, biological, hormonal, and psychological characteristics follows a certain rhythm. Body temperature, hormone levels, sleep-wakefulness, and some other cognitive functions in humans also change with the circadian rhythm. Its synthesis and release begin with darkness and end with light. This review study aims to reveal the properties of melatonin, such as its stimulating function of antioxidant enzymes, restricting the oxidation of lipids and protecting brain cells from oxidative damage, stopping the proliferation of cancer cells and preventing tumor formation. It, which was previously known only as an animal hormone, has been found to also exist in plants. Studies have shown that melatonin is present in almost most plant species analyzed to date and performs functions similar to those in animals. It plays an important role in coping with various stress factors in plants. In addition, melatonin acts as an important antioxidant in post-harvest technology and extends the post-harvest shelf life of vegetables and fruits. It also has an important function in the regulation of stress genes and activation of antioxidant enzymes. Among the most functional roles of melatonin in plants are the control of circadian rhythm, growth, development and increasing plant resistance in case of various environmental stress factors. The review reveals the effects of melatonin as an extremely important secondary metabolite, on human, animal, and plant metabolism. The use of PRISMA guidelines was used for reporting, search, selection, and synthesis. Information up to 2024 was searched from search engines for the occurrence, nature and function of melatonin. Key words such as structural function, hormonal function, secretion and metabolism were used in the search of publications.

Keywords: melatonin; immunity; cancer; circadian rhythm; growth and development; aging; plant; seed; seed viability

1. Introduction

The pineal gland was identified by Herophilus in the third century BC. 450 years later, Galen revealed that this is a tiny endocrine gland in the middle of the brain tissue and has a similar function to the lymph nodes [1–3]. The pineal gland is a red-gray gland located in the central part of the brain, on the roof of the third ventricle of vertebrates, that produces the hormone melatonin, a derivative of serotonin that affects sleep-wake modulation patterns and seasonal functions.[4]. Galen, (129 – 216 AD) used the Latin word "conarium" to describe the human pineal gland, which he likened to the top of a pine tree (Emre, 1993). Although it is very small compared to body size, it is the second organ that receives the most blood after the kidneys. Although many peptide hormones are synthesized in the pineal gland, the main hormone is melatonin [2,5,6]. Melatonin hormone was first discovered by dermatologist Lerner in 1958 and its function was revealed [7].

The formula of melatonin (N-acetyl-5-methoxytryptamine), an indoleamine tryptophan derivative shown in Figure 1, was reported in bovine pineal gland tissue in the late 1950s and became an important discovery for the scientific world [7]. In general, it is the main hormone secreted by the pineal gland. Secondary sources of this hormone are other structures such as the retina, intestine, skin, platelets, and bone marrow [8,9]. This methoxy indole compound is synthesized from serotonin. The melatonin has been reported to lightens the skin color, hence its name which is a combination of the Latin words "melas" meaning black, and "tosos" meaning wife [10,11]. It is found in all living organisms, especially vertebrates and mammals and detected in the blood [12] (Figure 1).

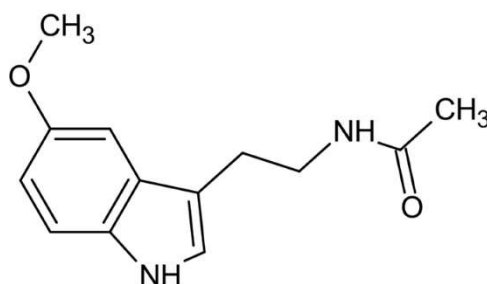


Figure 1. N-acetyl-5-methoxy tryptamine (Melatonin).

Melatonin was first found in algae and was later thought to be in the structures of different plants [13]. As a result of the studies, it has been determined that the roots, leaves, seeds and fruits of many plant species contain significant levels of melatonin [3,14].

Additionally, melatonin has been found to be synthesized by subphyla including bacteria [15–17]. Melatonin hormone, which is secreted from the pineal gland and known to increase in the dark, is a powerful antioxidant and is known to play a role in important functions such as cell renewal, strengthening the immune system, sleep rhythm and body temperature regulation. The circadian rhythm in melatonin release becomes irregular with age. It has been determined that the decrease in melatonin production is effective not only in physiological conditions but also in some clinical disorders such as mood disorders [18]. The metabolism of melatonin starts as tryptophan, an amino acid found in plants, animals, algae, and yeast. Tryptophan is first converted into serotonin which is then converted to melatonin in pinealocytes [10]. Tryptophan hydroxylase enzyme uses tetrahydrobiopterin (BH₄) and O₂ as cofactors, and vitamin B6 serves as a coenzyme in this reaction [19]. Although, melatonin is synthesized from the tryptophan precursor in different ways, the most commonly accepted way is; It is in the form of Tryptophan, Tryptamine, Serotonin, 5-methoxytryptamine, Melatonin and a wide variety of enzymes are involved during this synthesis [20].

Research as shown that melatonin hormone is secreted more during long nights in winter and less in summer. The function of the hormone Melatonin, is regulation of human biochemical metabolism and physiological rhythm while alleviating related disorders such as jet lag and insomnia, scavenging free radicals, and strengthening the immune system. Melatonin has been implicated as the cause of the phenomenon of jet lag. Studies have shown that people who work at night get sick more quickly and are more likely to get cancer. Additionally, this compound has anti-aging, anti-cancer effects as well as neuroprotective effects. It has also been shown that it has effects in the control of chronic diseases such as heart, diabetes and obesity [18,21].

