



Age-Related Melatonin Decline: Interactions Among Mitochondrial Dysfunction, Pineal Aging, Circadian Disruption, and the Gut Microbiome

Roman Rozencwaig^{1*}, Felix Polyak²

1. Montreal General Hospital, Montreal, Quebec, Canada H3G 1A4

2. Department of Chemistry, Université de Montréal, Montreal, Quebec, Canada H2V 0B3

Abstract: This review article summarizes the roles of mitochondria, melatonin, circadian rhythms, and the microbiota/microbiome in aging and cellular senescence, both at the cellular level and in the whole organism. Mitochondria are central to cellular energy metabolism, intercellular signaling, and regulation of programmed cell death. Numerous age-related diseases have been linked to mitochondrial dysfunction [1]. Mitochondrial quality control (MQC)—the processes that maintain mitochondrial homeostasis—is therefore critical for health and for delaying age-related disorders. Melatonin, which is synthesized and metabolized within mitochondria, also reaches mitochondria via transport from the pineal gland in a circadian manner. Its actions on mitochondria are essential for the preservation of MQC, while additional anti-aging effects of melatonin extend beyond mitochondrial function. Because pineal melatonin production is under circadian regulation, circadian rhythms also directly influence mitochondrial quality control. In mammals, aging follows a parallel and interconnected sequence: (1) pineal gland aging, (2) decline in melatonin production, (3) circadian rhythm disruption, (4) mitochondrial dysfunction, and (5) age-related alterations in the microbiome. In this review, we highlight the interdependence of melatonin decline, circadian dysregulation, and mitochondrial dysfunction as key drivers of aging at cellular, subcellular, and organismal levels.

Keywords: Melatonin, mitochondrial quality control (MQC), circadian rhythms, mitochondrial biogenesis, autophagy, oxidative phosphorylation, mitochondrial fusion, inflammaging, microbiota, microbiome.

THE MECHANISMS THAT LEAD TO AGING PROCESSES

Aging, or senescence, occurs universally in all living beings. It manifests at multiple levels: chemical, biochemical, genetic, subcellular, cellular, tissue, organ, and ultimately the entire organism. Aging is characterized by a progressive decline in physiological functions, heightened oxidative stress, reduced ability to respond to stress, and an increased risk of age-associated disorders. Although many aging processes occur independently, they are also deeply interconnected. Changes at the cellular level drive aging of the organism, while systemic aging can in turn accelerate dysfunction at the subcellular and cellular levels. Aging of mitochondria, the nucleus, and other organelles contributes directly to the diseases of old age. These conditions increase morbidity and frailty, reduce longevity, and pose major challenges to health systems.

Medicine traditionally combats the diseases of aging—such as diabetes, cardiovascular disease, cancer, stroke, neurodegenerative and autoimmune disorders—to extend lifespan. Interestingly, many drugs used in these treatments, including metformin,

have demonstrated anti-aging effects at the cellular and subcellular levels. With advancing knowledge and new technologies, it may become possible not only to slow but also to prevent or even reverse aging processes at their root. Achieving this would help prevent age-related diseases, extend lifespan, and, more importantly, increase health span while reducing the unsustainable healthcare costs of rapidly aging populations.

Successful aging means maintaining normal physiological function without vulnerability to age-related diseases. According to the report of WHO “Ageing and health” (October 1, 2025), 1 in 6 people in the world will be aged 60 years or over. Within this group, cardiovascular and neurodegenerative diseases are projected to account for over 50% of deaths, alongside cancer, autoimmune and metabolic disorders such as diabetes, kidney disease, and the general frailty of old age.

The following are the main mechanisms of aging:

Cellular and Molecular Mechanisms of Aging

1. Free radical theory of aging.
2. Decreased autophagy (autophagy normally removes damage caused by free radicals).
3. Mitochondrial aging.
4. Telomere shortening.
5. Senescent cells and senolytics.
6. Epigenetic changes.
7. Stem cell aging (stem cells require circadian cycles for proper differentiation).
8. Decline in sirtuins.
9. Decline in NAD⁺.
10. mTOR overactivation with aging.
11. AMPK decline with aging.
12. Klotho deficiency.
13. Altered FOXO signaling.
14. Yamanaka factors.
15. Systemic and Organ-Level Mechanisms of Aging
16. Chronic inflammation (“inflammaging”).
17. Immunosenescence.
18. Effects of hypocaloric diet.
19. Cardiovascular aging.
20. Brain aging
21. Neuroendocrine and endocrine aging.
22. Cancer prevention and failure of surveillance.
23. Stress and aging.

24. Pineal gland aging and decline in melatonin.
25. Circadian rhythm disruption.
26. Sleep and aging.
27. Microbiota and aging.

Although these mechanisms may appear independent, most are closely related to mitochondrial dysfunction, pineal gland aging, reduced melatonin (both systemic and intracellular), disrupted circadian rhythmicity, and alterations in the microbiota and microbiome.

INTERCONNECTIONS OF AGING MECHANISMS

As Hardeland Rüdiger notes [2], classic theories of aging, such as the free radical theory and its mitochondria-centered versions, initially focused on only a few specific processes of senescence. However, research has since revealed extensive interconnections among age-dependent changes once thought to occur independently. For example, increased free radical damage is not only linked to mitochondrial dysfunction but also to inflammaging, which arises from immune remodeling and the release of proinflammatory cytokines by mitotically arrested, DNA-damaged cells that exhibit the senescence-associated secretory phenotype (SASP). SASP contributes to mutational damage in stem cells, thereby reducing their regenerative potential or, in the worst case, giving rise to cancer stem cells. Oxidative stress is also a driver of telomere attrition, while damage caused by free radicals is associated with impaired circadian rhythmicity.

Another important nexus connects cellular oscillators with metabolic sensing systems, particularly the aging-suppressor SIRT1, which acts as an accessory clock protein. Melatonin, as a highly pleiotropic regulatory molecule, interacts—directly or indirectly—with all these processes [3].

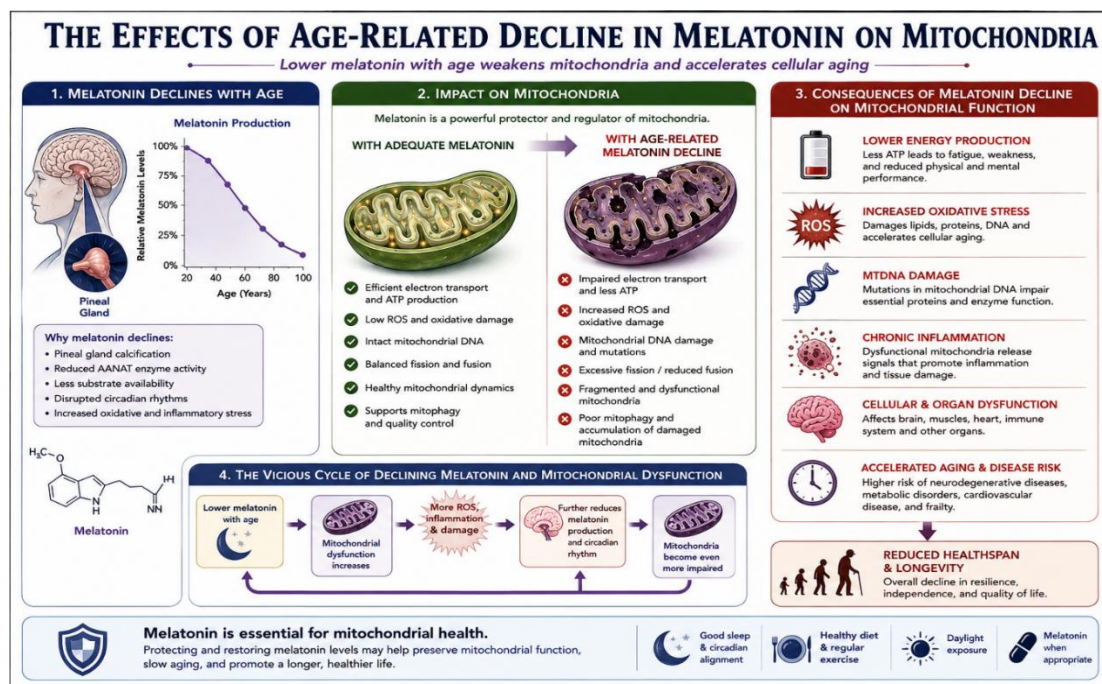
This review therefore focuses on the effects of mitochondria, melatonin, and circadian rhythmicity on aging, particularly in mammals and humans. Special attention is given to the role of melatonin in mitochondrial health and its contribution to healthy aging, as well as to the prevention of disorders associated with aging, including brain, neuroendocrine, and cardiovascular aging, cancer, and changes in the microbiota and microbiome.

