



Review



Gut microbiota in neurological diseases: Melatonin plays an important regulatory role

Somayeh Ahmadi^{a,b}, Mohammad Taghizadieh^c, Elham Mehdizadehfard^d, Alka Hasani^{b,e}, Javad Khalili Fard^f, Hadi Feizi^{b,g}, Hamed Hamishehkar^f, Masood Ansarin^f, Mina Yekani^{h,i,*}, Mohammad Yousef Memar^{j,**}

^a Students Research Committee, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

^b Department of Bacteriology and Virology, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

^c Department of Pathology, School of Medicine, Center for Women's Health Research Zahra, Tabriz University of Medical Sciences, Tabriz, Iran

^d Department of Neurosciences, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

^e Clinical Research Development Unit, Sina Educational, Research and Treatment Center, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

^f Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

^g Department of Medical Microbiology, Aalinasab Hospital, Social Security Organization, Tabriz, Iran

^h Department of Microbiology, Faculty of Medicine, Kashan University of Medical Sciences, Kashan, Iran

ⁱ Student Research Committee, Kashan University of Medical Sciences, Kashan, Iran

^j Infectious and Tropical Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

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ABSTRACT

Melatonin is a highly conserved molecule produced in the human pineal gland as a hormone. It is known for its essential biological effects, such as antioxidant activity, circadian rhythm regulator, and immunomodulatory effects. The gut is one of the primary known sources of melatonin. The gut microbiota helps produce melatonin from tryptophan, and melatonin has been shown to have a beneficial effect on gut barrier function and microbial population. Dysbiosis of the intestinal microbiota is associated with bacterial imbalance and decreased beneficial microbial metabolites, including melatonin. In this way, low melatonin levels may be related to several human diseases. Melatonin has shown both preventive and therapeutic effects against various conditions, including neurological diseases such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis. This review was aimed to discuss the role of melatonin in the body, and to describe the possible relationship between gut microbiota and melatonin production, as well as the potential therapeutic effects of melatonin on neurological diseases.

1. Introduction

Melatonin is a hormone first isolated and characterized from the bovine pineal gland [1]. The retinal ganglion cells (RGCs) in the eye contain a melanopsin protein. It is a G family- related receptor that responds to natural or artificial light. When RGCs are activated by light, the signals are sent to the suprachiasmatic nucleus (SCN), which inhibit the melatonin production by the pineal gland. Conversely, during periods of darkness, melatonin production and secretion are induced due to decreased activation of the SCN (Fig. 1) [2].

Melatonin is principally secreted by the pineal gland. However, it is

also detected in various other organs and tissues, such as the brain, thymus, retina, lens, cochlea, harderian gland, skin, airway epithelium, gastrointestinal tract (GIT), liver, kidney, pancreas, thyroid, spleen, immune system cells, carotid body, reproductive tract, and endothelial cells. Many of these organs possess the required enzymes for melatonin synthesis [3]. Melatonin is produced in the gut by bacteria [4]. The gut microbiota is a heterogeneous community of microorganisms residing in the intestine. Microbiota roles in several physiological features of the host body have been extensively described in recent years. Optimal amounts and diversity of gut microbiota are associated with a healthy host. In contrast, dysbiosis or disruption of the gut microbiota has been

* Corresponding author at: Department of Microbiology, Faculty of Medicine, Kashan University of Medical Sciences, Kashan, Iran.

** Corresponding author.

E-mail addresses: Mina.yekani71@yahoo.com (M. Yekani), y.memar@yahoo.com (M.Y. Memar).

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described to be associated with diseases or some organs deficiency [5–8]. A significant relationship has been established between the gut microbiota and melatonin, whereby the gut microbiota positively affects the biosynthesis of melatonin from the precursor amino acid, tryptophan. In addition, some studies have shown the beneficial effect of melatonin on the function of the intestinal barrier and intestinal microbiota [9], which can be applied for the treatment or prevention of these conditions [10]. Several studies have been shown that individuals with neurological disorders often produce low levels of melatonin than healthy peoples. Melatonin exhibited both preventive and therapeutic effects on some diseases, including neurological conditions such as Alzheimer's disease (AD) [11], Parkinson's disease (PD) [12], and multiple sclerosis (MS) [10]. This review was aimed to outline the link and interaction between gut microbiota and neurological diseases included AD, PD and MS. The second section discussed the direct and indirect regulatory effects of melatonin on neurological diseases through gut microbiome modification.

2. Microbiome-gut-brain axis

The "gut-microbiota-brain (MGB) axis" refers to a network of interconnections among numerous biological systems, which enables mutual interaction between the brain and gut microbiota. MGB axis is essential in preserving homeostasis of gastrointestinal, central nervous, and microbial systems. These biological communication routes encompass direct and indirect signaling through chemical transmitters, the immune system, and neuronal pathways, as elucidated below [13]. MGB

plays an essential role in the central nervous system (CNS) function due to three mechanisms [14,15]. The first mechanism is immunoregulation, where microbiota interact with immune cells, altering cytokines levels, cytokine-responsive factors, and prostaglandin-E, consequently influencing brain function [16]. The second mechanism is the neuroendocrine interactions. The intestine is the largest endocrine organ in the human's body that contains over than 20 types of enteroendocrine cells (EECs) [17].