There are many important factors that ensure the synthesis and release of melatonin, the most important of which is light. In other words, the light-dark, day-night rhythm provides control of the synthesis and release of the compound. This regulation mechanism is defined as "photo neuroendocrine control". Light intensity is especially important in measuring the suppression level of melatonin, and as the brightness of the light stimulus increases, the suppression power increases [22,23]. Melatonin shows its effect through specific receptors located in target tissues.

In addition to the pineal gland, receptors have been reported to be present in most peripheral tissues such as the retina, brain, pituitary gland, spleen, retinal erythrocyte, leukocyte, thyroid gland, thymus, placenta, endometrium and gastrointestinal tract [11,12,24].

This review aims to reveal the effects of melatonin on human, animal, and plant metabolism, based on all its functional properties.

To source out the results in this review, a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were formulated using the online scholar databases such as google scholar, BMC, science direct and PubMed. Information from this article was based on development of keywords such as structural function, hormonal function, secretion and metabolism. An overview of scientific publications (research articles) until March 2024 and those focused on structural function in human, animals, chemistry, and *in vitro* systems published in English language were used. A total of 356 research articles were screened by the authors (ARN, AKY, N.Ç. and H.Ö.D) to assess their relevance on the objective of the proposed review paper. Therefore, all authors' separately recorded 'yes' or 'no' as whether that article should be included. Later after the assessment, a total of 134 articles were included as of the data based on the motive of the study. In cases where the articles would meet a set criteria of relevance full paper article were downloaded and saved in the Menderly® referencing tool. Selection criteria of articles were constructed on the compound, melatonin. However, to a great extent, articles without adequate data, reproducible results and methods, and article written in other languages apart for English were excluded. In addition, in cases where results in different articles would show a contradicting fact, consultation with other colleagues whom are experts in this filed was done. Data extraction from the reviewed literature followed a standardized procedure. The extracted data included: materials and methods, results, interpretations and discussions. Data were extracted autonomously by the authors (ARN, AKY, XXXXX), and incongruities were resolved through constant discussions. Therefore, the use of PRISMA guidelines were used for reporting, search, selection, and synthesis.

2. The Importance of Melatonin in Humans and Animals

2.1. Melatonin Functions

Melatonin has exhibited anti-oxidative, metabolism regulator, immune/defense system booster, melanogenesis regulation, nervous system regulation, bioenergetic (energy) regulation, anti-inflammatory properties, sleep regulation, circadian (periodic behavior) rhythm regulation, onco-static (preventing tumor development) effects [24,25]. Melatonin is a powerful heart-healthy and exerts significant beneficial effects on cardiological disorders and many other health problems [26,27]. Additionally, melatonin has been shown to play a role in regulating human mood, sleep and wake cycles and reproduction. It is also known to reduce anxiety and stimulate immunity [28]. Melatonin is a lipophilic and hydrophilic substance and quickly passes into the blood and other body fluids before being stored in the body. Since it is soluble in water and lipid phases, it quickly passes into all intracellular components and has a potential antioxidant effect by effectively protecting the cell membrane, organelles and nucleus from free radical damage [29,30]. At least 70% of melatonin in the blood binds to albumin and is metabolized first in the liver and secondly in the kidneys to 6-hydroxy melatonin sulfate and 6-hydroxy melatonin glucuronide, and the resulting metabolites are excreted in the urine [5,19].

Melatonin has remarkable importance as a growth and development regulator in plants. It has important effects on plants such as increasing tolerance to environmental factors, protecting chlorophyll, and supporting root regeneration [31]. The effect of melatonin on its role in plant physiology has been demonstrated by many studies. It acts as an antistress agent against abiotic stress factors such as melatonin and biotic stress factors such as microbial infections. It also regulates plant growth and photosynthesis [28].

2.2. Factors Affecting Melatonin Synthesis and Release

Although many factors affect the synthesis and release of melatonin, the most important factor affecting this situation is light. This hormone, dark-light; controls the regulation of day-night rhythm. This mechanism is known as "photo neuroendocrine control". Although light synchronizes the circadian rhythm in pineal melatonin synthesis, it can also severely suppress melatonin synthesis.

Exposure of the eyes to artificial light during the night also causes a rapid decrease in melatonin synthesis and release. The intensity of light is an important factor in determining the level of suppression of melatonin, and as the brightness of the light increases, the level of suppression also increases [11,32–34].

2.3. Melatonin Biosynthesis and Sources

Melatonin is produced from tryptophan taken from the bloodstream and converted into serotonin. Serotonin is converted into melatonin in a two-step process as a result of the activity of two enzymes. Serotonin-N-acetyl transferase and hydroxyindole-O-methyl transferase, which are limiting enzymes for melatonin synthesis, are involved. mRNAs encoding these enzymes are synthesized in the pineal region depending on the day/night rhythm [35].