THE PINEAL THEORY OF AGING

In the beginning of 90th Peter Klöden and Otto Rössler [4], and independently Russell J. Reiter [5,6], arrived at similar suggestion which outlines the fact that the production of melatonin by the pineal gland decreases with age, impacting physiological processes. They also explores the idea that the decline in the circadian melatonin rhythm, the role of melatonin as a free radical scavenger, and the potential neurobiological effects of this age-related attenuation, such as contributing to age-related degenerative disorders could be major contribution to “The Pineal Theory of Aging“. The Pineal Theory of Aging posits that aging is a direct consequence of the progressive decline in melatonin production, caused by exhaustion of the pineal gland and linked to Earth’s circadian rotation. This decline leads

to disorganization and desynchronization of the neuroendocrine and immune systems, resulting in maladaptation, age-related disease, and ultimately death [7].

At the present time, mitochondrial dysfunction is widely recognized as a central mechanism of aging. The close relationship between melatonin and mitochondrial health is very important as far as aging is concerned. Melatonin not only protects mitochondria but also influences other major aging mechanisms. Taken together, the decline in melatonin and mitochondrial dysfunction form a powerful “one-two” combination that drives aging at the cellular and organismal levels. In addition, circadian rhythm disruption and microbiota alterations further reinforce this interlinked system, with mitochondria and melatonin at its core [8].

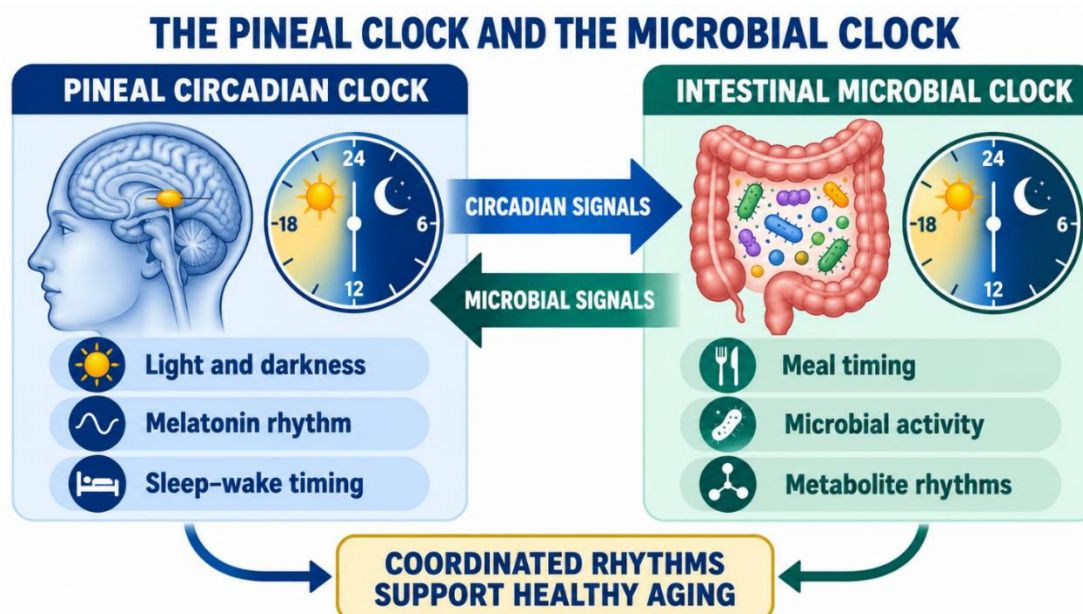


MELATONIN, MITOCHONDRIA, AND CIRCADIAN RHYTHMS

Mitochondria symbolize both the vitality of youth and the decline of old age. Melatonin can be synthesized and metabolized within mitochondria, but it can also be transported into them from circulation [9]. This dual source underscores melatonin’s critical role in mitochondrial homeostasis and mitochondrial quality control (MQC) [10].

Healthy sleep further enhances mitochondrial resilience by clearing harmful metabolic byproducts from neurons. Since every cell in the body operates on a circadian clock, synchronization is essential. Even bacteria possess circadian cycles, highlighting their universality in life. Melatonin, by regulating the sleep-wake cycle and circadian rhythms, ensures proper coordination across cells, tissues, and systems.

Research indicates a close relationship between circadian rhythms and mitochondrial function. Disruption of circadian rhythms can lead to reduced cellular energy production [11]. Melatonin, a key regulator of our biological clocks, plays a central role in maintaining circadian rhythmicity.[12]. Circadian rhythms revealed unraveling the genetic physiological behavioral tapestry of human biological clocks and rhythms [13].



In addition to pineal melatonin, which is synthesized at night and governs systemic circadian rhythms, melatonin is also produced in every cell of the body, particularly within mitochondria, where oxidative processes are abundant. Intracellular melatonin functions as a potent antioxidant, protecting organelles—such as mitochondria and DNA—from oxidative damage. Unlike pineal melatonin, this intracellular melatonin does not enter the circulation. However, circulating pineal melatonin coordinates with intracellular melatonin production, maintaining proper cellular function [14].

With aging, the decline in melatonin disrupts the circadian pacemaker, leading to internal desynchronization of the neuroendocrine system and contributing to poor health. This relationship is further supported by the presence of melatonin receptors in the suprachiasmatic nucleus (SCN). Armstrong and Redman (1991) suggested that melatonin might exert beneficial effects on aging due to its association with the circadian timing system [15]. Each evening, the rise in pineal melatonin synchronizes the central circadian pacemaker in the hypothalamic SCN with peripheral cellular clocks—a phenomenon known as the “chronobiotic effect” of melatonin.

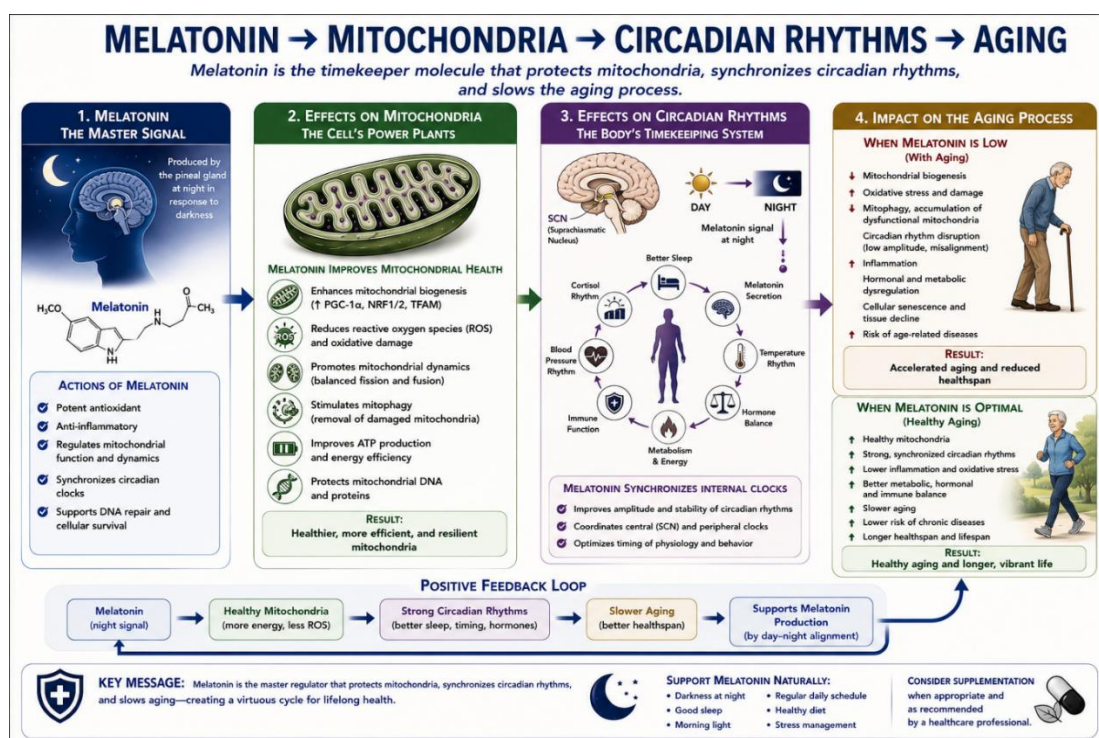
Circadian disruptions, including poor sleep and chronic inflammation, are integral to the aging process and contribute to metabolic disorders. The age-related decline in plasma melatonin plays a central role in endocrine changes associated with aging. Sleep disturbances further exacerbate these effects, inducing pathophysiological changes that accelerate aging in the central nervous system [16], also disrupted sleep impairs clearance of waste molecules from the brain, which can contribute to neurodegeneration [17].

