THE ROLES AND FUNCTIONS OF MELATONIN DEVELOPED AND ADAPTED IN RELATION TO THE EVOLUTIONARY PROCESSES OF LIVING ORGANISMS

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Abstract

Melatonin is a complex substance that was initially described as a hormone involved in regulating the circadian rhythm; it is the primary molecule that prompts vertebrates to fall asleep. The complexity of this substance is due, first and foremost, to its association with the circadian rhythm and the physiological state of sleep, and secondly to the multiple effects that melatonin has on animal and plant organisms. Melatonin is considered an ancient molecule, due to its presence in primitive forms of bacteria and eukaryotes, which have been reported to produce melatonin for use as an antioxidant. In this review article, we have presented the data and information available in the scientific literature on melatonin, up to and including the year 2026, with the aim of providing a detailed description of both how this substance was produced by primitive organisms to neutralize free radicals and how melatonin developed and adapted its roles and functions in relation to evolutionary processes and the organisms in which it was present.

Keywords: *melatonin, circadian rhythm, sleep, ancient molecule, antioxidant*

INTRODUCTION

Melatonin (known by the abbreviations MEL and MT, and by the scientific names N-acetyl -5-methoxytryptamine and 5-methoxy-N-acetyltryptamine) is produced primarily by the pineal gland of vertebrates when the intensity of light reaching the surface of the eyeball is less than 10 lx, or up to 30 lx depending on the individual [1-4]. Produced in the pineal gland as the body's natural response to the perception of darkness, and widely present in nature in a wide variety of living organisms (vertebrates, invertebrates, plants, fungi, and microorganisms), melatonin is a key molecule that underlies the regulation of physiological, metabolic, and biological processes occurring in relation to circadian rhythms [4,5].

Melatonin is known to be a molecule that predates advanced eukaryotes; it has been determined that it was produced on Earth by primitive organisms more than 2.5 to 3.5 billion years ago [6-9]. Some specialized studies have reported that melatonin is also produced by photosensitive cyanobacteria and α-protobacteria, a finding that has laid the groundwork for a theory explaining how and when melatonin first appeared, as well as the evolution of this molecule's roles and functions in relation to the evolutionary processes of living organisms. Melatonin is naturally produced by most living organisms; it has the same chemical

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The manuscript was received: 10.02.2026
Accepted for publication: 07.04.2026

structure regardless of the source of synthesis, but differs primarily in the roles and functions it performs, so that the effects of this substance vary depending on the organism on which it acts [10-13].

The chemical structure of melatonin consists of an indole with an acetamide side chain ($-CH_2CONH_2$) and a methoxy group ($-OCH_3$) attached to the benzene ring [6].

Melatonin is produced by the pineal gland in vertebrates, also known as the epiphysis, as a result of the activity of pinealocytes (the main cells of the epiphysis) [14,15].

The pineal gland contains two main types of cells: pinealocytes, which account for approximately 95% of all pineal cells, and scattered glial cells, which make up the remaining approximately 5% and include astrocytic and phagocytic subtypes. Three types of pinealocytes have been identified in the pineal gland: type I cells, also known as light cells; type II cells, also known as dark cells; and type III cells [16].

The evolutionary conservation of melatonin across all biological kingdoms suggests that its primary biological role predates the emergence of complex multicellularity. At the same time, this observation supports the idea that melatonin's original function was fundamental to cellular survival, independent of the neuroendocrine systems that developed later in the course of the evolution of living organisms. In this context, the antioxidant function of melatonin is considered to be the molecule's ancestral role, acting both by directly neutralizing oxygen and nitrogen free radicals and by activating antioxidant enzyme systems [17].

The roles and functions of melatonin appear to represent a series of independent functional adaptations that reflect a progressive expansion of an ancestral molecular function, which has been conserved and reinterpreted in increasingly complex biological contexts [18].

Melatonin has been extensively studied since its discovery in plants in 1995 through 2026, both in the context of circadian regulation and the control of the physiological state of sleep, as well as for potential clinical applications [19,20]. However, the evolutionary trajectory of this molecule, from a primitive antioxidant to a pleiotropic signaling mediator, remains insufficiently integrated into a unified conceptual framework. Thus, the relationship between its ancestral function and its modern physiological roles has not yet been fully elucidated.

In the early stages of melatonin's biological evolution, this molecule primarily exerted its functions through receptor-independent mechanisms, particularly by directly neutralizing reactive oxygen species (ROS) and reactive nitrogen species (RNS). However, with the emergence of multicellular organisms and the increase in physiological complexity, melatonin evolved to serve the needs of the organisms that produced it. As a result, a specialized signaling system has evolved that is capable of coordinating integrated responses at both the tissue and systemic levels. In this evolutionary context, melatonin receptors emerged, primarily MT1 and MT2, which belong to the class of G protein-coupled receptors (GPCRs); these receptors are involved in metabolic signal transduction and in the synchronization of biological processes that depend on light-dark cycles [16-25].

In this review, we set out to examine the evolution of melatonin's functions, tracing its transition from its primary role as an antioxidant to its involvement in cellular signaling and circadian regulation, highlighting the evolutionary continuity and functional adaptations that have allowed this molecule to be conserved across all forms of life.

MATERIALS AND METHODS

This study was based on a systematic review of the relevant literature covering the period from 1917 to 2026.

The search for the scientific articles included in the bibliography of this review was conducted in the digital databases Web of Science, Google Scholar, PubMed, and Scopus, using the keywords listed in Table 1. Table 1 also includes the total number of scientific papers identified in digital databases based on the keywords used, as well as the final number of scientific papers included in the study after applying the inclusion and exclusion criteria.