When it gets dark, photoreceptors in the retina are stimulated and this information is transmitted to the suprachiasmatic nucleus (SCN) in the hypothalamus via the monosynaptic retinohypothalamic pathway. This system works autonomously, centrally and circadianly. Incoming signals pass to the paraventricular nucleus and from there they combine in the medial forebrain stem and reticular formation and go to the intermediolateral nucleus of the spinal cord. The signals received by the preganglionic adrenergic nerves of the sympathetic nervous system are carried to the upper cervical ganglion, and the final sympathetic information from here reaches the pineal gland. Sympathetic nerves rhythmically secrete norepinephrine in the terminals of the parenchymal cells of the pineal gland, depending on daily light-dark changes. This substance is recognized by β -adrenergic receptors in the pinealocyte membrane and accordingly the cyclic nucleotide system is stimulated. [36–38]. In mammals, the pineal gland acts as a neuroendocrine transformer, converting electrical impulses into hormonal secretions. It is in high concentration during the night because melatonin synthesis and release are affected by light. In the dark, the stimulus from the superior sympathetic ganglion via β -adrenergic post-ganglionic sympathetic fibers increases its synthesis, while in bright conditions its synthesis is inhibited [33,39–41].

Melatonin shows its effect in animal cells mostly through membrane-bound G-protein coupled receptors [42]. In mammals, three nuclear receptors of melatonin, called MT1, MT2, and MT3, have been identified [43,44]. Melatonin receptors are found in many organs, especially in the brain, cardiovascular system, aorta, heart ventricular wall, cerebral and coronary arteries, gallbladder, liver, retina, parotid gland, appendix, cecum, colon, skin, pancreas, platelets, and immune system. [45,46]. The majority of melatonin receptors are typically found in the jejunal and colonic mucosa of the gastrointestinal tract [36]. Melatonin shows its effect with the participation of various molecular pathways. The most described pathways involve the activation of specific membrane receptors, namely high affinity (ML1) and low affinity (ML2) domains [47,48]. ML1 acts directly on target cells or through G-protein coupled receptors. There are three types of receptors in the synthesis of melatonin: MT1, MT2 and MT3: MT1 and MT2 show G-protein-mediated effects. While MT1 has high affinity, MT2 has low affinity [49]. The third type belonging to the quinone reductase family is the MT3 protein [50]. Depending on their chromosome location and molecular structure, MT1 and MT2 melatonin receptors are defined as different subtypes [43,44,51–53]. MT1 receptors are located in the pars tuberalis part of the pituitary, and MT2 receptors are located in the retina. Additionally, both receptors were found in the suprachiasmatic nucleus of the hypothalamus. The presence of the MT3 receptor has also been demonstrated in amphibians and birds. It is thought that circadian and reproductive effects occur through the MT1 receptor, and the MT2 receptor is associated with dopaminergic functions in the brain and retina.

As expressed in Figure 2, the amino acid tryptophan is the precursor of melatonin synthesis and is taken from the plasma by the pineal gland [54]. Tryptophan is hydroxylated to 5-hydroxytryptophan by tryptophan hydroxylase (Figure 2). Vitamin B6 serves as a coenzyme in this reaction. The resulting 5-hydroxytryptophan is a naturally occurring intermediate metabolite. 5-hydroxytryptophan can easily cross the blood-brain barrier and turns into serotonin by losing its carboxyl group through the L-amino acid decarboxylase enzyme. Serotonin cannot cross the blood-brain barrier. However, it is then acetylated by the N-acetyltransferase enzyme and converted into N

acetylserotonin, which in turn is converted into melatonin by the hydroxyindole-O-methyltransferase enzyme (Figure 2) [5,11,23,28].

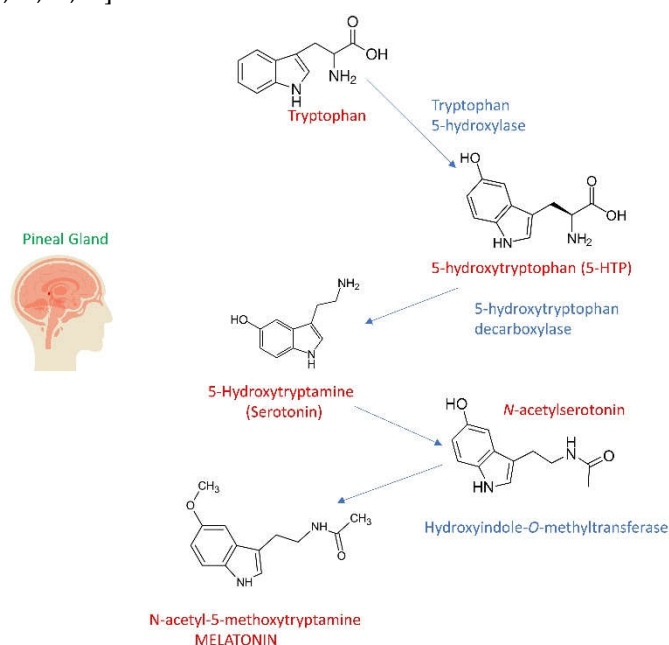


Figure 2. Melatonin synthesis [23].

Melatonin has high lipid and water solubility, which facilitates passage through cell membranes. After being released into circulation, it passes into various fluids such as saliva, urine, cerebrospinal fluid, semen, amniotic fluid and milk [1].