The hypothalamic-pituitary-adrenal (HPA) axis and the CNS may be affected by the gut microbiome's control over releasing neurotransmitters such as the cortisol, tryptophan, and serotonin. The vagus nerve is the third pathway. The sensory neurons of the intestinal myenteric plexus are exposed to the gut microbiota and connect synaptically to the motor neurons of the intestine, which control intestinal motility and the release of gut hormones. Additionally, the vagus nerve, which joins the colon to the brain, and the intestinal nervous system make synaptic connections [18], which could be referred as the gut microbiota-enteric nervous system (ENS)-vagus-brain pathway, is a channel for the transfer of information (Fig. 2) [19]. The gut microbiome interacts with the brain via the effects on the expression and synthesis of some neurotransmitters, including serotonin, melatonin, gamma-aminobutyric acid, histamine and acetylcholine, and neurotrophic factors, including brain-derived neurotrophic factors, which in turn influences enteric nervous system activity [20]. Vagus nerve and ENS are essential in this interaction [21].

Gut dysbiosis is often used in microbiome research to describe the gut microbiome in an imbalanced state [22]. Gut dysbiosis has the

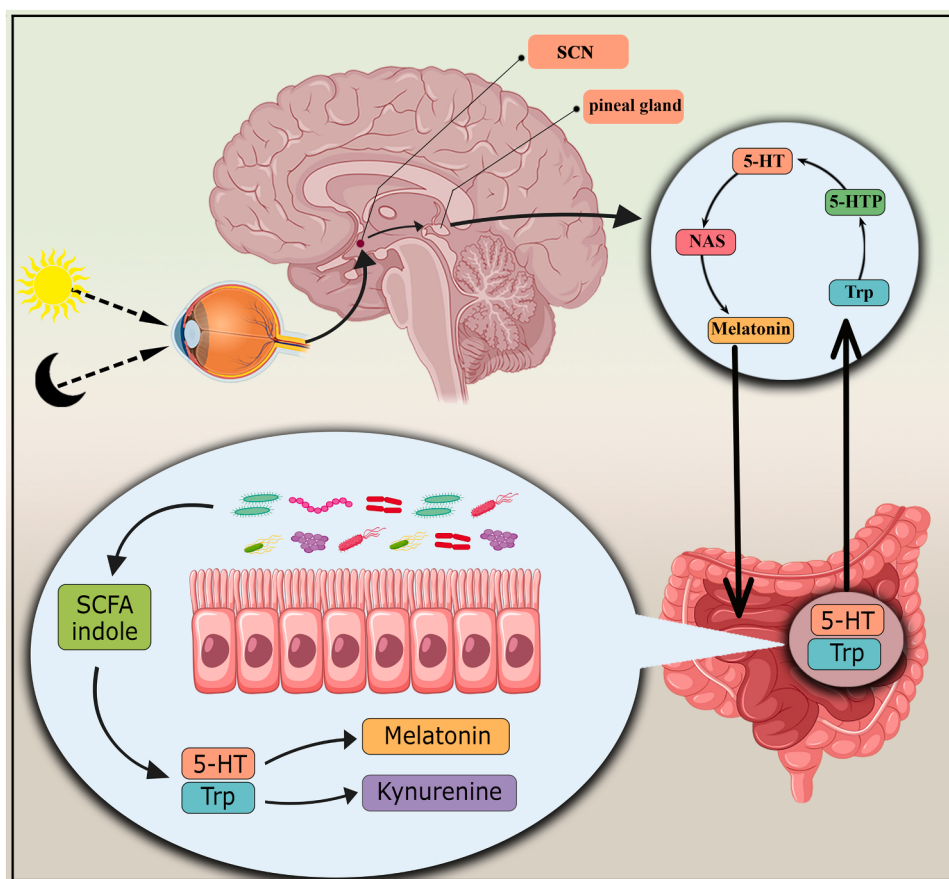


Fig. 1. Melatonin originates from serotonin through the tryptophan-serotonin biosynthesis process in the pineal gland. The gut is a most important source of melatonin, producing much more than the pineal gland. When the intestinal barrier becomes permeable due to inflammation or dysbiosis, pathogens and endotoxins can enter the bloodstream. This activates the immune system, inducing pro-inflammatory cytokines like IL-1 β , IL-6, IL-18, and interferon- γ . These cytokines stimulate indoleamine 2,3-dioxygenase (IDO), diverting tryptophan away from melatonin synthesis toward kynurenine pathway products like kynurenic acid and quinolinic acid and decrease melatonin levels.