Table 1. Number of scientific papers identified based on the keywords used

Keywords used	Number of scientific papers
Melatonin	53,725
The production of melatonin	347
The Origin of Melatonin	514
The Discovery of Melatonin	901
The roles of melatonin	12,331
Melatonin and its antioxidant role	1,576
Primitive antioxidant systems	54
The roles of melatonin in vertebrates	380
The roles of melatonin in invertebrates	30
The roles of melatonin in plants	1,601
The roles of melatonin in microorganisms	58
Melatonin and the circadian rhythm	10,947
Melatonin signaling pathways	3,227
The pleiotropic effects of melatonin	238
TOTAL	**85,929**
NUMBER OF SELECTED WORKS	**85**

The inclusion criteria for the identified scientific papers were as follows:

- ✓ Only studies that were thematically relevant and that described the biological roles of melatonin, as well as its evolutionary origin or phylogenetic distribution, were included;
- ✓ Only studies for which we had access to the full text and which were published in English were included;
- ✓ Studies presenting reproducible and well-documented experimental data were included.

The exclusion criteria for scientific works identified in digital databases were as follows:

- ✓ Duplicate entries were excluded;
- ✓ Studies containing information that was identical or at least similar to that in other selected scientific articles were excluded;
- ✓ Articles in which the experimental design was unclear or insufficiently described were excluded.

THE HISTORY OF MELATONIN RESEARCH AND STUDY

Historically, melatonin was discovered in 1958 by Lerner A.B. and his colleagues [26]. However, from an experimental perspective, the first evidence suggesting the existence of melatonin was reported as early as 1917, when McCord C.P. and Allen F.B. [27] documented a discovery stating that the bovine pineal gland contained one or more substances capable of depigmenting the skin of amphibians and affecting the reproductive system of young mammals. Subsequently, between 1958 and 1960, melatonin was identified, characterized, and described as a pineal hormone by Lerner A.B. and his colleagues [26,28,29]. Since the discovery of melatonin, studies and research conducted up to and including 2026 on this molecule have advanced, increasingly highlighting the complexity of this substance. Thus, based on various pieces of evidence and findings, it has been reported that the origin

of melatonin coincides with the period when life first emerged on Earth, leading to melatonin being referred to as the "ancient molecule". In light of this information, to facilitate an understanding of the evolutionary stages that melatonin has undergone, we have divided the periods of melatonin's evolution, research/study, and understanding into three distinct time intervals (the pre-discovery period, the post-discovery period 1, and the post-discovery period 2), starting from the point of origin of this field of scientific research, which is represented by the year of melatonin's discovery, namely 1958. Table 2 presents the most significant findings regarding melatonin from the three periods of development and research in this field.

Table 2. Evenimente marcante în cercetarea melatoninei

The year	Event Description	References
The pre-discovery era of melatonin		
1917	The first evidence has been reported regarding the presence of one or more molecules in the bovine pineal gland capable of depigmenting the skin of amphibians.	[27]
The post-discovery era 1 / The pineal melatonin era (1958-1995)		
1958-1960	The discovery, identification, isolation, and chemical characterization of melatonin.	[26,28,29]
1975	Melatonin is officially recognized as the darkness hormone following evidence of its role as a circadian modulator.	[30]
1977	The first trial of melatonin administration in human patients is conducted with the aim of inducing skin depigmentation.	[31]
1993	Melatonin's ability to neutralize reactive oxygen and nitrogen species has been confirmed.	[32]
Post-discovery period 2 / The era of universal melatonin (1995-under investigation)		
1995	Melatonin was discovered in plants.	[33-35]
1999	Melatonin was discovered in microorganisms.	[36]
2002	It has been suggested that this is associated with energy homeostasis and oxidative stress, and a protective role for mitochondria has been proposed.	[37]
2004	The concept of phytomelatonin is introduced in the literature.	[38]
2008	The first results are reported on the potential to increase melatonin concentrations in cow's milk by supplementing feed rations with protected L-tryptophan.	[39]
2010	The concept of melatonin as a multitasking molecule and its high biological safety profile have been confirmed.	[40]
2015	Melatonin is defined as an evolutionarily ancient molecule, and its origin as an ancient antioxidant is supported.	[41]
2021-2022	Antioxidant, immunomodulatory, and neuroprotective functions are integrated into a unified model.	[42]
2022	Melatonin is associated with the gut-brain axis and the body's immune function.	[43]
2024-2026	Melatonin is incorporated into systemic medicine and longevity medicine.	[44,45]

The pre-discovery period of melatonin refers to the time span between the emergence of melatonin on Earth and its discovery by Lerner A.B. and his colleagues [26]. The information and data on melatonin that fall within this time frame are characterized by the fact that they have been attributed to this period based on the evidence and genetic traces that melatonin has left over time-like fingerprints that prove and characterize the presence and evolution of this substance dating back to the time when life first emerged on Earth.

The post-discovery period 1, which we have also termed the pineal melatonin period, spans the years 1958 (the year melatonin was discovered in the pineal gland of cattle) and 1995 (the year melatonin was discovered in plants) [33-35]. Following the initial discovery of melatonin in the pineal gland of cattle [26], it was believed and reported for a fairly long period of time (approximately 37 years) that melatonin was a product exclusively of the pineal gland and that it was characteristic only of vertebrates, since only these organisms possess a pineal gland. Subsequently, following the discovery of melatonin in plants as well, the scope of research into this substance expanded considerably.

The Post-Discovery Period 2, which we have also termed the Universal Melatonin Period, began in 1995, when melatonin was discovered in plants, and continues to the present day (2026), as the scope of research into this substance has expanded following its discovery in plants. Thus, our understanding of melatonin has advanced considerably (from a simple substance initially believed to lighten the skin, we have come to discover that melatonin is the primary substance involved in regulating the circadian rhythm, in controlling the physiological state of sleep, while also serving as an antioxidant, anti-inflammatory, anticarcinogenic, anti-aging, and anti-apoptotic agent, etc.).