In humans, melatonin release begins immediately after darkness falls (20:00-23:00), reaches peak levels in the middle of the night (02:00-04:00), and ends in the morning hours (07:00-09:00). Nocturnal melatonin production in young adults is typically around 10–80 g [55]. In a study conducted on 170 people (85 women; 26.2 ± 6.0 years), it was reported that the highest melatonin concentration ranged between 2 and 84 pg/mL [56]. It is stated that the concentrations of melatonin in the blood and cells at night are 3-10 times higher than during the day [11]. Melatonin level in serum varies according to age. In newborns, melatonin levels are quite low. After the third month, melatonin secretion becomes rhythmic. While the highest melatonin level in the life cycle is detected between the third and fifth years of life, melatonin secretion and level decrease with advancing age [57–59].

Although melatonin is found in many food sources, melatonin content varies greatly among foods. The richest sources of melatonin taken externally (exogenously) through the diet are products such as eggs, fish, mushrooms, barley, oats, sprouted seeds, nuts, and medicinal plants [60]. Studies are showing that the seeds, roots, leaves, and fruits of plants are good sources of melatonin. The change in melatonin level varies depending on the type of plant, climatic conditions, horticultural practices, processing and storage conditions [28]. Melatonin levels in plants not only vary from species to species. It may also differ between genotypes and cultivars within the same species or at different growth stages of individuals of the same genotype [61,62].

2.4. Melatonin Synthesis Sites

Melatonin is secreted from the pineal gland, ovaries, lens and bone marrow cells, and the bile and gastrointestinal systems of mammals [34]. The pineal gland synthesizes approximately 80% of the amount of melatonin in the bloodstream. In many species, the main source of melatonin other than the pineal gland is the gastrointestinal tract. The intestines contain 400 times more melatonin than the pineal gland. Although the release of melatonin, synthesized in enterochromaffin cells in the gastrointestinal tract, shows a diurnal rhythm in birds, it is dependent on the presence of nutritional factors in many other species [63]. Melatonin, synthesized in the retina, plays a role in regulating retinal pigment epithelial function and the response of the retina to day-night variation in

photoreceptors. Melatonin, which is responsible for the change of pigment granules in the skin and the protection of deep tissues against harmful radiation of the sun, is synthesized in enterochromaffin cells in the gastrointestinal tract and released into the circulation postprandial. Melatonin, synthesized in bile, protects the mucosa and epithelium of the biliary tract against oxidative damage against oxidized cholesterol derivatives and bile acid. However, the contribution of this synthesized amount to the melatonin level in the bloodstream is very small [1,23,38].

2.5. Effects of Melatonin on Physiological Functions

2.5.1. Effect on Lymphoid Tissues

Melatonin increases the size of tissues and organs directly related to immune function, such as the thymus and spleen of mammals. It has been reported that the thymus gland atrophy in animals whose pineal gland was removed experimentally or in which drugs were used to suppress the pineal function, and when melatonin was given externally to these animals, hyperplasia was observed in the thymus gland [64].

2.5.2. Presence of Melatonin in the Digestive System

In general, the level of melatonin secreted from the gastrointestinal system is 10-100 times higher than the level of melatonin secreted from the pineal gland. In particular, there are different levels of melatonin in different parts of the digestive system, and the amount of melatonin in this region is completely related to the serotonin concentration [8].

2.5.3. Effect of Melatonin on the Cardiovascular System

The function of melatonin on the cardiovascular system occurs through two different mechanisms. These are mechanisms with and without receptors. Melatonin causes vasoconstriction in cerebral arteries and vasodilation in peripheral vascular beds. Studies have reported that melatonin levels are very low in coronary heart patients at risk of myocardial infarction and sudden death [52,65]. Additionally, melatonin levels are low in people with high LDL-cholesterol levels, as well as in the body of hypertensive patients, and melatonin has been found to lower blood pressure. The role of melatonin's vasodilator effect in inducing sleep through thermoregulation is also very important [66].

2.5.4. Daily and Annual Rhythm Regulation and Photoperiodic Response

Melatonin has been found to act as a photoperiodic regulator or circadian rhythm regulator in animals and humans, as the number of changes in blood helps tissues and cells sense the time of day or year and mimics the dark application of external melatonin applications [5]. Circadian rhythm or circadian clock, also known as the biological clock, regulates the physiological, behavioral, and metabolic functions of a wide variety of organisms, from bacteria and fungi to plants and animals, in approximately 24-hour cycles, depending on the time it takes for the Earth to rotate once around itself. Cells and organisms react to the time of day according to their internal clock, thus cell renewal and the secretion of hormones occur, and control is provided over events such as photosynthesis and flowering in plants. According to some researchers, melatonin; can regulate many biological processes in plants, including circadian rhythm, regulation of genes and metabolites, protein stability, daily and seasonal cycles, increases photosynthesis and growth rates, can increase seed yield in the product by affecting flowering, and can affect biotic and abiotic responses [67,68]. It has been reported that it functions as a photoperiodic regulator or 24-hour rhythm regulator in plants. In addition, research has shown that although melatonin varies depending on the species, its amount increases especially at night or in the dark, and some plants it peaks a second time during the day. In the first study, in which a change similar to that in animals was observed in plants and the change in melatonin within 24 hours was revealed, it was found that the amount of melatonin in *Chenopodium rubrum* L. plants was at a very low level in the light but reached the highest level towards the end of

the dark period [69]. Although it has been reported that melatonin acts as a 24-hour rhythm regulator in plants and that the amount of synthesis generally increases in the dark, some researchers have reported that the amount of synthesis reaches the highest level just before sunset [70,71]. In some research, it is reported that melatonin is constantly present in plants, with level changes during the day [3]. For example, in a study conducted with water hyacinth, it was observed that the melatonin level in plants grown under natural conditions increased towards the end of the light period, unlike the rhythm detected in animals, and the reason for this was related to the processes of photosynthesis and protection from light. It has been stated that it may be possible [71]. In another study examining the melatonin change in apples during the day, it was found that the melatonin level in leaves peaked twice during the day, at 14:30 and 05:30 [72].