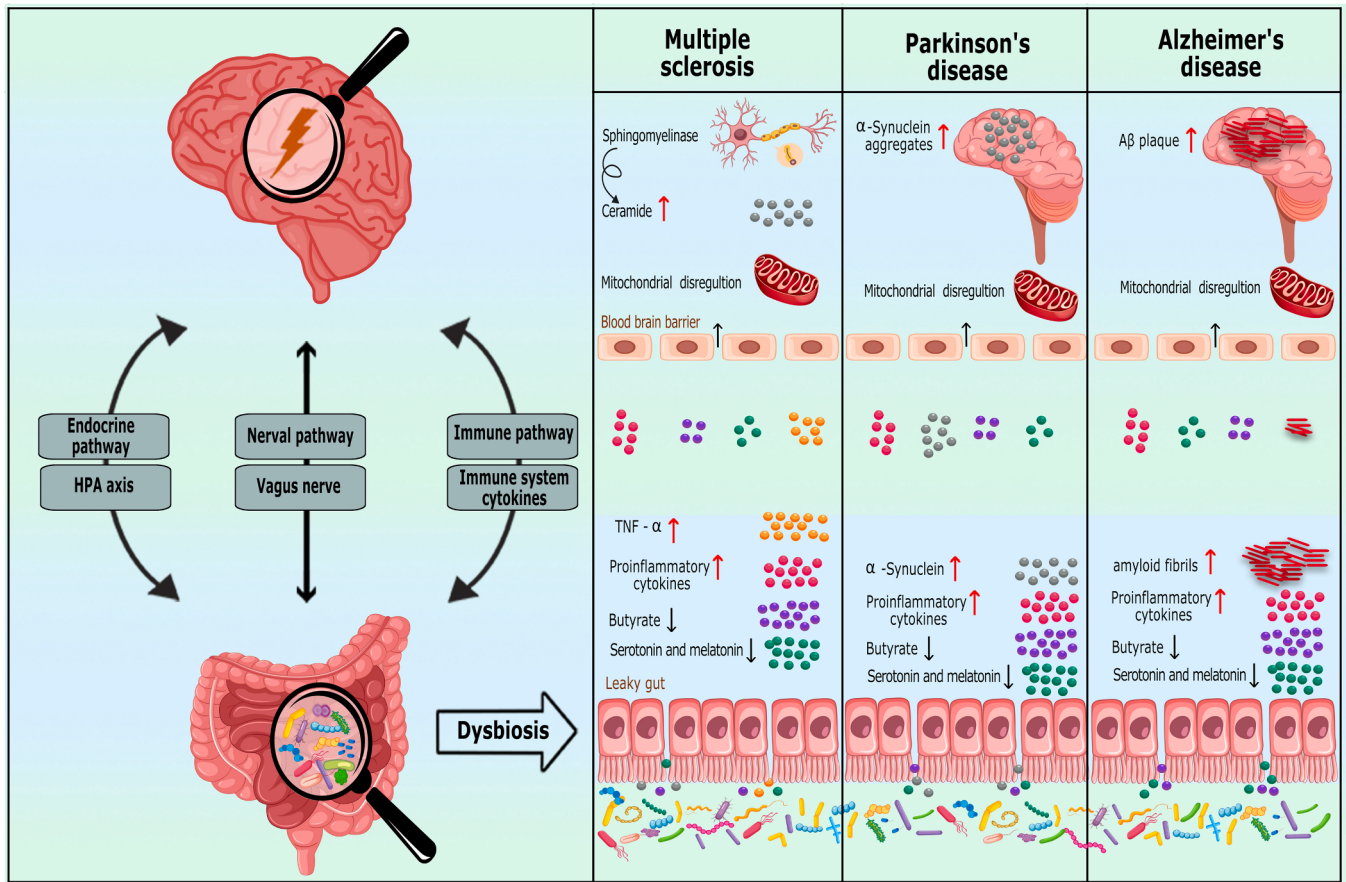


Fig. 2. The bidirectional microbiome-gut-brain axis communicates through immunological, neuroendocrine, and neural pathways. In MS, gut dysbiosis and increased gut permeability activate the immune system, thus increasing TNF- α and reducing melatonin, serotonin and butyrate levels. This leads to mitochondrial dysfunction, neuroinflammation, and demyelination. In PD, misfolded α -synuclein proteins originate in the gut and spread to the brain, contributing to neuroinflammation and cell death. Gut dysbiosis reduces butyrate and melatonin, impacting mitochondrial function and the inflammatory response. In AD, amyloid proteins and bacterial endotoxins activate the immune system and cross the BBB, leading to amyloid plaque formation and neurodegeneration. Gut dysbiosis and reduced melatonin accelerate this process by causing mitochondrial dysfunction, chronic inflammation, and impaired lymphatic drainage.

potential to induce alterations within the gut itself, thereby influencing the mitochondrial functions within the intricate intestinal ecosystem. There are two critical aspects of these changes: increased intestinal permeability induces the toll-like receptors (TLR) activity, circulating lipopolysaccharide (LPS), and exosomal high-mobility group box-1 (HMGB-1). LPS and HMGB-1 increase inducible nitric oxide synthase and superoxide, which causes the acidic sphingomyelinase formation and ceramides to be driven by peroxynitrite [23]. Furthermore, alterations in gut microbial composition and elevated intestinal permeability result in increased levels of LPS and various other factors.