Melatonin is a molecule found in all living organisms that has been passed down from prokaryotes to eukaryotes, and thus to humans, through evolutionary processes [46].

THE ROLE OF MELATONIN AS A MULTIFUNCTIONAL MOLECULE

Melatonin is primarily classified as a hormone, strictly speaking in reference to melatonin of pineal origin; however, following the discovery of this substance in most life forms on Earth, and due to the multiple roles and functions exhibited by this bioactive compound in living organisms, melatonin has been given several names that classify it as a vitamin-like molecule [47,48], or a growth stimulator [49]. Pineal melatonin has been described by numerous researchers as the hormone responsible for regulating the circadian rhythm and controlling the physiological state of sleep; it serves as the biomarker that informs the vertebrate organism of the time of day as manifested in the natural environment and the season of the year, and is thus referred to as the "chemical expression of darkness" [50].

Melatonin is not officially classified as a vitamin because it can be synthesized endogenously from tryptophan in various tissues throughout the vertebrate body, and there is no specific clinical syndrome associated with a deficiency of this molecule that would be comparable to the classic definition of vitamins. However, the widespread distribution of melatonin in aerobic organisms, its presence in numerous food sources, and its pleiotropic antioxidant and cytoprotective properties have led to melatonin being considered a vitamin-like molecule, or conditionally essential. This perspective stems from melatonin's fundamental role in maintaining redox homeostasis, mitochondrial protection, and cellular adaptation to oxidative stress. At the same time, the gradual decline in melatonin production with advancing age supports the hypothesis that melatonin may play a role similar to that of a conditional vitamin in the context of aging and diseases associated with oxidative stress.

The synthesis of pineal melatonin occurs under the influence of physical and chemical factors. From a physiological standpoint, natural and/or artificial light that enters the surface of the eyeball follows a complex pathway that involves capturing environmental information and transmitting it to the hypothalamus and the pineal gland, where it is converted, depending on its location, from environmental information into biological information and subsequently

into electrical impulses. Once environmental information is perceived by the eyeball, it is converted by the retina into biological information so that it can be transmitted to the hypothalamus, and the hypothalamus converts the biological information into electrical impulses to transmit it to the pineal gland. From a chemical standpoint, in the pineal gland, tryptophan is converted into serotonin during the day or when artificial light is detected in the external environment, and serotonin is converted into melatonin at night or when darkness or the absence of light is detected in the external environment. Figure 1 schematically illustrates the pathway that information regarding the presence or absence of light takes from the external environment to the pineal gland.

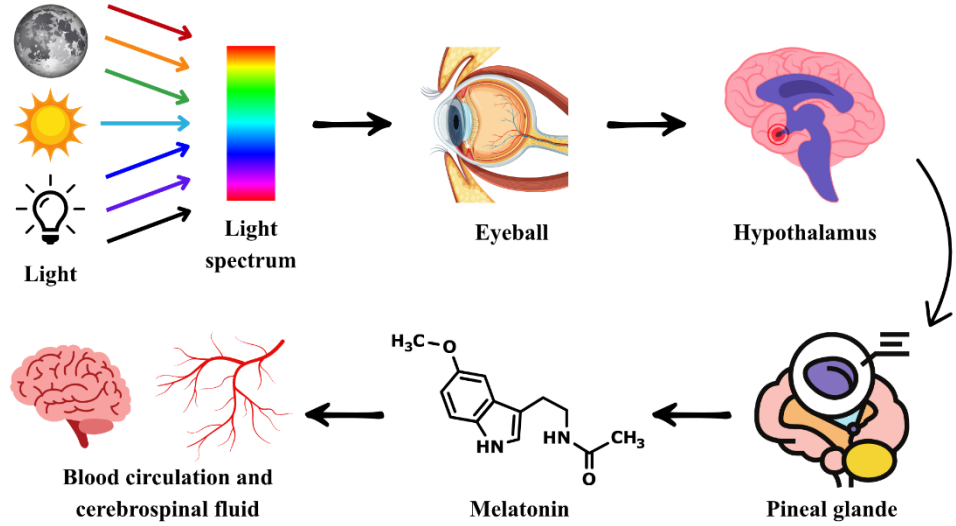

Figure 1 Schematic representation of the process of pineal melatonin synthesis, beginning with the perception of light from the external environment

Given the role that melatonin plays in stimulating plant growth and development, some researchers have studied the effects of fertilizing agricultural crops using melatonin as a growth stimulant [51-58].

Phytomelatonin is widely used as a source of exogenous melatonin for the human body, which can be obtained either through a diet that includes fruits and vegetables high in melatonin (cherries, walnuts, etc.) or through dietary supplements [53,54].

The presence of melatonin in a wide variety of medicinal and edible plants, as well as the broad spectrum of biological activities performed by this molecule, were the factors that led to the hypothesis that phytomelatonin has high nutraceutical potential. Due to its antioxidant, anti-inflammatory, mitochondrial protective, and cytoprotective properties, phytomelatonin, and, by extension, plants and foods rich in phytomelatonin, have been investigated as potential functional nutraceuticals with applications in supporting healthy aging, improving sleep quality, regulating metabolism, and even reducing oxidative stress [54].

OXIDATIVE STRESS AS A FACTOR IN THE EVOLUTIONARY CONSERVATION OF MELATONIN

Melatonin was originally produced by primitive forms of bacteria to serve as an antioxidant. Throughout the course of evolution, melatonin has been retained by

living organisms and passed on to the more advanced forms that have developed over time.