2.5.5. Effect of Melatonin on Aging

In animals, melatonin has been found to prevent aging-related disorders and extend the lifespan of some mammals to some extent, depending on genetic conditions [73]. In studies on the aging process in plants, researchers focus on the aging effect occurring in the leaves rather than the life of the organism, so a different process is experienced than the aging seen in animals. However, the common point seen in both is that as aging progresses, the damage caused by oxidative damage in the relevant cell increases. In both cases, it is a known fact that the antioxidant activity of melatonin contributes to delaying aging [74].

2.5.6. Effects of Melatonin on the Immune System and Cancer

Melatonin is a powerful free radical scavenger and has an antioxidant effect by blocking nitric oxide synthase enzyme activity [71,75]. It also prevents oxidative damage caused by neutrophil activation in tissues in inflammation cases such as burn sepsis, ischemia re-perfusion injury [75]. Another function of melatonin on the immune system is its anti-inflammatory effect. It has also been suggested that melatonin may have an effect on diseases that may involve viruses and be contagious, such as bacterial infections, cancer, and HIV[76].

Melatonin also provides daily and seasonal regulation of immune system cells [77]. In studies conducted at the in vivo level, it has been determined that high doses of melatonin provide general immune system stimulation. It has been determined that it increases T cell activation, lymphocyte growth, humoral response and inhibits thymus involution that occurs with age. (Simonneaux and Ribelayga 2003). In vitro studies have shown that melatonin increases helper T cell and NK cell activity, IL-2 and IFN γ production, and IL 1 mRNA expression in human monocytes [77]. In addition, considering the helplessness experienced during the treatment of viral infections, it has been reported that melatonin can act as a supporter in the treatment of many viral infections [78].

It has been demonstrated that MT1 melatonin receptors are constantly active in breast and prostate cancer cells and, as a result, inhibit the proliferation of cancer cells [79]. In recent years, the majority of research on the effects of melatonin on cancer has focused on breast cancer. The results of the studies have revealed that nighttime applications of melatonin provide more successful results in cancer [3,80]. The effect of seasons on cancer development is proportional to melatonin. During the winter months, when nights are long, melatonin production is high and tumor development slows down during this period [81].

Melatonin has a pure anticarcinogenic effect by reducing the receptors that allow linoleic acid, one of the substances that the cancer cell needs for growth, to enter the cancer cell, puts the cancer cell to sleep through the Ca-calmodulin complex, and slows down the growth of the tumor [82]. It has been determined that melatonin binds to Ca²⁺ activated calmodulin with high affinity. Thus, it has been suggested that melatonin prevents tumor growth by removing calmodulin from calcium, slowing down the cell cycle. Melatonin also has the feature of preventing the formation of apoptosis in healthy cells [3,76].

2.5.7. Free Radical Scavenging and Antioxidant Effect of Melatonin

Oxygen, which makes up 21% of the Earth's atmosphere, is necessary for aerobic organisms to survive. The majority of inhaled oxygen is used in the production of ATP, and a relatively significant portion of inhaled oxygen (about 5%) is converted into extremely toxic free radicals. Melatonin is a powerful hydroxyl and peroxy radical scavenger and its radical scavenging effect is lower than vitamin E and therefore has less neutralizing effect against the lipoperoxy radical [75,83].

This is due to the production of free radicals during oxidative phosphorylation in mitochondria and fatty acid oxidation in peroxisomes. These free radicals are toxic substances called hydroxyl radicals (OH), hydrogen peroxide radicals (H₂O₂), superoxide anion radicals or singlet oxygen radicals (O₂) [84,85]. Melatonin is a powerful antioxidant that eliminates the hydroxyl radical, the most harmful radical, thus preventing lipid peroxidation [85]. Melatonin has also been shown to have indirect effects on free radicals. Melatonin also has an antioxidant effect by activating the GSH-Px enzyme that metabolizes hydroperoxides, increasing the SOD activity that catalyzes the O₂⁻ radical to H₂O₂, preventing the decrease in catalase activity during oxidative stress, and inhibiting the nitric oxide synthase (NOS) enzyme responsible for NO formation [1,86,87].

Oxidative stress caused by some toxins that cause oxidative tissue damage is prevented by melatonin. Since melatonin is soluble in both water and lipid phases, it easily reaches all intracellular components and effectively protects the cell membrane, organelles and nucleus from free radical damage. Melatonin binds to the out of the cell membrane surface, traps radicals before they enter the membrane, and protects the membrane by detoxifying them. It also reduces the production of radicals such as oxygen (O₂), hydrogen peroxide (H₂O₂) and hydroxy (OH) that occur in mitochondrial respiration. Its ability to reach the nucleus protects DNA against oxidative damage [88].