Consequently, these factors stimulate the microglia activation. This microglia activation further enhances the synthesis and secretion of tumor necrosis factor- α (TNF- α) and peroxynitrite (ONOO⁻). The latter compound induces the levels of acidic sphingomyelinase (aSMase) in astrocytes, subsequently leading to an increase in the release of ceramide, including its presence within exosomes [24]. TNF- α and ceramide both reduce the quantities of orexin, which is produced during the day, and melatonin, which is produced at night. This prevents orexin and melatonin from optimizing mitochondrial activity and oxidative phosphorylation during the day and night, respectively [25].

3. Biosynthesis and function of Melatonin

Melatonin originates from serotonin through the tryptophan-serotonin biosynthesis process in the pineal gland. Melatonin levels vary depending on the brain's circadian center input and increase in the

evening and decrease in the morning that help to promote sleep at night and wakefulness during the day [26]. Melatonin is produced within pinealocytes and other tissues, as a final product in tryptophan and serotonin synthesis pathways. The process starts with tryptophan entering the cell and being converted into serotonin by tryptophan-5-hydroxylase and 5-hydroxytryptophan decarboxylase enzymes. Serotonin then undergoes acetylation by arylalkylamine-N-acetyltransferase (AA-NAT) and methylation by acetylserotonin-O-methyltransferase (ASMT, also known as hydroxyindole-O-methyltransferase or HIOMT) to create melatonin. AA-NAT, the rate-limiting enzyme in melatonin production, is a potential regulatory site (Fig. 1) [27]. Some studies have shown that the release of melatonin decreases with age [28]. Melatonin's primary function is to transmit information regarding the daily light and darkness cycle [29], and it is vital in controlling the sleep-awakens cycle, memory formation and seasonal adaptation [30]. Furthermore, melatonin is known to be a multifunctional molecule [31], and is known to possess anti-oxidant and anti-inflammatory properties [32]. It also plays an essential role in immune responses and mitochondrial homeostasis [33], and contributes to the differentiation and survival of various brain cells [34].

4. Melatonin and gut microbiota

GIT contains more than a trillion different types of microorganisms [35]. Firmicutes and Bacteroidetes comprise 90% of the digestive tract's dominant microbiota [6]. The phylum Firmicutes includes