Understanding the evolutionary origin of melatonin requires an analysis of the physicochemical conditions characteristic of the early Earth, where the first forms of life evolved under intense oxidative stress. According to data available in the scientific literature, the primordial environment during the early stages of life's emergence on Earth was characterized by intense ultraviolet radiation, the absence of an ozone layer, and atmospheric chemistry conducive to the generation of ROS and RNS. In the absence of complex antioxidant mechanisms, primitive organisms were constantly exposed to the cytotoxic effects of free radicals, which compromised the integrity of proteins, lipid membranes, and the genetic material of primitive cells [6].

The emergence and development of oxygenic photosynthesis and the gradual increase in atmospheric oxygen concentrations were critical events in biological evolution. The Great Oxidation Event refers to the phenomenon of rising atmospheric oxygen concentrations, and although it enabled the development of aerobic metabolism and increased energy efficiency, it simultaneously led to an increase in cellular oxidative stress. Under these conditions, molecules capable of effectively neutralizing free radicals and thereby limiting cellular damage provided a significant adaptive advantage and were favored in the course of evolution.

Due to its amphiphilic properties, its ability to easily cross biological barriers, and its direct and indirect antioxidant activity, melatonin is considered to be one of the cytoprotective molecules that evolved early in the history of living organisms. The increase in oxidative metabolism associated with the emergence of mitochondrial endosymbiosis has led to a rise in the intracellular production of reactive oxygen species, highlighting the need to develop effective antioxidant mechanisms at the subcellular level. Thus, it is possible that melatonin's ancestral antioxidant properties served as the biochemical foundation upon which its multiple metabolic, immunological, and circadian functions subsequently developed.

The oxidative stresses characteristic of the primordial environment, which shaped the early stages of life's development on Earth, may have provided the evolutionary context that favored the preservation of melatonin as a multifunctional cytoprotective molecule, long before the emergence and development of its modern chronobiological and endocrine functions. At the same time, the functional pleiotropy of melatonin may reflect the progressive expansion of a fundamental ancestral function, namely the maintenance of redox balance at the cellular level.

MELATONIN: AN ANCIENT ANTIOXIDANT

From an evolutionary perspective, melatonin has been produced by living organisms for billions of years. The presence of melatonin in primitive forms of bacteria, such as photosynthetic cyanobacteria and α-protobacteria, provided the primary scientific evidence that led to the hypothesis that melatonin was first produced by living organisms as an antioxidant, after which the other known roles and functions of this substance, and the receptors through which it acts, evolved over time.

Zhao D. et al. [6] proposed the idea that both the presence of melatonin in most life forms on Earth and the ability of living organisms to produce melatonin are due to endosymbiotic evolutionary processes. According to the endosymbiosis theory, as described by Zhao D. et al. [6], during early evolution, bacteria were engulfed by primitive eukaryotes because of their nutritional value. However, the bacteria that were ingested by primitive eukaryotes subsequently adapted to their new

environment, developing and maintaining a symbiotic relationship with their host. Thus, α-protobacteria evolved into mitochondria, and cyanobacteria evolved into chloroplasts, with both forms of life retaining the ability to produce melatonin in order to reduce the oxidative damage caused by oxygen and nitrogen free radicals. In light of this theory, and given that mitochondria and chloroplasts are organelles that have survived evolution and are still present in living organisms, a hypothesis has been formulated suggesting that all living organisms that have ever lived on Earth but have since become extinct, as well as those that still exist, had/still have the ability to produce melatonin [6]. Figure 2 visually illustrates the process by which the ability to produce melatonin was transferred from primitive forms of bacteria to primitive forms of eukaryotes, in conjunction with the process of endosymbiotic evolution.

The presence of melatonin in both plants and animal-derived raw materials allows vertebrates (including humans) to obtain this molecule endogenously through their diet. Melatonin obtained through dietary intake contributes to a certain extent to the total amount of melatonin in the bloodstream; it has been reported to improve sleep quality and also play a role in other processes, such as combating oxidative stress and inflammation. Figure 3 schematically illustrates how the evolutionary processes of α-protobacteria and photosynthetic cyanobacteria are linked to the universal melatonin theory, as well as the nutritional component that enables the production of endogenous melatonin through dietary intake. Based on this information, the hypothesis/theory of universal melatonin was formulated, suggesting that melatonin is a molecule present in all forms of life, however, as of 2026, there have been no reports confirming that melatonin is produced by all known life forms, and furthermore, not all species of living organisms have been discovered globally. Thus, the universal melatonin hypothesis remains merely an extremely well-founded theory, with numerous arguments supporting the validity of the idea.

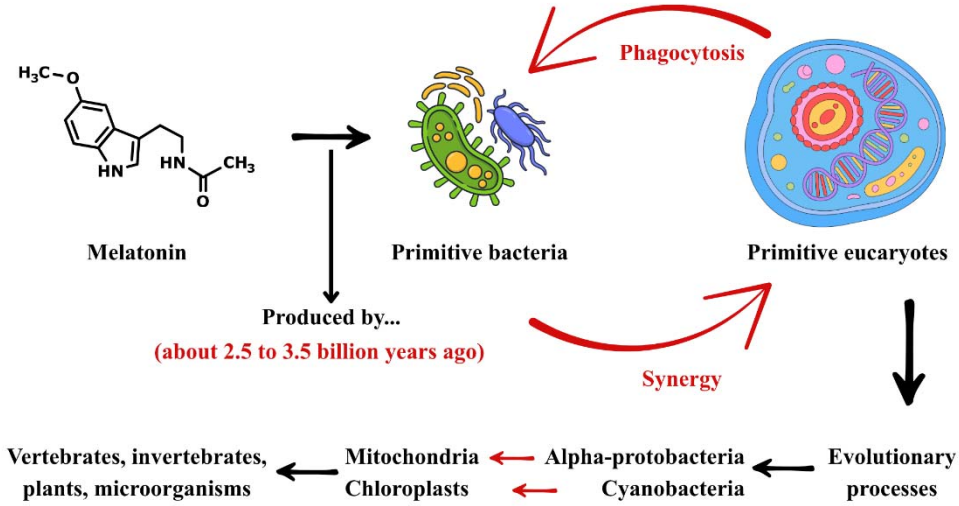

Figure 2 A visual representation of the process by which the ability to produce melatonin was transferred from primitive forms of bacteria to primitive forms of eukaryotes