Aging also promotes dysfunction of the pineal gland, a major source of melatonin, thereby affecting multiple physiological processes, particularly those governed by circadian rhythms. Administration of exogenous melatonin has been observed to prevent or mitigate pineal dysfunction associated with aging, suggesting a vicious cycle: melatonin synthesis decreases with age, and melatonin deficiency in turn accelerates aging [18].

The relationship between melatonin and aging is so robust that both pineal and extrapineal melatonin are now considered useful biomarkers of an organism’s aging rate. Melatonin levels can serve as predictors or indicators of numerous age-related diseases [19]

- 20]. For example, reduced melatonin levels in buccal cells, blood plasma, and other tissues correlate with increasing age, the development of Alzheimer's disease, and the severity of menopausal symptoms, among other aging-related conditions [21].

Beyond its chronobiotic role, melatonin exerts significant cytoprotective effects. It buffers free radicals, modulates pro-inflammatory cytokines, suppresses low-grade inflammation, and prevents insulin resistance. Melhuish Beaupre et al. (2021) reported a tenfold decrease in pineal melatonin production in octogenarians compared to teenagers, leading to reduced antioxidant, anti-inflammatory, and mitochondrial function [22]. This decline contributes to immunosenescence and inflammaging, which may be mitigated by nighttime pineal melatonin through resynchronization of immune cell mitochondrial activity [23, 24].

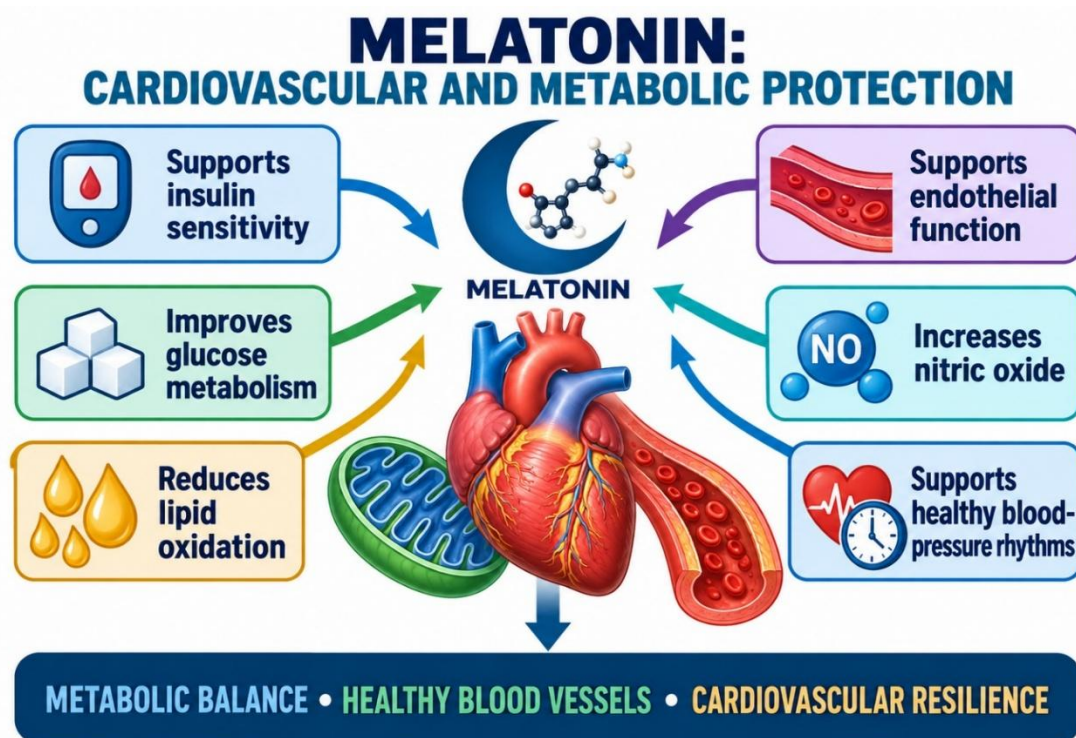


In this context, exogenous melatonin may act as a powerful antioxidant and anti-aging agent. It can restore mitochondrial membrane permeability and stimulate antioxidant enzymes, including glutathione peroxidase, superoxide dismutase, glutathione reductase, and catalase [25]. Melatonin also inhibits lipoxygenase and may enhance resistance to oxidative damage by repairing microsomal membranes (Sharafati-Chaleshtori et al., 2017) [26]. Furthermore, exogenous melatonin has been shown to increase the expression of suppressors of cytokine signaling, thereby enhancing immune response and contributing to anti-aging effects (Vinod and Jagota, 2017) [27]. Consequently, Karadas et al, 2019, proposed that melatonin could be a molecule capable of extending lifespan by promoting healthy aging [28].

The age-related decline in melatonin is associated with neuronal dysfunctions affecting cognition, memory, neurogenesis, and neurorestorative mechanisms, contributing to the development of neurodegenerative diseases such as Parkinson's and Alzheimer's. Melatonin deficiency in older adults has also been linked to cardiovascular disorders, including myocardial infarction, cardiac hypertrophy, vascular dysfunction, arrhythmias, atherosclerosis, vascular calcification, and stroke (Ozkalayci et al., 2021) [21].

Exogenous melatonin is considered a multitasking molecule, capable of mitigating several aging-related processes, including circadian rhythm dysregulation, metabolic alterations, inflammation, oxidative stress, and mitochondrial dysfunction. Its anti-inflammatory and antioxidant effects, particularly at the mitochondrial level, provide protection against inflammaging, thereby preventing or mitigating multiple cardiovascular and neurodegenerative diseases (Cardinali and Hardeland, 2017) [29].

The protective functions of melatonin for mitochondria are evolutionarily conserved across diverse organisms, including bacteria, plants, and animals, highlighting its fundamental role in maintaining mitochondrial health and function. According to the mitochondrial free radical theory of aging, the rate of mitochondrial ROS (mitROS) production is a central feature of the aging process (Barja, 2019) [30]. These ROS can act as second messengers, coordinating multiple molecular pathways within cells.



Mitochondrial quality control depends on a tightly coordinated network involving mitochondrial biogenesis, dynamics, and mitophagy. Key regulators include mTOR, PGC-1 α , sirtuins, nuclear respiratory factor 1 (NRF1), AMPK, mitochondrial transcription factor A (TFAM), and the PINK1/PARKIN pathway (Gureev et al., 2019) [31]. Melatonin, by supporting these processes, plays a crucial role in preserving mitochondrial integrity and function during aging.