Gram-positive bacteria, with rigid or semi-rigid cell walls predominantly, from the genera *Bacillus*, *Clostridium*, *Enterococcus*, *Lactobacillus*, and *Ruminococcus* [36,37]. Bacteroidetes phylum encompasses an estimated 7000 distinct species of Gram-negative bacteria, predominantly from the genera *Bacteroides*, *Parabacteroides*, *Prevotella*, and *Alistipes* [38]. The gut microbiota contributes to host health through several effects, including the preservation of an intact intestinal barrier, prevention of pathogens colonization, control of host physiology and immune responses, metabolism regulation, and vitamin production [39–41]. GIT is the primary source of enzymes required for melatonin synthesis, and its level in the GIT is higher than in other tissues [42]. For instance, melatonin concentration in the gastrointestinal tissues is approximately 10–100 and 400 times higher than its concentration in the blood and pineal gland, respectively [43]. Unlike the pineal gland, the GIT does not exhibit a photoperiodic cycle in melatonin secretion [44]. Gut microbiota can influence the levels of melatonin secretion through various mechanisms, such as promoting the production of short-chain fatty acids (SCFAs), and serotonin (a precursor of melatonin) with high-fiber diets, and promoted the up-regulation of the mRNA for tryptophan hydroxylase (TPH1) [45]. Additionally, SCFAs and tryptophan metabolites can stimulate the production of 5-HT, affecting melatonin secretion via aralkyl-amine N-acetyltransferase (AANAT) and ASMT (Fig. 1) [46]. It was reported that increasing the availability of 5-HT induced melatonin secretion both during both the day and at night. Primary evidence also revealed a role for 5-HT receptor dependent control of night-time melatonin expression in the pineal gland [47]. Besides, SCFAs may stimulate serotonin production by enterochromaffin cells, thus, increasing melatonin's level in the gut. High levels of tryptophan or melatonin in foods can increase melatonin production and its concentration in the gut. Melatonin has both local and systemic effects after synthesis and is transferred into the bloodstream or gut lumen [10]. Melatonin also has a considerable effect on the intestinal microbiota, which provides the gut's barrier integrity by reducing inflammation and oxidative stress. It also boosts the amount of intestinal microbiota by affecting their metabolism. Additionally, by controlling the metabolism of tryptophan and serotonin, the gut microbiota can affect the production of melatonin [48,49]. Accumulating evidence has shown that melatonin can modulate the composition and abundance of the gut bacterial population in normal conditions [50], increase the diversity and frequency of intestinal microbiota, decrease the frequency of Bacteroides, and increase the frequency of firmicutes [51–53]. Melatonin also increases Akkermansia flora's frequency [54]. In the animal model of spinal cord injury (SCI), melatonin decreased the frequency of *Clostridium* and increase the a frequency of *Lactobacillus* [55], *Streptococcus mucophagophagus*, and *Myxobacteria* [56]. When dysbiosis occurs, the permeability of the intestinal barrier increases, resulting in damage to the mucus and intestinal epithelial cells. As a result, large undesirable molecules and commensal bacteria can enter the lamina propria [57]. This leads to the activation of the immune system and the production of inflammatory cytokines such as interferons, interleukin IL-17, IL-1B, IL-6, IL-8, IL-12, and TNF- α . Additionally, there is an increase in calcium-dependent oxidative stress [58]. Induction of indoleamine 2, 3-dioxygenase (IDO) is a significant result of increased proinflammatory cytokines IL-1, IL-6, IL-18, and especially interferon-gamma (INF- γ). IDO induce producing several neuroregulatory compounds, including kynurenic acid (KYNA) and the excitotoxic quinolinic acid (QUIN), by diverting tryptophan away from the production of serotonin and melatonin and along the kynurenine pathway (Fig. 1) [59]. Cytokines and other inflammatory factors, as well as bacterial metabolites, traverse the CNS through blood vessels and the enteric nervous system (ENS), or via the afferent fibers of the vagus nerve, thereby disrupting the integrity of the blood-brain barrier (BBB). The BBB, a natural protective membrane, regulates the transportation of molecules and cells, thereby safeguarding the brain's well-being. Therefore, BBB disruption can lead to neuroinflammation, which in turn has the potential to exacerbate neurological disorders [60]. Among the metabolites that

change due to dysbiosis are the levels of serotonin and melatonin, which decrease simultaneously [60]. These changes are related to variations in neural activity, interregional patterning and mitochondrial function control because melatonin has antioxidant and neuroprotective effects, and prevents mitochondrial destruction [61–63]. Changes in neuro-immuno-endocrine function are significantly influenced by the equilibrium between the control of the kynurenine and serotonin/melatonin arms of tryptophan metabolism. On the other hand, some hormones can affect the cytokines effects. Melatonin can reduce the production and effects of pro-inflammatory cytokines [64].

In addition to provide a barrier or intestinal epithelial cells and increasing junctional integrity [65], butyrate (a common SCFAs) can inhibit essential pathways for the proinflammatory mediators production [66]. Both *in vivo* and *in vitro* studies have shown that butyrate stimulates the expression of colonic serotonin and stimulates melatonin formation by Caco-2 cells [67]. Some studies have also suggested a possible association between melatonin and the MGB axis, indicating that the gut microbiota may play a significant role in brain-related diseases through melatonin modulation in the gut [10,12].

5. Gut microbiome-melatonin- multiple sclerosis

MS is an autoimmune inflammatory and chronic condition that mainly affects the CNS. MS is characterized by the demyelination and loss of axons, resulting in lesions in the spinal cord and brain. It often affects persons in their early thirties and is more prevalent in women than males. Individuals with MS have muscular weakening and dysfunction that may progress to paralysis. Changes in the quantity, composition, and function of gut microbiota are reported to have a substantial impact on the development of MS [68].

Gut microbiota dysbiosis has lately been linked to the pathogenesis of MS. Considerable alterations in gut microbiota species have been reported to be associated with induced pro-inflammatory responses that may cause or exacerbate disease [69]. IL-12 and IL-23 are implicated in the development of autoimmune illnesses such as MS. It has been established that gut microbiome dysbiosis may be directly associated with MS owing to the interaction between the gut microbiome and the IL-23/IL-17 axis. Both of these cytokines boost Th17 cells, which, upon entering the CNS, myelin-specific T cells react to myelin self-antigens and promote demyelination [70].

It has been well described that gut microbiota dysbiosis is associated with reduced SCFA production, resulting in a decrease in melatonin and butyrate, and an increase in ceramide [71]. Butyrate is an essential positive regulator of mitochondrial function and also suppresses ceramide levels and its effects [72]. Melatonin and butyrate improve mitochondrial oxidative phosphorylation partly by disinhibiting the pyruvate dehydrogenase complex, leading to increased acetyl-coenzyme A (CoA). CoA is an essential co-substrate for activating the mitochondrial melatonergic pathway [73,74]. Moreover, it increases the activity of the complex I and IV enzymes NADH-coenzyme Q reductase and cytochrome C oxidase, both essential for mitochondrial oxidative phosphorylation, enabling melatonin to optimize mitochondrial function [75].