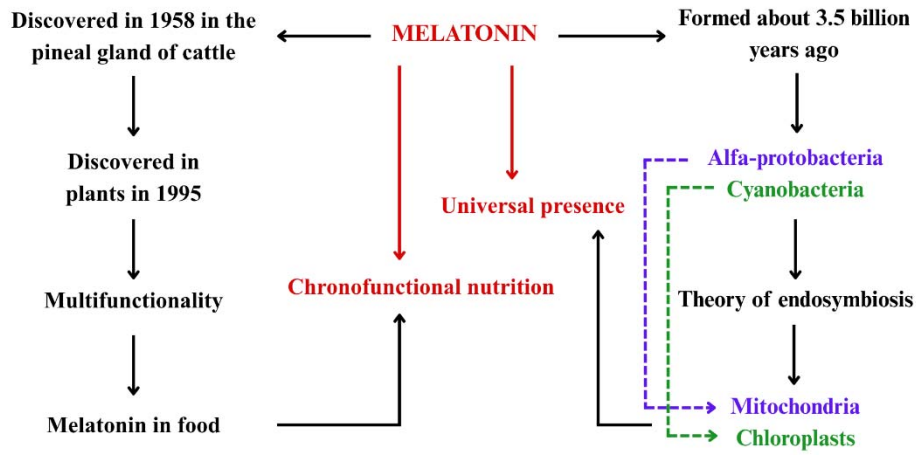

Figure 3 The conceptual evolution and endosymbiotic origin of melatonin

Melatonin is considered one of the most powerful antioxidants due to the numerous mechanisms through which it acts to neutralize ROS and RNS, as well as its ability to inhibit the production of free radicals. Based on the data and information available in the scientific literature through 2026, we have identified 14 antioxidant mechanisms through which melatonin acts; of these, 8 are universally present in every cell of the body, while 6 are context-dependent, being activated only under certain conditions and occurring only in specific organs, tissues, or cells. The 14 antioxidant mechanisms through which melatonin acts are shown schematically in Figure 4.

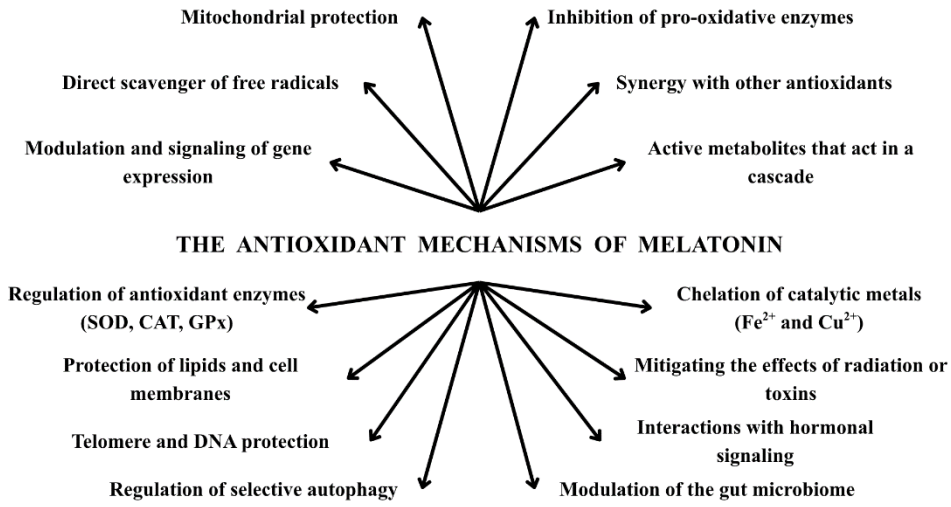

Figure 4 The mechanisms by which melatonin acts as an antioxidant

The antioxidant mechanisms of melatonin (shown in Figure 4) are divided into two categories based on their mode of action. The two categories are: universal antioxidant mechanisms, which are active in all cells of living organisms where melatonin is present, and specific antioxidant mechanisms, whose action is manifested under certain conditions and modulated by various factors.

The universal antioxidant mechanisms of melatonin are: direct scavenging of ROS and RNS; antioxidant cascade mediated by active metabolites; mitochondrial protection/reduction of mitochondrial ROS; upregulation of antioxidant enzymes; inhibition of pro-oxidative enzymes; protection of lipids and membranes (anti-lipid peroxidation); protection of telomeres and DNA; modulation of redox gene expression. These antioxidant mechanisms are universally present in any cell where melatonin is found.

Context-dependent antioxidant mechanisms of melatonin: regulation of autophagy and mitophagy; synergism with other antioxidants; chelation of catalytic metals (Fe^{2+}, Cu^{2+}); protection against radiation and toxins; interactions with hormonal signaling; modulation of the gut microbiome.