INFLAMMATION, ROS, AND THE GUT MICROBIOME IN AGING

Reactive oxygen species (ROS) are key effectors of inflammation. Persistent and excessive ROS production by immune cells causes direct cellular damage and recruits additional inflammatory cells to affected sites, further amplifying oxidative and inflammatory stress [32]. Multiple pathways link oxidative stress and inflammation, and chronic low-grade systemic inflammation—often referred to as inflammaging—is believed to underlie many

age-associated diseases, including atherosclerosis, cardiovascular and neurodegenerative disorders, cognitive decline, physical frailty, cancers, chronic obstructive pulmonary disease (COPD), arthritis, and diabetes. (Luigi Ferrucci et al., 2018) [33]

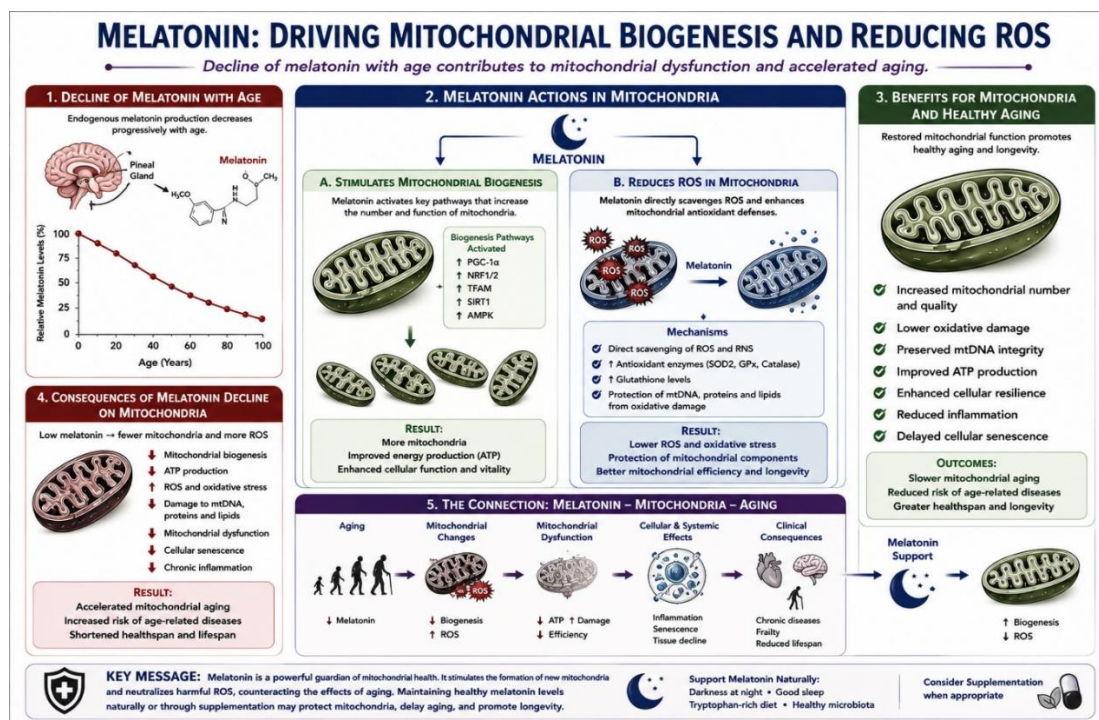
Sources of inflammaging include accumulated cellular damage, senescent cells, stress, insufficient clearance of senescent cells and macromolecules, immunosenescence, harmful products produced by the gut microbiome, chronic infections, and autoimmune conditions. Among these, gut microbiome-derived products play a particularly significant role, as the gut is intimately linked to many aging-associated conditions, including neurodegenerative [34, 35] and cardiovascular diseases [36].

The gut and its microbiota produce substantial amounts of melatonin, both locally and influenced by circadian rhythms of circulatory melatonin. In the gastrointestinal tract, melatonin originates from the pineal gland, the gut itself, and melatonin-containing foods (e.g., eggs, milk, berries, tart cherries, oats, nuts, and seeds). Recent studies suggest that melatonin can modulate the gut microbiome [37] (Kim et al., 2020). Notably, melatonin concentrations in the gut are approximately 400-fold higher than circulating pineal melatonin [38] (Bubenik et al.), highlighting distinct melatonin pools. Pinealectomy does not significantly alter gut melatonin levels (Chen et al., 2011; Cryan et al., 2019) [39,40], and gut-derived melatonin does not enter systemic circulation.

There appears to be coordination between the microbial clock and the pineal circadian clock. The composition of the gut microbiota is influenced by host circadian rhythms, and in turn, gut microbes help regulate the host's circadian pathways. Because of this reciprocal relationship—and given the links between circadian disruption and metabolic, inflammatory, and stress-related diseases—there is growing interest in circadian regulation of the host-microbiome-immune axis (Segers et al., 2021) [41].

One intriguing possibility is that gut-derived melatonin acts as a zeitgeber for the microbiome, providing a mechanism for the host to influence microbial rhythmicity. Many beneficial effects of the gut microbiome are mediated through the production of short-chain fatty acids such as butyrate, which optimize mitochondrial function. This effect appears to require upregulation of the melatonergic pathway [42, 43], and butyrate itself can enhance intestinal melatonin synthesis [44], linking gut microbiome health directly to melatonin regulation.

The human gut hosts approximately 10^{14} microbes belonging to 400-500 species [45] (Moore and Holdeman, 1974), with seven major prevalent microbial phyla in the colon [46] (Santorù et al., 2017). It was reported that host circadian rhythms influence the microbiota composition, and the microbiota, in turn, regulate circadian pathways [47], highlighting the intertwined roles of melatonin, circadian biology, and microbiome function in aging-related physiology [48].



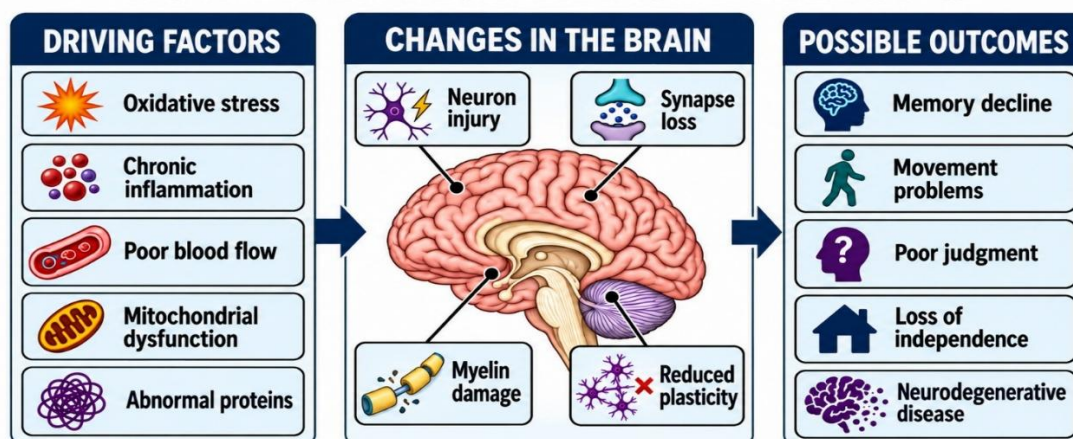
CIRCADIAN RHYTHMS, MICROBIOTA, AND HEALTH

Several studies have examined how interactions among circadian rhythms, the microbiota, and the brain influence disease risk and severity. A comprehensive review of melatonin's effects on the microbiome, circadian rhythms, immunity, and aging was provided in 2022 [49].

Melatonin promotes a healthy diversity of gut microbiota. Disruption of circadian rhythms can disturb the microbiota, favoring the growth of disadvantageous bacteria at the expense of beneficial species such as *Lactobacillus* and *Bifidobacteria*. Jordan Cryan et al (2020) have proposed that gut bacteria and circadian rhythms act together to influence overall health and disease susceptibility [50]. These effects of melatonin serve as biomarkers of healthspan in both animal models and humans.

Human gut microbiota diversity is closely correlated with aging. A relatively stable microbiome is established by approximately age four, and it subsequently adapts over the lifespan in response to diet, health status, genetics, and other environmental factors, following a microbiome aging clock (Galkin et al., 2019) [51].

HOW BRAIN DEGENERATION DEVELOPS



MITOCHONDRIAL AGING

Mitochondria play a central role in the aging process. Age-related mitochondrial changes include dysfunction of the respiratory chain, increased formation of reactive oxygen species (ROS), and damage to mitochondrial proteins, lipids, and DNA. ROS levels and oxidative damage to macromolecules increase with age. Mitochondrial defects have been particularly observed in high-energy-demand tissues such as skeletal muscle and the brain, which rely heavily on oxidative phosphorylation [52]. Although aging arises from multiple mechanisms, mitochondrial aging follows its own age-related trajectory, exhibiting a distinct curve of functional decline over time [53].

MITOCHONDRIAL DYSFUNCTION, AGING, AND MELATONIN

Mitochondrial dysfunction plays a central role in aging and nearly all age-related diseases, as mitochondria serve as the powerhouse of our cells [54, 55]. Over time, both the number and function of mitochondria, as well as mitochondrial DNA integrity, decline. This loss contributes significantly to aging, reduces lifespan, and increases vulnerability to diseases such as coronary artery disease, neurodegeneration, cancer, diabetes, obesity, and others.