2.5.8. Effect of Melatonin on Sleep

Melatonin ensures homeostasis as an endogenous regulator. It provides information to all cells with daily, monthly and annual secretion differences with the signals coming from the SCN. This hormone epigenetically controls clock genes in cells [18,82]. It is known that its effects on sleep are probably chronobiological effects. It is known that the effect of melatonin synthesis on sleep is related to the onset, quality and latent phase of sleep rather than the length of total sleep time and that this is achieved through the hypothermic effect and thermoregulation. Melatonin increases the nocturnal temperature drop and makes it easier to fall asleep [18]. While sleep is not necessary for melatonin production, a dark environment is sufficient [89].

Sleep is a very important time period for human health. The basic mechanism that ensures sleep is; It was the light-dark cycle. The dark environment stimulates the nerve network that starts from the retina and extends to the hypothalamic region of the brain. The suprachiasmatic nucleus in the hypothalamic region of the brain acts as a "biological clock" by regulating activities that affect the whole body by giving signals that control body temperature, hormones, sleep-wake status and other regions [90].

The pineal gland remains inactive until darkness falls, and the production of sleep-related melatonin and other similar hormones is restricted. When the environment darkens, the signals that suppress melatonin production created by the suprachiasmatic nucleus disappear and the pineal gland is stimulated to release melatonin. As the melatonin level increases, less stimulation is perceived in the brain and the likelihood of falling asleep increases. It has been found that melatonin level is related to the onset, latent phase and sleep quality rather than the length of the total sleep cycle. [91].

2.5.9. Melatonin's Relationship with the Reproductive System and Other Hormones

It has been determined in numerous studies that melatonin release affects the reproductive system [92,93]. Exogenous melatonin also regulates reproduction, although it varies depending on species, age, dose and time of administration [85]. It has been suggested that melatonin may have an

inhibitory effect on the hypothalamic pituitary gonadal system and also it has antigonadotropic effects [94]. Reportedly as a result of the chronic melatonin administration in adult females, ovarian size decreases and the frequency of estrus decreases [95]. While high doses of melatonin decrease gonadotropin levels, it increases prolactin and growth hormone levels. Melatonin controls reproductive activity in seasonally breeding animals [96].

While Melatonin has a stimulating effect on the gonads in animals that reproduce in short days, such as goats, sheep and deer, it has an inhibitory effect in animals that reproduce in long days, such as hamsters, camels and horses [97]. Especially in seasonally breeding hamsters, prolonged darkness prevents reproduction by causing more melatonin secretion and causes testicles to shrink in male hamsters and anoestrus in females. Epidemiological studies show that although there is no seasonal reproduction in humans; It shows that pregnancy and birth rates have a seasonal distribution in different geographical regions. It has been revealed that in regions where winters are long, hypothalamo-gonadal system activation and pregnancy rate are lower compared to summer months [98].

It is a center that regulates endocrinological activity in the organism with the help of the pineal gland, thyroid, adrenal gland, gonads and pituitary [54]. It is accepted that melatonin and therefore the pineal gland have effects on the release of gonadotropic hormones as well as other hormones from the pituitary. Administration of melatonin increases prolactin secretion in women. Melatonin application in adult men increases basal growth hormone secretion and leads to an increase in the effect of growth hormone release hormone on growth hormone secretion. Melatonin probably exerts this effect by inhibiting somatostatin secretion from the hypothalamus [99,100] showed in their study that 1 mg melatonin given to people at 09.00 in the morning reduced PRL and LH levels, but did not affect GH, FSH and TSH levels.

2.5.10. Effect of Melatonin on Aging

In recent studies, it has been determined that the plasma melatonin level in humans decreases with aging. In parallel with this, the circadian rhythm of melatonin changes. In studies determined that the plasma melatonin level detected in elderly people was 40-50% lower than its normal value [54,84].

It has been determined that anatomical and functional degeneration in organs with aging is associated with the decrease in antioxidant capacity that occurs with the decrease in melatonin level and the damage caused by increased free radicals [101]. As it is known, melatonin has the effect of protecting brain tissue from oxidative damage, preventing lipid peroxidation and stimulating antioxidative enzymes. Research has revealed that neurodegenerative damage in the brain occurs as a result of an increase in free radicals due to a decrease in melatonin [102]. The decrease in melatonin, an important radical scavenger, over time causes brain tissue to become vulnerable to oxidative attacks [102]. With age, the number of β -adrenergic receptors in the pinealocyte membrane decreases and probably melatonin synthesis in the pineal gland decreases. β -adrenergic receptors mediate the secretion of norepinephrine from sympathetic neurons to the pineal gland at night and initiate a series of reactions that increase melatonin synthesis [84,101].

2.5.11. Effect of Melatonin on Jetlag

Studies have revealed that transmeridian journeys have an effect on sleep, circadian rhythm and daily activity [103]. Flight dysrhythmia, as it is known, manifests itself with symptoms such as inability to loss of appetite, wake up, daytime fatigue, jetlag, nighttime insomnia, poor psychomotor coordination, digestive problems, poor cognition, and depressive mood, [103]. To relieve jetlag symptoms, especially on flights from west to east; Studies have shown that the most effective treatment is melatonin application [103].

2.5.12. Effect of Melatonin on Insulin Secretion

There is evidence that the circadian rhythm of melatonin affects the pancreas and ensures insulin secretion [104,105]. Many studies suggest that melatonin has a suppressive effect on the activity of the pineal gland, β -cell, as it reduces insulin levels in rats [106] and revealed that these effects are compatible with the decrease in glucose tolerance. Increased insulin rate has an inhibitory effect on the pineal gland and melatonin. This situation reveals the fact that there is a functional antagonism between insulin and melatonin [107, 108].