The primary mechanism by which melatonin acts as a powerful antioxidant is the direct neutralization of free radicals. Through its potent role as a scavenger of ROS and RNS, melatonin directly neutralizes singlet oxygen radicals ($^1O_2$), superoxide anions (O_2•-), hydroxyl radicals (•OH), hypochlorous acid (HOCl), hydrogen peroxide (H_2O_2), nitric oxide (NO), and peroxynitrite anions ($ONOO^-$) [59-61]. One mechanism that distinguishes melatonin from other antioxidants, such as vitamins E and D, is its ability to neutralize free radicals in a cascade reaction. Essentially, after donating a hydrogen atom to neutralize free radicals, melatonin is converted into another derivative that possesses the same ability to neutralize ROS and RNS. This process is also repeated with the other melatonin derivatives that are produced after the neutralization of free radicals. At the mitochondrial level, melatonin exerts a powerful antioxidant effect through several mechanisms that involve the direct neutralization of ROS and RNS, the stimulation of antioxidant enzymes, and the optimization of respiratory flux. Melatonin can be produced directly by mitochondria in certain cellular compartments, but it can also be transported from the rest of the body into the mitochondria due to its amphiphilic nature. Another mechanism by which melatonin protects mitochondria from oxidative damage involves the protection of lipids and proteins. Melatonin may protect membrane lipids from peroxidation and essential proteins from oxidation [59-62].

Melatonin also indirectly helps improve the antioxidant capacity of the body's cells by stimulating the activity of certain enzymes that act as antioxidants, such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). At the same time, melatonin has the ability to activate various signaling pathways that induce the expression of antioxidant genes, such as nuclear factor erythroid 2 (Nrf2) and sirtuin 3 (SIRT3) [62].

Beyond its direct role in neutralizing free radicals, melatonin enhances the body's defenses against oxidative damage through synergistic interactions with other endogenous antioxidants such as glutathione, vitamin E, and vitamin C, thereby stimulating the activity and expression of antioxidant enzymes via redox-sensitive signaling pathways, including FOXO (transcription factors of the Forkhead box O family), SIRT1 (sirtuin 1), and Nrf2 (nuclear factor erythroid 2-related factor 2) [62,63]. At the same time, melatonin reduces oxidative stress at its source by inhibiting the action of pro-oxidative enzymes, such as nicotinamide

adenine dinucleotide phosphate in its reduced form (NADPH oxidase) and the inducible form of nitric oxide synthase (iNOS), thereby limiting the excessive production of ROS and RNS [62].

At the genomic level, melatonin can protect the integrity of nuclear and mitochondrial DNA by reducing the formation of oxidative adducts and helping to stabilize telomeres, effects that are associated with delaying cellular senescence and maintaining genomic stability [64,65]. Totodată, melatonina reglează autofagia selectivă și mitofagia, facilitând astfel procesul de eliminare a mitocondriilor disfuncționale și a macroelementelor oxidate, contribuind la homeostazia redox intracelulară [66]. Numerous authors have demonstrated in specialized studies that melatonin has the ability to modulate the gut microbiota and the integrity of the intestinal barrier, thereby indirectly reducing systemic inflammation and oxidative stress associated with endotoxemia and dysbiosis [67]. The antioxidant properties of melatonin may be further enhanced by interactions with endocrine and circadian signaling pathways, particularly through the modulation of cortisol, insulin, and metabolic responses to stress [63].

Melatonin also exhibits chelating properties toward transition metals, such as iron and copper, thereby reducing the formation of free radicals that can be generated through the Fenton reaction [62]. Taken together, all these mechanisms through which melatonin acts as an antioxidant endow this molecule with the remarkable ability to mitigate oxidative damage induced by radiation, ischemia-reperfusion, xenobiotics, and other toxic agents, suggesting its role as a cytoprotective molecule and multifunctional regulator of redox homeostasis. Melatonin's antioxidant role, as its primary function in primitive organisms, served as the foundation upon which its other roles, which emerged later during endosymbiotic evolutionary processes, developed and adapted [62-67].

OTHER ROLES AND FUNCTIONS OF MELATONIN

Going beyond the common perception that limits melatonin's action solely to that of a hormone regulating sleep and the circadian rhythm, and moving beyond its role as a powerful antioxidant produced some 2.5 to 3.5 billion years ago, melatonin fulfills many other roles in living organisms, roles that vary depending on the organism in which it acts, the target tissue, and the control mechanism. Table 3 presents the most studied roles and functions of melatonin up to 2026, grouped according to the type of organism in which they are observed.

Melatonin is also found in invertebrates and fungi. In invertebrates, melatonin acts primarily as a chemical signal for the photoperiod, integrating light-dark information to regulate the organism's circadian rhythms and daily behavior. Melatonin levels rise at night and regulate locomotor activity, feeding, and reproduction, thereby synchronizing the body's physiology with the surrounding environment. At the same time, melatonin also plays a role in regulating development and metamorphosis in certain groups of invertebrates, such as insects, where it can influence ontogenetic transitions and the timing of growth cycles. Another role that melatonin plays in invertebrates is that of an antioxidant [73].

In fungi, melatonin is primarily involved in regulating the stress response and in metabolic adaptation to environmental variations, particularly light-dark cycles and temperature fluctuations. The effect of melatonin on fungi is associated with antioxidant defense and the modulation of mycelial growth, thereby influencing the rhythmicity of fungal development. Although it does not act as a

classic circadian hormone as in vertebrates, fungal melatonin functions more as a pleiotropic cell signaling molecule, integrating oxidative stress and environmental signals into the regulation of growth and survival [77].