Chronic illnesses further deplete mitochondrial number and quality, creating a vicious cycle that accelerates systemic aging. When mitochondrial damage reaches approximately 25-30%, major illnesses can occur, and by age 75, a person typically loses about 50% of their healthy mitochondria. Strategies aimed at rejuvenating mitochondrial function or improving mitochondrial quality may therefore be effective interventions against aging [56]. Mitochondrial metabolism, ROS generation, and cellular senescence are tightly linked. Aging is generally associated with decreased mitochondrial enzyme activity, reduced respiratory capacity, increased ROS production, and impaired mitochondrial function. Notably, younger stem cells contain more functional mitochondria than older stem cells, highlighting the role of mitochondrial integrity in cellular renewal [57].

Melatonin, as an amphiphilic molecule, can cross cell membranes directly and can also be transported into cells via membrane receptor-mediated mechanisms. Within the cell, melatonin acts as a potent antioxidant and regulator of autophagy. It promotes mitochondrial fusion, maintains a healthy mitochondrial network, regulates mitochondrial

dynamics, and supports mitochondrial homeostasis and biogenesis, protecting against mitochondrial dysfunction. Melatonin additionally chelates metal ions [58], prevents electron leakage from the electron transport chain, and collaborates post-translationally with SIRT3 to regulate mitochondrial ROS generation and removal. It neutralizes ROS, upregulates antioxidant enzymes, and downregulates pro-oxidant enzymes [59], further reinforcing mitochondrial health and contributing to healthy aging.

MELATONIN AND MITOCHONDRIAL PROTECTION

Melatonin enhances mitochondrial dynamics and promotes the intercellular transfer of mitochondria via tunneling nanotubes (TNTs) following oxygen-glucose deprivation and reoxygenation (OGD/R). This mitochondrial transfer through TNTs may represent a novel mechanism by which melatonin mediates cell survival [60]. However, recent cancer research suggests that in certain metastatic cancers, mitochondrial byproducts and TNTs may be detrimental, indicating that in these cases, strategies to improve mitochondrial function—including melatonin supplementation—should be approached with caution [61].

Melatonin also protects mitochondrial membranes from oxidative damage and regulates mitochondrial permeability, maintaining membrane integrity, preventing the release of pro-apoptotic proteins, and protecting against cell death [62]. Additionally, melatonin influences mitochondrial biogenesis by modulating metabolism and the redox state. Studies indicate that melatonin can regulate mitochondrial acetyl-CoA levels, thereby adjusting mitochondrial metabolism [1, 6].

In 2017, studies demonstrated that melatonin supplementation dramatically reduced mitochondrial damage associated with aging. Melatonin boosts the levels of CNPase, an enzyme critical for mitochondrial protection. Animal studies showed that CNPase declines by 34% with age, resulting in up to 69% loss of mitochondrial function. These findings suggest that melatonin supplementation supports normal tissue and organ function, enhances disease resistance, and slows aging [64].

Given that melatonin levels decline with age, this reduction contributes to diminished mitochondrial function and the development of age-related diseases. Melatonin supports several mechanisms critical for mitochondrial health, including the maintenance of cardiolipin, a phospholipid of the inner mitochondrial membrane essential for bioenergetics, apoptosis regulation, membrane stability, and dynamics. Cardiolipin alterations are associated with mitochondrial bioenergetic decline in multiple tissues under various pathological conditions, including aging. By preventing cardiolipin oxidation, melatonin serves as a major protector of mitochondrial bioenergetic function and overall cellular health [65].

MELATONIN, MITOCHONDRIAL METABOLISM, AND AUTOPHAGY

Melatonin can be taken up from the circulation into mitochondria or synthesized within the mitochondria themselves. Recent evidence indicates that mitochondrial membranes possess specific transporters that facilitate the rapid uptake of melatonin against a concentration gradient. High mitochondrial melatonin content is critical, as mitochondria are major sources of free radicals. By scavenging these radicals, melatonin reduces oxidative damage,

supporting the free radical theory of aging and potentially protecting against age-related organismal decline and multiple free radical-associated diseases [66].

Melatonin regulates mitochondrial metabolism and the cellular redox state by modulating acetyl-CoA concentration, electron transport chain (ETC) activity, oxidative phosphorylation (OXPHOS), ROS generation, and antioxidant enzyme expression. It enhances ETC and OXPHOS activity, promoting adenosine triphosphate (ATP) synthesis in rat brain and liver mitochondria [67 - 69]. Some studies also show that melatonin can shift cellular energy metabolism from cytosolic glycolysis to mitochondrial OXPHOS in cancer cells [70].

Melatonin exhibits potent antioxidant properties, directly scavenging ROS such as superoxide anions, hydroxyl radicals, and hydrogen peroxide through cascade reactions [71-73]. It also upregulates antioxidant enzymes, including superoxide dismutase (MnSOD), glutathione peroxidase (GSH-Px), and catalase (CAT), to prevent cellular stress and injury [74].

Autophagy plays a central role in maintaining cellular oxidative balance, particularly in mitochondria, which are major ROS-generating organelles. Melatonin can modulate autophagy via its effects on mitochondria and oxidative stress [75 - 77]. Notably, melatonin has a dual role in regulating autophagy: under conditions of insufficient autophagy, it enhances autophagic processes to remove excess ROS and damaged mitochondria; conversely, under conditions of excessive autophagy, it can downregulate autophagy to prevent cell death. Recent studies demonstrate that mitochondrial biogenesis, dynamics, and autophagy are tightly regulated by melatonin, highlighting its central role in maintaining mitochondrial integrity and cellular homeostasis [9, 77, 78].

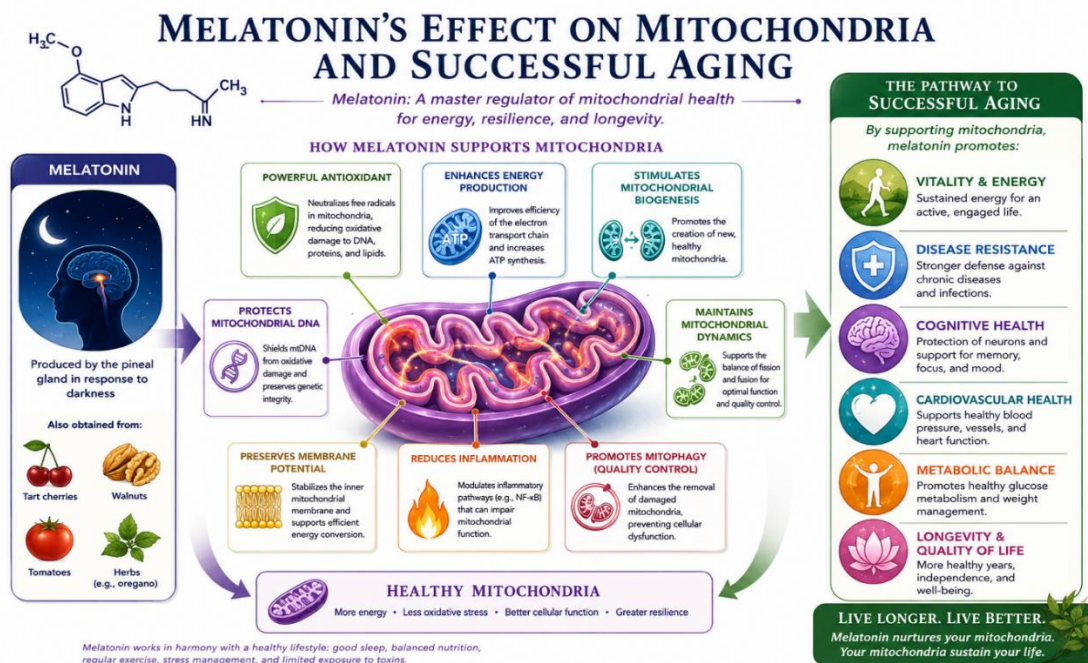
MITOCHONDRIAL QUALITY CONTROL AND MELATONIN

Mitochondria are highly dynamic organelles, and their quality is maintained through complex, interacting processes including mitochondrial biogenesis, dynamics, and mitophagy. Collectively, these regulatory mechanisms are referred to as mitochondrial quality control (MQC). Dysregulation of MQC is associated with various diseases, including aging-related disorders, and understanding the molecular mechanisms underlying MQC dysfunction may offer new therapeutic opportunities. Melatonin appears to be a major regulator of MQC [1,9].