3. Presence of Melatonin in Plants

Studies investigating melatonin in plants have a shorter history than those in animals. Recently, significant progress has been made in research based on the effects of melatonin in plants. It has been determined that melatonin controls many physiological processes, especially during vegetative and reproductive periods, due to its ability to reduce oxidative stress in plants [109–111]. Melatonin regulates circadian rhythm and photoperiodic properties in plants.

It also has effects such as regulating growth, gene expression and development, protecting plants by preparing against endo- or exogenous biological stress factors, ensuring interaction with biotic substances (e.g. herbivores/pests) and slowing down aging. Additionally, as an indoleamine neurotransmitter, it functions primarily as an antioxidant agent by controlling reactive oxygen and nitrogen in plants. Melatonin, a signaling agent, increases growth, rooting, photosynthesis, carbon fixation, seed germination and defense against various biotic and abiotic stress factors in plants and induces a variety of specific physiological responses. It also functions as an important mediator in the metabolism of cytokinin, gibberellin, ethylene, indole-3-acetic acid, and oxygen carrier proteins, as well as gene expression related to plant hormones. Again, regulation of stress-specific genes and activation of pathogenesis-related protein and antioxidant enzyme genes under stress conditions have made it a versatile molecule. Melatonin is one of the main function regulators of plants due to its diversity of effects and its role in regulating plant growth, development, and behavior [109–112].

3.1. Melatonin Formation in Plants

Melatonin production in plants occurs differently than in animals. Melatonin biosynthesis in plants occurs in main regions such as chloroplast and mitochondria. These organelles contain enzyme groups that synthesize melatonin through different procedures. Melatonin production can occur in two ways. If melatonin production is prevented in mitochondria, synthesis takes place in chloroplasts. Production in plants occurs by a specific M3H enzyme [113]. Although the amount of melatonin in plants varies depending on plant tissues and light level, melatonin has been detected in almost all plant species. It has been determined that the melatonin level in leaves and aromatic plants is higher than in seeds [16,20]. In higher plants, melatonin was first identified in 1993 in the fruits of Convolvulaceae, namely ivy morning glory and tomato plants [114,115]. Especially plants belonging to the Rosaceae, Apiaceae, Brassicaceae, Poaceae and Vitaceae families contain more endogenous melatonin than other plant species. Over the last decade, many researchers have reported that melatonin concentration varies among varieties of the same species, depending on factors such as location, growth stage, part of the plant, and harvest time [116,117].

3.2. Edible Vegetable Sources of Melatonin

Melatonin is found especially in edible plants and various plant-based food products. Plants contain not only melatonin but also its precursor. Melatonin, a bioactive substance, is found in different compositions and concentrations in fruits, vegetables, and herbs such as tomatoes, strawberries, grapes, rice, walnuts, oranges, cherries, olive oil, and barley. Melatonin levels in plants are universal; However, concentrations in plant tissues can vary from picograms to micrograms. In the growth and germination of seeds in plants, in reducing oxidative stress, in increasing resistance to stress factors (drought, salinity, toxic chemicals, heavy metals, UV rays, high and low and high ambient temperature, and light), in stimulating the immune system, in regulating circadian rhythms,

in leaves. It plays an important role in controlling stomatal closure. In addition, since melatonin contributes to the development of various properties such as antibacterial, antifungal and antiviral, it also contributes to coping with biotic stress in plants [117,118].

3.3. Melatonin Uptake in Plants

Plants containing melatonin can synthesize this indolamine; It is also possible for them to receive melatonin applied externally to the growing medium, that is, the soil or the plant itself (leaf) [75]. Studies have shown that melatonin is not only taken from the roots but also the seeds and leaves can absorb it. For example, it was determined that the amount of melatonin in barley leaves given different amounts of melatonin increased depending on the concentration [119].

3.4. Function of Melatonin in the Regulation of Plant Development and Physiology

While melatonin is known to improve the overall growth of plants, its primary function is as an antioxidant activity [118,120]. Melatonin plays a role in the control of growth and development, coping with stress, antioxidant defense mechanism and various physiological processes in plants. In plants grown in the garden, it can control seed germination, root development, shoot release and biomass increase. It also plays a role in ensuring vegetative reproduction and growth stages, flower formation and regulating leaf senescence [60,121]. A similar role of melatonin was also determined in etiolated *Lupinus albus* L.; here it was found to be responsible for promoting vegetative growth and regeneration of lateral and adventitious roots [122]. Again, in a study conducted on cucumbers, melatonin was applied to cucumber plants under conditions of intense salt stress, and as a result, it was found that there was an increase in ide growth, improvement in nutrient uptake and productivity, and an increase in nitrogen metabolism [123]. In another study, it was found that melatonin supplementation stimulated root growth and elongation, increased photosynthetic activity, and improved redox homeostasis in wheat, barley and rice [124]. In summary, melatonin can be regarded as an important biological plant growth regulator that increases the reproductive rate in plants.

3.4.1. Function of Melatonin on Seed Germination

Germination and seedling formation are two important steps in the formation of plant populations. Melatonin has an important contribution to this. In the natural cycle, melatonin level increases rapidly in the initial phase of seed germination and reaches its highest level at the end of the 14-hour period. However, as the germination period progresses, its concentration begins to decrease and reaches a steady state in the later stages of seedling formation. In particular, the increase in melatonin in the cytoplasm at the beginning of the plant development process may contribute to faster delivery of nutrients to the metabolic regions of germinating seeds [125].