Furthermore, butyrate has been shown to possess immunomodulatory and anti-inflammatory properties [76]. It was reported that butyrate decreased pro-inflammatory cytokine expression, such as TNF- α , IL-6, and IL-12, and a decrease of butyrate may be associated with inflammation [77], and induce IDO expression [78]. IDO directs tryptophan down the kynurenine pathway, resulting in the production of neuroregulatory products such as KYNA and QUIN, while also reduce serotonin and melatonin levels. This mechanism connects pro-inflammatory cytokine activity with changes in neuronal activity, inter-area patterning, and mitochondrial function [11]. Gut-driven changes in ceramide and mitochondrial function, along with the loss of circadian rhythm regulation of optimal mitochondrial function, alter the coordination of cellular function across various cell types, such as

oligodendrocytes, immune cells, and BBB cells, particularly in glia and immune cells, underlying MS pathophysiology [73]. In reality, mitochondria already have all the co-factors and enzymes required to activate the melatonergic pathway, including the proteins AANAT, ASMT, acetyl-CoA, and 14-3-3. The first enzyme in the mitochondrial melatonergic pathway, AANAT stabilization, is reduced by ceramide's suppression of 14-3-3 protein levels. Due to its beneficial effects on sirtuin-3, oxidative phosphorylation, and antioxidant control, mitochondrial melatonin is lost when AANAT stabilization declines [79,80].

There is evidence that abnormalities in the mitochondria, such as ineffective mitochondrial enzyme activities and inefficient mitochondrial DNA repair activities, may affect cellular pathways, resulting in damage to axons, loss of neurons, and atrophy of the CNS, all of which can cause permanent neurological disability [81]. In a mouse model of MS, treatment with melatonin has prevented pathological alterations by restoring mitochondrial respiratory enzyme activity and fusion and fission processes. At the same time, also reduce intra-axonal mitochondria accumulation [82]. Furthermore, a recent report has demonstrated significant clinical improvement in a patient with primary progressive MS following low-dose melatonin treatment [83]. Melatonin administration (25 mg of melatonin to the patients orally over the course of six months) has shown promising effects in decreasing the levels of proinflammatory cytokines and oxidative stress markers in the blood of MS patients [84]. Melatonin usage (5 mg/day) for 90 days leads to significant decrease in plasma lipid hydroxy peroxide levels in MS patient. Lipids play a key role in the immunopathogenesis of MS [85,86].

6. Gut microbiome-melatonin- Parkinson's disease

PD is a neurodegenerative disorder that ranks second in mortality rates, following AD.[87] Currently, PD is diagnosed based on a motor triad consisting of stiffness, bradykinesia, and resting tremor. PD is a complex and progressive disease characterized by the presence of Lewy bodies and Lewy neuritis, which result from the breakdown of dopaminergic neurons in the substantia nigra pars compacta and the production of α -Synuclein (α -Syn) [88]. Intracellular protein accumulations or inclusions are common in various neurodegenerative disorders, including Lewy bodies in PD [89]. The gut microbiome has recently attracted attention for its possible role in PD's underlying mechanisms [90]. Recent findings suggested that α -synuclein could originate in the gut and transported to the brain via a neuronal circuit connecting the gut and the nervous system, implicating the gut as a potential primary source for PD [91]. Recent research indicates that gut α -synuclein enhances gut inflammation, which may contribute to the pro-inflammatory environment in PD, which itself can cause more α -synuclein production. (Figure –2)[90]. The process by which microglia transport α -Syn from the enteric nervous system (ENS) to the central nervous system (CNS) may result in the subsequent accumulation of α -Syn in the CNS. This accumulation is accompanied by the release of pro-inflammatory cytokines, namely IL-1, IL-6, and TNF, by activated microglia. These cytokines have the potential to induce neuroinflammation, oxidative stress, and the aggregation and dissemination of α -Syn, all of which have been implicated in the apoptotic death of neurons [92].