Mitochondrial biogenesis is strongly associated with the circadian rhythm of melatonin in pinealocytes. Beyond pinealocytes, melatonin has been reported to regulate mitochondrial fission and fusion in other cell types. The fission/fusion machinery is critical for maintaining mitochondrial health: fission helps eliminate damaged or non-repairable mitochondria, whereas fusion promotes the generation and maintenance of young, functional mitochondria. Fission is often associated with cellular injury and apoptosis, while fusion is linked to healthy cell function [9].

Aging is generally accompanied by a decline in mitochondrial enzyme activity, reduced respiratory capacity, increased ROS production, and diminished overall mitochondrial function. Interestingly, when stem cells divide, younger stem cells contain a higher proportion of functional mitochondria compared to older stem cells [57, 75].

A strong link exists between mitochondrial metabolism, ROS generation, and cellular senescence. Mitochondria and the nucleus engage in bidirectional signaling - nuclear stresses such as DNA damage trigger mitochondrial responses, and mitochondrial stress can elicit nuclear DNA responses. Aging is also accompanied by low-grade, chronic inflammation, known as inflammaging, which can be traced back to the bacterial origins of mitochondria. From an epigenetic perspective, nuclear DNA undergoes significant methylation, whereas mitochondrial DNA (mtDNA) is less methylated; however, methylation patterns in mtDNA may serve as biomarkers for conditions and diseases related to mitochondrial function [79 - 81].



MELATONIN, LONGEVITY, AND ANTI-CANCER PROPERTIES

Melatonin increases longevity-associated proteins, including SIRT1 and SIRT3, and plays a critical role in regulating mitochondrial biogenesis via activation of Sirtuins and PGC-1 α [68, 82, 83]. Beyond its effects on mitochondria, melatonin has significant anti-tumor properties, influencing cancer initiation, promotion, and progression. It modulates gene expression and growth suppression in cancer cells, while also enhancing the immune response by activating T helper cells, which coordinate other immune cells to combat pathogens. Emerging research indicates that melatonin can both prevent cancer onset and induce cancer cell death once malignancy occurs. These anti-carcinogenic effects are attributed to its antioxidant, anti-inflammatory, antiproliferative, and hormone-modulating properties.

Melatonin further contributes to cancer prevention by regulating cellular metabolism. It functions as a glycolytic regulator, inhibiting the Warburg effect, thereby promoting pyruvate entry into mitochondria for normal glucose oxidation. This restores mitochondrial homeostasis and may help inhibit tumor growth. These mechanisms underscore melatonin's potential to support health span, prevent acute and chronic diseases, and improve longevity in cancer patients [68, 70, 84].

CONCLUSION

This review summarizes the effects of melatonin, circadian rhythms, and mitochondria on aging processes, while also highlighting the role of the microbiome and microbiota, which interact with melatonin, circadian rhythms, and mitochondrial function. Aging is a universal process affecting all living organisms. Although multiple mechanisms contribute to senescence, this review emphasizes four primary drivers of aging:

1. Mitochondrial dysfunction
2. Decline of melatonin and pineal gland aging, leading to reduced nocturnal melatonin production
3. Dysregulation of circadian rhythms
4. Age-related changes in the microbiome and microbiota

These four mechanisms encompass most other known pro-aging processes. By targeting them, it may be possible to delay, postpone, or even reverse aspects of aging, thereby preventing or mitigating age-related diseases—the major causes of morbidity and mortality in modern societies. Such interventions could also substantially reduce healthcare costs as populations age. This review highlights that exogenous melatonin can improve mitochondrial health, restore circadian rhythms, enhance pineal function, and positively influence the microbiome and microbiota.

Melatonin has also shown utility in managing acute and long COVID, exhibits antiviral properties, which can be used against future viral pandemics that may come to our world. Also, melatonin may mitigate radiation-induced damage during nuclear emergencies. Despite these benefits, melatonin is not yet widely utilized by medical professionals for prevention or treatment of age-related disorders. Finally, this review proposes the development of novel biomarkers of aging, including melatonin levels, circadian rhythm patterns, mitochondrial biogenesis markers, and microbiome health indicators. These biomarkers, alongside continued clinical application and research, may help optimize healthy aging strategies.

Acknowledgement: Not applicable.

Funding Statement: This work was supported by authors.

Author Contributions: The authors confirm contribution to the paper as follows:

RR - conceptualization, writing - original draft preparation, FP - writing - review and editing.

All authors reviewed the results and approved the final version of the manuscript.

Availability of Data and Materials: Not applicable.

Ethics Approval: Not applicable.

Conflicts of Interest: The authors declare no conflicts of interest to report regarding the present study.

REFERENCES

1. Lei X., Xu Z., Huang, L., et al. The potential influence of melatonin on mitochondrial quality control: a review. *Front Pharmacol.* 2024;14:1332567. doi:10.3389/fphar.2024.1332567.
2. Hardeland R. Melatonin and the theories of aging: a critical appraisal of melatonin's role in antiaging mechanisms. *J Pineal Res.* 2013;55(4):325-356. doi:10.1111/jpi.12090.
3. Hardeland R. Redox biology of melatonin: discriminating between circadian and noncircadian functions. *Antioxid Redox Signal.* 2022;37(10-12):704-725. doi:10.1089/ars.2021.0275.
4. Kloeden PE, Rössler R, Rössler OE. Timekeeping in genetically programmed aging. *Exp Gerontol.* 1993;28(2):109-118. doi:10.1016/0531-5565(93)9001-t.
5. Reiter RJ. Pineal function during aging: attenuation of the melatonin rhythm and its neurobiological consequences. *Acta Neurobiol Exp (Wars).* 1994;54(Suppl):31-39.
6. Reiter RJ. The pineal gland and melatonin in relation to aging: a summary of the theories and of the data. *Exp Gerontol.* 1995;30(3-4):199-212. doi: 10.1016/0531-5565(94)00045-5.
7. Karasek M. Melatonin, human aging, and age-related diseases. *Exp Gerontol.* 2004;39(11-12):1723-1729. doi:10.1016/j.exger.2004.04.012.
8. Bartman S, Coppotelli G, Ross JM. Mitochondrial dysfunction: a key player in brain aging and diseases. *Curr Issues Mol Biol.* 2024;46(3):1987-2026. doi: 10.3390/cimb46030130.
9. Tan DX, Manchester LC, Quin L, Reiter RJ. Melatonin: a mitochondrial targeting molecule involving mitochondrial protection and dynamics. *Int J Mol Sci.* 2016;17(12):2124. doi:10.3390/ijms17122124.
10. Reiter RJ, Sharma R, Rosales-Corral S, et al. Melatonin: a mitochondrial resident with a diverse skill set. *Life Sci.* 2022;301:120612. doi:10.1080/19768354.2024.2347503
11. Kim J, Sun W. Circadian coordination: understanding interplay between circadian clock and mitochondria. *Anim Cells Syst.* 2024;28(1):228-236. doi:10.1080/19768354.2024. 2347530.
12. Begemann K, Rawashdeh O, Olejniczak I, et al. Endocrine regulation of circadian rhythms. *NPJ Biol Timing Sleep.* 2025;2(10). doi:10.1038/s44323-025-00024-6.
13. Morin R, Forest G, Imbeault P. Circadian rhythms revealed: unraveling the genetic, physiological, and behavioral tapestry of the human biological clock and rhythms. *Front Sleep.* 2025;4:1544945. doi:10.3389/frsle.2025.1544945
14. Arendt J, Aulinas A. Physiology of the pineal gland and melatonin. In: Feingold KR, Anawalt B, Boyce A, et al., editors. *Endotext.* South Dartmouth (MA): MDText.com, Inc.; 2022.
15. Armstrong SM, Redman JR. Melatonin: a chronobiotic with anti-aging properties? *Med Hypotheses.* 1991;34(4):300-309. doi:10.1016/0306-9877(91)90046-2.
16. Carroll JE, Prather AA. Sleep and biological aging: a short review. *Curr Opin Endocr Metab Res.* 2021;16:159-164. doi:10.1016/j.coemr.2021.03.021
17. Wafford KA. Aberrant waste disposal in neurodegeneration: why improved sleep could be the solution. *Cerebral Circ Cogn Behav.* 2021;2:100025. doi:10.1016/j.cccb.2021.100025
18. Hardeland R. Aging, melatonin, and the pro- and anti-inflammatory networks. *Int J Mol Sci.* 2019;20:1223. doi:10.3390/ijms20051223.
19. Konovalov SS, Polyakova VO, Drobintseva AO, et al. Melatonin: the possibility to analyze the marker of age-related pathology in the buccal epithelium and urine. *Klin Med (Mosk).* 2017;95:136-139.