Table 3. Rolurile și funcțiile melatoninei

Role/function	Description	References
Vertebrate		
Falling asleep	For vertebrates, melatonin serves as the primary signal that informs the body about the type of photoperiod in the environment, thereby signaling the need to initiate sleep in response to the absence of light. Melatonin produced by the pineal gland does not act as a sedative, but rather as a signaling molecule that prompts the body to create the conditions conducive to the onset and, consequently, the achievement of sleep (lowered body temperature and the induction of a state of calm).	[68]
Regulation of the circadian rhythm	The vertebrate body perceives seasonal changes in the environment through the increased production of melatonin during the cold season, which is a result of the longer period of darkness compared to the warm season.	[68]
Anti-inflammatory	Melatonin has the ability to exert an anti-inflammatory effect through several mechanisms of action, such as by reducing the levels of certain inflammatory mediators, such as IL-6 and IL-8, and by limiting the production of other mediators of the inflammatory response. Some examples of such mediators include prostanoids, leukotrienes, chemokines, adhesion molecules, and CRP.	[63,64]
Anti-aging	Melatonin may exert its anti-aging effects through several mechanisms of action, including protection against oxidative stress at the cerebral level (affecting neurons) and at the molecular level (affecting DNA), as well as by stimulating and improving sleep quality, which leads to a reduction in blood cortisol levels.	[69]
Anticancer	Melatonin can influence the development of cancerous tumors both directly and indirectly. Specifically, melatonin has the ability to inhibit the growth and proliferation of tumor cells, thereby preventing healthy cells from becoming neoplastic and promoting the process of cell renewal. Indirectly, melatonin may help reduce the risk of cancer onset and progression by neutralizing free radicals.	[70]
Anti-apoptotic	Melatonin has the ability to modulate the expression of proteins involved in apoptosis, thereby inhibiting the activity of pro-apoptotic proteins, such as Bax, and activating anti-apoptotic proteins, such as Bcl-2. At the same time, by acting as an antioxidant, melatonin provides cellular protection against oxidative stress throughout the body, which in turn enhances the anti-apoptotic effect of this substance.	[71]
Body temperature regulation	Once melatonin produced by the pineal gland is released into the bloodstream, it travels via the blood to the hypothalamus, which, upon detecting higher levels of melatonin in the body, sends specific signals throughout the body to lower body temperature and induce a state of relaxation designed to promote sleep.	[68]

Role/function	Description	References
Vertebrate		
Regulation of nervous system functions	Achieving a balance between the type of photoperiod and the physiological state of sleep leads to the synthesis of pineal melatonin only at the appropriate times of day, which maintains an optimal rhythm for cognitive activities and modulates the production of neurotransmitters such as γ-aminobutyric acid (GABA) and serotonin, which are involved in promoting a state of calm and well-being.	[72]
Regulation of immune system functions	Melatonin has the ability to act as a modulator of the immune system, inhibiting or stimulating the body's immune activity as needed, by stimulating the production of macrophages, NK cells, T cells, and B cells, and by inhibiting cytokine production.	[72]
Regulation of cardiovascular system functions	As the primary circadian regulator, melatonin indirectly helps maintain a stable heart rate, lower blood pressure, and protect blood vessels from oxidative stress.	[70]
Regulation of biological system functions	By regulating the circadian rhythm and the sleep-wake cycle, melatonin acts directly on the vertebrate organism as a modulator of the biological rhythm, due to its role as a signal indicating the time of day, an action that stimulates or slows down physiological, metabolic, and biological processes, which occur with varying intensity depending on the time of day.	[72,73]
Mediating reproductive changes	Melatonin has the ability to mediate seasonal behavioral changes in both seasonally breeding animals and those that do not breed seasonally. Melatonin's mechanisms of action on the reproductive system are primarily mediated by MT1 and MT2 receptors located in the peripheral tissues, testes, and ovaries, as well as by its antioxidant protective effects on sperm and eggs.	[71]
Plants		
Regulation of Growth and Development	Melatonin has the ability to stimulate or inhibit plant growth and development, depending on the amount of melatonin present in the plant and environmental conditions.	[57]
Antioxidant	By acting as a direct scavenger of ROS and RNS and by stimulating the activity of antioxidant enzymes such as SOD, CAT, and POD, melatonin plays a significant role in reducing oxidative stress and protecting proteins, lipids, and DNA.	[52,57,58]
Response to abiotic stress	Melatonin helps maintain redox homeostasis and regulate senescence genes, thereby increasing resistance to drought, salinity, and extreme temperatures.	[51,52]
Response to biotic stress	Melatonin helps boost resistance to pathogens by activating defense mechanisms and inducing the synthesis of antimicrobial compounds.	[51,52]
Regulation of gene expression	Melatonin acts as a signaling molecule that modulates the expression of genes involved in defense, stress, and metabolism, particularly through pathways dependent on cellular redox status.	[55]
Hormonal interactions	Melatonin has the ability to interact with other phytohormones, such as abscisic acid and auxins, as well as with various signaling molecules, such as nitric oxide, thereby influencing growth processes and stress responses through various integrated hormonal networks.	[58]