As a result of dysbiosis, the IDO pathway simultaneously reduces the level of serotonin and melatonin [59], and also induce inflammatory cytokines. This pro-inflammatory cytokine may significantly affect IDO activity due to mitochondrial function is affected. Some studies have described the optimized mitochondrial function of melatonin in part by increasing the levels of sirtuins, which are critical mitochondrial regulators [93]. Mitochondrially located sirtuin-3 has been shown to protect dopaminergic neurons against oxidative stress generated in their own mitochondria and also rescue them in an α -synuclein model of PD [94]. Sirtuin-3 has been shown to be involved in mitochondrial quality control, including refolding or degradation of unfolded/unfolded proteins, mitochondrial dynamics, mitophagy, and mitochondrial biogenesis, all

of which are implicated in neurodegenerative diseases such as Parkinson's disease (PD) [95]. Melatonin has neuroprotective effects in PD by increasing dendritic numbers, restoring synaptic plasticity, and inhibiting α -synuclein aggregation and toxicity [96], reducing oxidative stress and improving mitochondrial function, Reduction of neuroinflammation [97]. Therefore, the combination of Sirtuin-3 and melatonin may have a synergistic effect in rescuing dopamine neurons in an α -synuclein model of PD. The inhibitory effects of melatonin against PD generally are mediated by several mechanisms. As an antioxidant, melatonin decreases the destructive effects of reactive oxygen species (ROs) that damage macromolecules and induce apoptosis. Melatonin also has anti-apoptotic effects in dopaminergic neurons. It activates mitochondrial metabolism and decreases microglia activity and the inflammatory mediators [98,99].

7. Gut microbiome-melatonin- Alzheimer's disease

AD is a chronic neurodegenerative disease that results in the demise of neurons [100]. AD has been widely addressed as the most common cause of dementia across the globe, primarily affecting the elderly [101, 102]. The likelihood of women being affected by AD is higher. AD is an extremely debilitating condition that may lead to mortality in the long term [103]. The disease progresses from mild memory loss to a complete loss of cognitive function [104]. AD is characterized by extracellular amyloid-beta ($A\beta$) plaques, the establishment of intracellular neurofibrillary tangles (NFTs), escalated oxidative impairment, and neuronal depletion [105]. The gut microbiome has recently attracted attention for its potential in AD progressing mechanisms. The onset of AD may start in the gut before progressing to the brain. It was suggested the injection of A1-42 oligomers into the intestinal wall of mice, which led to the observation of amyloid migration from the colon to the brain for a year. The translocation of type-A oligomers from the gut to the brain may be significantly associated with AD and neuroinflammation [106]. Certain bacterial strains such as *Escherichia coli*, *Salmonella enterica*, *Staphylococcus aureus*, *Bacillus subtilis*, and *Mycobacterium tuberculosis* have produced functional extracellular amyloid fibers [107,108]. The development of amyloid fibrils is triggered by neuroinflammation induced by bacterial endotoxin [109]. These amyloid proteins facilitate biofilm formation and promote a strong interaction between bacterial strains, thus enabling them to withstand destruction from environmental and immunological factors. Furthermore, bacterial amyloid in the gut can activate the immune system, which may lead to enhanced immunological responses and endogenous neuronal amyloid production in the brain (Fig. 2)[108]. Certain bacterial strains in the gut microbiome can activate the immune system and produce IDO, which is linked to AD and other pathologic conditions. This process leads to the production of neuroregulatory products like KYNA and QUIN via the kynurenine pathway. Pro-inflammatory cytokines activity is associated with changes in neuronal activity, inter-area patterning, and mitochondrial function [11]. Furthermore, it has been reported that aged individuals with AD exhibit a diminished quantity of microbiome bacteria, leading to a decline in butyrate levels [110]. Butyrate, in turn, plays a primary role in sustaining the function of intestinal epithelial cells and strengthening junctional integrity [65]. Additionally, it has been found that butyrate can impede pathways needed to produce pro-inflammatory cytokines and stimulate the expression of colonic serotonin, which serves as a precursor of melatonin [66,67]. Butyrate induces N-acetylserotonin and melatonin synthesis in the gut, thus indicating that some of its effects are mediated by its induction of the melatonergic pathway [11]. In summary, gut microbiota dysbiosis significantly affects central and systemic balance, due to decreasing amounts of butyrate and melatonin, which result in decreased mitochondrial activity, in turn, the pathophysiology of numerous medical diseases linked to gut microbiota dysbiosis and reduced melatonin synthesis are consequently profoundly affected by this [111]. The reduction of endogenous melatonin has resulted in dysbiosis of the gut