20. Zuev VA, Trifonov VI, Linkova NS, et al. Melatonin as a molecular marker of age-related pathologies. *Adv Gerontol.* 2017;30:62-69.
21. Ozkalayci F, Kocabas U, Altun B. et al. Relationship between melatonin and cardiovascular disease. *Cureus.* 2021;13:e12935. doi:10.7759/cureus.12935.
22. Melhuish Beaupre L, Brown GM, Kennedy JL, Lam RW, McIntyre RS, Schaffer A, et al. Melatonin's neuroprotective role in mitochondria and its potential as a biomarker in aging, cognition, and psychiatric disorders. *Transl Psychiatry.* 2021;11:339. doi:10.1038/s41398-021-01464-x.
23. Anderson G., Maes M. Gut dysbiosis dysregulates central and systemic homeostasis via decreased melatonin and suboptimal mitochondrial functioning: Assessment, Treatment and Classification Implications. *Curr. Top Med Chem* 2020;20 (7):524-539. doi:10.2174/1568026620666200131094445.
24. Reiter RJ, Sharma R, Ma Q, et al. Inhibition of mitochondrial pyruvate dehydrogenase kinase: a proposed mechanism by which melatonin causes cancer cells to overcome cytosolic glycolysis, reduce tumor biomass, and reverse insensitivity to chemotherapy. *Melatonin Res.* 2019;2(3):105-119. doi: 10.32794/mr11250033.
25. Giménez V, de las Heras N, Tresguerres J, et al. Melatonin as an anti-aging therapy for age-related cardiovascular and neurodegenerative diseases. *Front Aging Neurosci.* 2022;14:888292. doi:10.3389/fnagi.2022.888292.
26. Sharafati-Chaleshtori R, Shirzad H, Rafieian-Kopaei M, et al. Melatonin and human mitochondrial diseases. *J Res Med Sci.* 2017;22:1-8. doi: 10.4103/1735-1995.199092.
27. Vinod C, Jagota A. Daily Socs1 rhythms alter with aging differentially in peripheral clocks in male Wistar rats: neuroprotective role of melatonin. *Biogerontology.* 2017;18:333-345. doi:10.1007/s10522-017-9687-x.
28. Karadas O, Ozpinar N., Bilgic E. et al. The physiological and lifespan alterations in *Caenorhabditis elegans* exposed to different dosages of melatonin. *Pak J Pharm Sci.* 2019;32(2):625-630.
29. Cardinali DP, Hardeland R. Inflammaging, metabolic syndrome, and melatonin: a call for treatment studies. *Neuroendocrinology.* 2017;104(4):382-397. doi: 10.1159/000446543.
30. Barja G. Towards a unified mechanistic theory of aging. *Exp Gerontol.* 2019;124:110627. doi: 10.1016/j.exger.2019.05.016.
31. Gureev AP, Shaforostova EA, Popov VN. Regulation of mitochondrial biogenesis as a way for active longevity: interaction between Nrf2 and PGC-1 α signaling pathways. *Front Genet.* 2019;10:435. doi:10.3389/fgene.2019.00435.
32. Federico A, Morgillo F, Tuccillo C, et al. Chronic inflammation and oxidative stress in human carcinogenesis. *Int J Cancer.* 2007;121(11):2381-2386. doi:10.1002/ijc.23192.
33. Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. *Nat Rev Cardiol.* 2018;15:505-522. doi:10.1038/s41569-018-0064-2.
34. Oliphant K, Allen-Vercoe E. Macronutrient metabolism by the gut microbiome: major fermentation by-products and their impact on host health. *Microbiome.* 2019;7:91. doi:10.1186/s40168-019-0704-8.
35. Zhu X, Li B, Lou P, et al. The relationship between the gut microbiome and neurodegenerative diseases. *Neurosci Bull.* 2021;37(10):1510-1522. doi:10.1007/s12264-021-00730-8.

36. Akylidiz AG, Biondi-Zoccai G, De Biase D. Impact of the gastrointestinal tract microbiota on cardiovascular health and pathophysiology. *J Cardiovasc Pharmacol.* 2022;80(1):13-30. doi:10.1097/FJC.0000000000001273.
37. Kim SW, Kim S, So M, et al. Melatonin controls microbiota in colitis by goblet cell differentiation and antimicrobial peptide production through Toll-like receptor 4 signaling. *Sci Rep.* 2020;10:2232. doi:10.1038/s41598-020- 59314-7.
38. Bubenik GA. Gastrointestinal melatonin: localization, function, and clinical relevance. *Dig Dis Sci.* 2002;47(10):2336-2348. doi: 10.1023/a:1020107915919.
39. Chen C-Q, Fichna J, Bashashati M, et al. Distribution, function, and physiological role of melatonin in the lower gut. *World J Gastroenterol.* 2011;17(34):3888-3898. doi:10.3748/wjg.v17.i34.3888.
40. Cryan JF, O'Riordan KJ, Cowan CSM, et al. The microbiota-gut-brain axis. *Physiol Rev.* 2019;99(4):1877-1913. doi:10.1152/physrev.00018.2018.
41. Segers A, Depoortere I. Circadian clocks in the digestive system. *Nat Rev Gastroenterol Hepatol.* 2021;18:239-251. doi:10.1038/s41575-020-00401-5.
42. Anderson G, Maes M. Gut dysbiosis dysregulates central and systemic homeostasis via suboptimal mitochondrial function: assessment, treatment, and classification implications. *Curr Top Med Chem.* 2020;20(7):524-539. doi: 10.2174/1568026620666200131094445.
43. Bonmati-Carrion M-A, Rol M-A. Melatonin as a mediator of gut microbiota-host interactions: implications for health and disease. *Antioxidants (Basel).* 2023;13(1):34. doi:10.3390/antiox13010034
44. Hodgkinson K, El Abbar F, Dobranowski P, et al. Butyrate's role in human health and the current progress towards its clinical application to treat gastrointestinal disease. *Clin Nutr.* 2023;42:61-75. doi:10.1016/j.clnu.2022.10.024
45. Moore WE, Holdeman LV. Human fecal flora: the normal flora of 20 Japanese-Hawaiians. *Appl Microbiol.* 1974;27(5):961-979. doi: 10.1128/am.27.5.961-979.1974.
46. Santoru ML, Piras C, Murgia A, et al. Cross-sectional evaluation of the gut-microbiome metabolome axis in an Italian cohort of IBD patients. *Sci Rep.* 2017;7:9523. doi:10.1038/s41598-017-10034-5.
47. Lopez DEG, Lashinger LM, Weinstock G, et al. Circadian rhythms and the gut microbiome synchronize the host's metabolic response to diet. *Cell Metab.* 2021;33(5):873-887. doi:10.1016/j.cmet.2021.03.015
48. Bishehsari F, Voigt RM, Keshavarzian A. Circadian rhythms and the gut microbiota: from metabolic syndrome to cancer. *Nat Rev Endocrinol.* 2020;16:731-749. doi:10.1038/s41574-020-00427-4.
49. Rozencwaig R. Melatonin in the gastrointestinal tract, circadian rhythms, immunity, and microbiota in health, disease, and aging. In: Glibetic M, editor. *Comprehensive Gut Microbiota.* Vol. 1. Amsterdam: Elsevier; 2022. p. 85-94.
50. Teichman EM, O'Riordan KJ, Gahan CGM, et al. When rhythms meet the blues: circadian interactions with the microbiota-gut-brain axis. *Cell Metab.* 2020;31(3):448-471. doi:10.1016/j.cmet.2020.01.007.
51. Galkin F, Mamoshina P, Aliper A. et al. Human Gut Microbiome Aging Clock Based on Taxonomic Profiling and Deep Learning. *iScience.* 2020; 23(6):101199. doi: 10.1016/j.isci.2020.101199.