Role/function	Description	References
Vertebrate		
Delaying the onset of aging	By regulating senescence genes and through mechanisms that reduce oxidative damage, melatonin maintains the integrity of chlorophyll and the photosynthetic activity of the plant.	[74,75]
Root development	Melatonin has the ability to influence the architecture of the root system, particularly the formation of lateral roots, through interactions with auxins and by reducing redox stress. However, the effect depends on the concentration of melatonin and the plant species.	[57]
General cellular protection	Thanks to its powerful antioxidant properties, melatonin stabilizes cell membranes and protects organelles (particularly chloroplasts and mitochondria), thereby maintaining normal plant cell function.	[76]
Microorganisms		
Antioxidant role and cellular protection	Melatonina are capacitatea de a proteja microorganismele de stresul oxidativ prin neutralizarea ROS și RNS, prevenind deteriorarea AND-ului și a membranelor celulare.	[77]
Bacteriostatic or antimicrobial activity	Melatonina are capacitatea de a încetini sau chiar de a opri creșterea unor bacterii prin interferența cu procesele lor metabolice.	[78]
Biofilm inhibition	Melatonina poate reduce capacitatea microorganismelor de a forma biofilme, slăbind astfel aderența și structura comunităților microbiene rezistente.	[78]
Modulation of quorum sensing	Melatonina perturbă comunicarea dintre bacterii, afectând astfel coordonarea comportamentelor de grup, inclusiv exprimarea genelor de virulență.	[79]
Reduction of microbial virulence	Melatonina scade capacitatea microorganismelor de a produce factori care pot provoca boli, reducând astfel agresivitatea infecțiilor.	[80]
Modulation of microbial metabolism	Melatonina poate influența activitatea enzimatică și utilizarea energiei, ceea ce poate modifica atât rata de creștere, cât și rata de adaptare a microorganismelor.	[81]
Adaptive or protective role in producer microbes	Unele microorganisme produc melatonină cu scopul de a-și crește rezistența la stresul de mediu indus de oxidare sau de variații de temperatură.	[82]

Abbreviations used: IL-6 - Interleukin 6; IL-8 - Interleukin 8; CRP - C-reactive protein; DNA - Deoxyribonucleic acid; Bax - Bcl-2 X-associated protein; Bcl-2 - B-cell lymphoma protein 2; NK - Natural Killer Cells; ROS - Reactive Oxygen Species; RNS - Reactive Nitrogen Species; SOD - Superoxide Dismutase; CAT - Catalase; POD - Peroxidase.

Melatonin is considered to be one of the oldest bioactive molecules produced by living organisms, and it is conserved across different species.

The presence of melatonin in all kingdoms, including plants and animals, allows this molecule to be transferred and temporarily stored in various plant- and animal-based raw materials. Plant materials with a high melatonin content can be processed and converted into animal feed, helping to address current animal nutrition challenges (characteristic of the 21st century) [83,84]. At the same time, plant and animal raw materials with a high melatonin content can also be used to produce functional foods intended for human consumption that support consumers' health [85].

The origins of melatonin are initially associated with its protective function, which is attributed to its antioxidant capacity. Based on the data and information available in the scientific literature through 2026, it has been reported that the early emergence of melatonin as a protector against oxidative stress was the factor that enabled the molecule's preservation over time, with the observation that most of the roles and functions that melatonin performs in modern organisms are, in fact, extensions of its ancestral antioxidant role, which have developed in relation to a series of more complex biological processes.

The functions of melatonin have evolved and diversified significantly in tandem with the increasing complexity of multicellular organisms, thereby transcending its role as a classic scavenger and becoming integrated into fundamental cellular and systemic regulatory processes.

In microorganisms and plants, melatonin helps protect against oxidative, thermal, osmotic, and UV stress by modulating energy metabolism, stabilizing mitochondrial and chloroplast functions, and helping organisms adapt to adverse environmental conditions. In the plant kingdom, melatonin also acts as a growth regulator, influencing circadian rhythms, seed germination, photosynthesis, and responses to biotic and abiotic stressors.

In invertebrates, melatonin plays a role in regulating biological rhythms, the reproductive system, developmental processes, and neuroprotection, while also maintaining its antioxidant function.

In vertebrates, the development of the endocrine and nervous systems has allowed melatonin to be integrated into a complex physiological network, where this molecule acts both as a chronobiotic hormone synthesized primarily by the pineal gland and as a pleiotropic regulator of redox homeostasis, immunity, mitochondrial function, energy metabolism, inflammation, and cell survival.

CONCLUSIONS

Melatonin is one of the most conserved and versatile molecules found in the biological evolution of living organisms. The widespread distribution of this molecule, ranging from prokaryotes and photosynthetic organisms to higher vertebrates, supports the hypothesis of a very early evolutionary origin, initially linked to the need to protect primitive living organisms from oxidative damage caused by aerobic metabolism and changes in early atmospheric conditions.

The ability to directly neutralize oxygen and nitrogen free radicals, stabilize mitochondrial function, and protect essential cellular structures gave primitive organisms a major adaptive advantage. This function represents the ancestral role of melatonin, which has not been lost over the course of evolution but has been preserved and integrated into all subsequent levels of biological complexity.

With the emergence of multicellularity and complex physiological systems, melatonin has undergone a progressive expansion of its functions. The molecule has been incorporated into cellular and endocrine signaling mechanisms, playing a role in the synchronization of circadian rhythms, the regulation of energy metabolism, immune function, neuroprotective function, and seasonal reproductive function. The evolution of melatonin-specific receptors has allowed for the amplification and specialization of its biological effects, thereby contributing to the transformation of a primitive antioxidant molecule into a pleiotropic regulator of the body's homeostasis.

The new functions acquired and developed by melatonin have not replaced its ancestral functions, but have overlapped with them, and this phenomenon reflects a pattern of functional expansion without substitution.

The importance of melatonin in maintaining redox and energy homeostasis,

as well as its role in aging and stress adaptation, are factors that highlight the significance of this molecule from both an evolutionary and a biomedical and nutritional perspective. In this context, the study on melatonin not only provides insights into the evolution of biological regulatory mechanisms but also offers valuable perspectives for the development of therapeutic strategies targeting oxidative stress, mitochondrial dysfunction, and diseases associated with a lack of quality sleep, circadian rhythm disruption, and aging. Overall, the evolutionary history of melatonin illustrates how a simple molecule, which originated as a basic cellular defense mechanism, has gradually become a key indicator of complex biological functions, while retaining traces of its ancestral role.

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