3.4.2. Function of Melatonin on Photosynthesis

Photosynthesis in plants is sensitive to biotic and abiotic factors. Under plant stress conditions, it delays fermentation by closing stomata, reducing chlorophyll content and destroying excitons in chloroplasts. However, melatonin supplementation to the plant is useful in alleviating these negative effects of stressors. In particular, it ensures the photosynthetic efficiency of the plant at the cellular level by increasing stomatal conductance, reducing the rate of chlorophyll degradation and helping stomata to both open and close. Thus, the plant shows a higher rate of CO₂ assimilation and photosynthetic efficiency, as well as an increase in antioxidative effect. Melatonin reduces the negative effects of abiotic stress factors as well as biotic stress factors. Thus, the chloroplast is protected, sugar assimilation is supported, and proline accumulation, which is necessary to maintain normal cellular functions under stress, is increased. [109,126]. Additionally, genes related to carbon assimilation, photosynthesis, and ascorbate biosynthesis are also stimulated by melatonin. In a study investigating the application of melatonin to cherry rootstocks under stress, it was determined that the production of photosynthetic pigments increased with the application of melatonin to the

rootstock, resulting in higher carbohydrate accumulation, an increase in proline content and an increase in biomass.[127,128]

3.4.3. The Function of Melatonin in the Regulation of Reproduction, Development and Circadian Rhythm of Plants

After the existence and importance of melatonin was discovered in plants, it was thought to have a similar function to that in mammals. To this end, initial studies focused on factors related to circadian rhythm, such as vernalization, photoreceptors, flowering, and hormones, and on identifying the potential role of melatonin [20,123,129].

3.4.4. Function of Melatonin on the Antioxidant Defense System

The main function of melatonin in plants is to act as an antioxidant and to protect the plant organism against various environmental pollutants. In the study conducted on barley (*Hordeum vulgare*), barley was exposed to multiple stressors such as salt, hydrogen peroxide and some heavy metals, and as a result, it was determined that there was an increase in the endogenous melatonin level of the plant. Similar results were also detected in *Lupinus albus* (lupine) seedlings [130–132].

3.4.5. Effect of Melatonin on Supporting Defense Mechanisms against Various Stress Elements in Plants

As explained in the previous sections, melatonin has a protective role and defense mechanism for the plant against various stress factors such as drought, heat, cold, chemicals, heavy metals, ultraviolet rays and salinity [127].

3.4.6. Function of Melatonin in Biomass Increase in Plants

Apart from the main factors mentioned, melatonin also has an effect on increasing the biomass of plants. Especially in order to develop transgenic plants, different modifications have been made on the metabolic indoleamine enzyme of melatonin and it has been determined that this increases plant biomass [118]. In addition, melatonin increases plant development and productivity, improves the germination of seeds and seedlings by developing defense mechanisms against external and internal factors, and increases plant biomass [133, 134].

4. Conclusions

Based on the available data and research in this review study, it is seen that melatonin has an undeniable importance in human, animal, plant and agricultural production. Melatonin is widely found in nature and is a biomolecule with very important functions produced by humans, animals, plants, fungi and single-celled organisms. In case of deficiencies in melatonin synthesis or impaired receptor in the organism, various abnormal conditions such as hypertension, diabetes, neurological and autoimmune disorders, mood changes, breast cancer, obesity and prostate cancer may occur. In particular, it has been revealed that the deficiency of the Melatonin molecule plays an important role in disorders such as sleep disorders and chronic insomnia. It is also vital in reducing oxidative damage. Therefore, exogenous melatonin is applied in the prevention and treatment of various diseases, as well as in many clinical applications. For this purpose, various melatonin agonists have been developed and produced to perform various treatments. Melatonin is also a hormonal molecule with very important functions in plants. Melatonin, an antioxidant, increases the resistance of plants to chemical pollutants, environmental factors, low and high temperatures, and other environmental factors. In addition, melatonin accelerates photosynthesis in plant metabolism by protecting chlorophyll against oxidative stress elements, and ensures root renewal by signaling the development of the root system. Due to all these important effects, it is of great importance to reveal and better understand the functions of the melatonin molecule in humans, animals, and plants.

Author Contributions: Conceptualization, A.R.N., A.K.Y., N.Ç. and H.Ö.D.; resources A.R.N., A.K.Y., N.Ç. and H.Ö.D.; data curation, A.R.N., A.K.Y., N.Ç. and H.Ö.D.; writing—original draft preparation, A.R.N., A.K.Y. and N.Ç.; writing—review and editing, A.R.N., A.K.Y., N.Ç. and H.Ö.D.; funding acquisition, A.R.N. All authors have read and agreed to the published version of the manuscript.

Funding: Please add: This research was funded by the Department of Science and Innovation, Pretoria (South African Government), grant number DSI-IKS DSI/CON C2235/2021.

Data Availability Statement: Not applicable.

Acknowledgments: The authors (A.R.N., A.K.Y., N.Ç. and H.Ö.D) acknowledge the funding provided by the Department of Science and Innovation, Pretoria, South African Government.

Conflicts of Interest: The authors declare no conflict of interest.

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