52. Tian Q, Bilgel M, Walker KA, et al. Skeletal muscle mitochondrial function predicts cognitive impairment and is associated with biomarkers of Alzheimer's disease and neurodegeneration. *Alzheimers Dement*. 2023;19(10): 4436-4445. doi: 10.1002/alz.13388.
53. Chistiakov DA, Sobenin IA, Revin VV, et al. Mitochondrial aging and age-related dysfunction of mitochondria. *Biomed Res Int*. 2014;2014:238463. doi:10.1155/2014/238463.
54. Nehlin JO. Senolytic and senomorphic interventions to defy senescence-associated mitochondrial dysfunction. *Adv Protein Chem Struct Biol*. 2023;136:217-247. doi:10.1016/bs.apcsb.2023.02.020.
55. Paradies G, Paradies V, Ruggiero FM, et al. Mitochondrial bioenergetics decay in aging: beneficial effect of melatonin. *Cell Mol Life Sci*. 2017;74:3897-3911. doi:10.1007/s00018-017-2619-5.
56. Seo DY, Lee SR, Kim N, et al. Age-related changes in skeletal muscle mitochondria: the role of exercise. *Integr Med Res*. 2016;5(3):182-186. doi:10.1016/j.imr.2016.07.003.
57. Katajisto P, Döhla J, Chaffer CL, et al. Asymmetric apportioning of aged mitochondria between daughter cells is required for stemness. *Science*. 2015;348(6232):340-343. doi:10.1126/science.1260384.
58. Hodzic E, Galijašević S., Balaban M. et al. The protective role of melatonin under heavy metal-induced stress in *Melissa officinalis* L. *Turk J Chem*. 2021;45(3):737-748. doi: 10.3906/kim-2012-7.
59. Fischer TW, Kleszczyński K, Hardkop LH, et al. Melatonin enhances antioxidative enzyme gene expression (CAT, GPx, SOD), prevents their UVR-induced depletion, and protects against the formation of DNA damage in ex vivo human skin. *J Pineal Res*. 2012;54(3):303-312. doi: 10.1111/jpi.12018.
60. Nasoni MG, Carloni S, Canonico B, et al. Melatonin reshapes the mitochondrial network and promotes intercellular mitochondrial transfer via tunneling nanotubes after ischemic-like injury in hippocampal HT22 cells. *J Pineal Res*. 2021;71(2):e12747. doi:10.1111/jpi.12747.
61. Marabitti V, Vulpis E, Nazio F, et al. Mitochondrial transfer as a strategy for enhancing cancer cell fitness: current insights and future directions. *Pharmacol Res*. 2024;208:107382. doi:10.1016/j.phrs.2024.107382.
62. Ma Zh, Xin Zh, Di W, et al. Melatonin and mitochondrial function during ischemia/reperfusion injury. *Cell Mol Life Sci*. 2017;74(21):3989-3998. doi:10.1007/s00018-017-2618-6.
63. Guerra-Librero A., Fernandez-Gil BI, Florido J. et al. Melatonin targets metabolism in head and neck cancer cells by regulating mitochondrial structure and function. *Antioxidants*. 2021;10(4):603. doi:10.3390/antiox10040603.
64. Baburina Y, Odinokova I, Azarashvili T, et al. 2',3'-Cyclic nucleotide 3' phosphodiesterase as a messenger of protection of the mitochondrial function during melatonin treatment in aging. *Biochim Biophys Acta Biomembr*. 2017;1859(1):94-103. doi:10.1016/j.bbamem.2016.10.003.
65. Paradies G, Petrosillo G, Paradies V, et al. Melatonin, cardiolipin, and mitochondrial bioenergetics in health and disease. *J Pineal Res*. 2010;48(4):297-310. doi:10.1111/j.1600-079X.2010.00759.x.
66. Reiter RJ, Tan DX, , Rosales-Corral S, et al. Mitochondria: central organelles for melatonin's antioxidant and anti-aging actions. *Molecules*. 2018;23(2):509. doi:10.3390/molecules23020509.
67. Reiter RJ, Sharma R, Manucha W, et al. Dysfunctional mitochondria in age-related neurodegeneration: utility of melatonin as an antioxidant treatment. *Ageing Res Rev*. 2024;101:102480. doi:10.1016/j.arr.2024.102480.

68. Reiter RJ, Rosales-Corral S, Tan DX, et al. Melatonin as a mitochondria-targeted antioxidant: one of evolution's best ideas. *Cell Mol Life Sci.* 2017;74(21):3863-3881. doi: 10.1007/s00018-017-2609-7.
69. Paradies G, Paradies V, Ruggiero FM, et al. Protective role of melatonin in mitochondrial dysfunction and related disorders. *Arch Toxicol.* 2015;89(6):923-939. doi: 10.1007/s00204-015-1475-z.
70. León J, Acuña-Castroviejo D, Escames G, et al. Melatonin mitigates mitochondrial malfunction. *J Pineal Res.* 2005;38(1):1-9. doi:10.1111/j.1600-079X.2004.00181.x.
71. Jin Y, Choi YJ, Heo K, et al. Melatonin as an oncostatic molecule based on its anti-aromatase role in breast cancer. *Int J Mol Sci.* 2021;22(1):438. doi:10.3390/ijms22010438.
72. Tan DX, Chen LD, Poeggeler B, et al. Melatonin: a potent, endogenous hydroxyl radical scavenger. *Endocr J.* 1993;1(1):57-60. doi:10.1507/endocrj.1.57.
73. Reiter RJ, Tan DX, Osuna C, et al. Actions of melatonin in the reduction of oxidative stress: a review. *J Biomed Sci.* 2000;7(6):444-458. doi:10.1007/BF02253360.
74. Galano A, Tan DX, Reiter RJ. Melatonin as a natural ally against oxidative stress: a physicochemical examination. *J Pineal Res.* 2011;51(1):1-16. doi:10.1111/j.1600-079X.2011.00916.x.
75. Fernández A, Ordóñez R, Reiter RJ, et al. Melatonin and endoplasmic reticulum stress: relation to autophagy and apoptosis. *J Pineal Res.* 2015;58(4):399-407. doi:10.1111/jpi.12264.
76. Coto-Montes A, Boga JA, Rosales-Corral S, et al. Role of melatonin in the regulation of autophagy and mitophagy: a review *Mol Cell Endocrinol*, 2012, 361(1-2):12-23. doi: 10.1016/j.mce.2012.04.009.
77. Wu J, Bai Y, Wang Y, et al. Melatonin and regulation of autophagy: Mechanisms and therapeutic implications. *Pharm Res.* 2021 163:105279. doi:10.1016/j.phrs.2020.105279.
78. Rahmani S, Roohbakhsh A, Pourbarkhordar V, et al. Melatonin regulates mitochondrial dynamics and mitophagy: cardiovascular protection. *J Cell Mol Med.* 2024;28(18):e70074. doi:10.1111/jcmm.70074.
79. Franceschi C, Garagnani P, Parini P, et al. Inflammaging: a new immune-metabolic viewpoint for age-related diseases. *Nat Rev Endocrinol.* 2018;14(10):576-590. doi:10.1038/s41574-018-0059-4.
80. Weinberg SE, Sena LA, Chandel NS. Mitochondria in the regulation of innate and adaptive immunity. *Immunity.* 2015;42(3):406-417. doi:10.1016/j.immuni.2015.02.002.
81. Stocco A., Coppede F. Mitochondrial DNA methylation and human Diseases. *Int J Mol Sci.* 2021, 22(9):4594. doi: 10.3390/ijms22094594.
82. Liu J, Guan O, Li, Sh., et al. Melatonin Alleviates MBP-Induced Oxidative Stress and Apoptosis in TM3 Cells via the SIRT1/PGC-1 α Signaling Pathway. *Int J Mol Sci.* 2025 26(12):5910. doi: 10.3390/ijms26125910.
83. Reiter RJ, Tan DX, Rosales-Corral, S. et al. Melatonin Mitigates Mitochondrial Meltdown: Interactions with SIRT3. *Int J Mol Sci.* 2018, 19, 2439; doi:10.3390/ijms19082439.
84. Hill SM, Blask DE. Effects of the pineal hormone melatonin on the proliferation and morphological characteristics of human breast cancer cells (MCF-7) in culture. *Cancer Res.* 1988;48(21):6121-6126.