microbiota, accompanied by inflammation and an increase in gut permeability. Consequently, micro-organisms and toxins present in the gut have the potential to enter the blood circulation, thus increasing the levels of pro-inflammatory factors such as TNF- α and MCP-1. This, in turn, leads to chronic systemic inflammation. The state of chronic systemic inflammation ultimately damages the tight junctions and cells that make up the BBB, facilitating the active transfer of pro-inflammatory factors from the blood into the brain. This phenomenon ultimately results in an AD-like phenotype, microglia activation, and A β protein deposition [11]. It should also be noted that A β is produced by reactive astrocytes, even when TLR-4 is activated [112]. Therefore, systemic processes that increase BBB permeability and astrocyte reactivity contribute to A β and neuronal apoptotic susceptibility. This includes alterations in the gut microbiome and increased gut permeability [113]. Importantly, the pathophysiology of AD has been linked to both neuroinflammation and systemic inflammation [114]. As a result, the gut microbiota represents a promising therapeutic target for various disorders, according to clinical and experimental studies. However, the connection between melatonin, gut microbiota, and AD has not been well addressed [11]. It was indicated that individuals with AD exhibit modified melatonin and pineal gland function. Some *in vitro* and *in vivo* studies have demonstrated that melatonin possesses promising neuroprotective properties against AD neuropathology. Melatonin can mitigate A β deposition, NFT accumulation, oxidative stress, neuroinflammation, apoptosis, mitochondrial dysfunction, and impairments in neuroplasticity and neurotransmission. Melatonin treatment exhibited improvements in behavior in AD animal models [115]. The administration of melatonin has been reported to increase the ability to prevent or decelerate AD progression. Melatonin also can potentially increase A β clearance through glymphatic-lymphatic drainage, transportation across the BBB, and degradation pathways, while also facilitating A β -induced neurotoxicity [116]. It has been suggested that melatonin governs the gut microbiota, and its treatment can elevate the ratio of Firmicutes to Bacteroidetes and Akkermansia, as well as reduce pathogenic bacteria in the gut [49]. Lower levels of melatonin were noted in individuals with AD in comparison to healthy controls with a similar age. Consequently, melatonin supplementation may exert neuroprotective effects on the brain [117].

8. Melatonin biological effects on the pathogenesis of neurodegenerative diseases

8.1. Antioxidative function

Cellular aerobic metabolism occurs in mitochondria and is associated with forming free radicals such as ROSs, which can damage DNA and other biological molecules [118,119]. ROSs formation is an effective reaction in neurological and autoimmune disorders, as well as inflammatory and mitochondrial disorders [120]. Biological molecules may be damaged and mutations may occur due to electrophiles, radicals, and the metabolic byproducts that produce in response to oxidative stress [121,122]. Melatonin decrease ROSs formation and has a more potent antioxidant effect than glutathione. Melatonin has a neuroprotective role in aging and pathogenic conditions like MS, AD, and PD due to its antioxidant effect in mitochondrial homeostasis. It promotes the synthesis of glutathione, an antioxidant that inhibits fat peroxidation and cell toxicity. It also improves mitochondrial function by preventing electron leakage and inducing the charge of electrons or enzymes that repair damaged respiratory chains [120,123].

8.2. Mitochondrial regulation

Mitochondrial dysfunction has been reported to be implicated in the pathogenesis of neurodegenerative disorders [124]. Melatonin exerts its effects by optimizing mitochondrial function, as indicated by recent data suggesting the presence of the melatonergic pathway in all cells, not just

those of the pineal gland, and its potential predominance within mitochondria [125]. Melatonin plays a vital role in the protection of mitochondria due to several mechanisms, including a decrease in mitochondrial oxidative stress [126], preservation of mitochondrial membrane potential [127], upregulation of antiapoptotic mitochondrial protein, and downregulation of proapoptotic mitochondrial protein Bax [128], enhancement of ATP synthesis efficiency [129], reduced release of cytochrome C into the cytosol and inhibition of caspase-3 activity [130].

8.3. Circadian rhythm

Recent findings suggest circadian disruption could pose a risk factor for neurological disorders. The circadian rhythm is a natural, internal process that regulates the sleep-wake cycle and other physiological processes in living organisms. Circadian rhythm is a 24-hour cycle that is influenced by some external factors, such as light and temperature. Melatonin plays a vital role in circadian synchronization. The levels of blood melatonin oscillate in 24-hour cycles in close accordance with the external illumination. The activity of the external illumination is subordinated to the central circadian clock located in the suprachiasmatic nucleus. The production of pineal melatonin occurs during the dark phase of the endogenous circadian cycle, and serves as a synchronizing signal for secondary oscillators in peripheral tissues. Although it is described that melatonin is produced by tissues other than the pineal gland, the extent of their involvement in circadian melatonin circulation remains uncertain [131]. Circadian disturbance can adversely affect physiological balance at various levels, including molecular, cellular, organ-system, and whole-organism. Many cerebrovascular incidents exhibit circadian temporal patterns. The circadian system's most robust output rhythms, the sleep-wake cycle, are significantly impacted by neurodegenerative disorders, which may manifest decades before the onset of such disorders and also influence their progression [132].

8.4. Immunomodulatory function

Melatonin can reduce the development of neurological diseases by regulating the immune response. Melatonin has the immune modulating effects due to a complex and multifactorial mechanisms. It is considered an "immune buffer" that can stimulate the immune response during immunosuppression and physiological conditions, while simultaneously downregulating it during inflammation [133]. The primary role of melatonin in maintaining the body's defense system is demonstrated by the results of *in vivo* studies on continuous light exposure or pharmacological inhibition with propranolol, which results in a deprivation of melatonin, showing a noticeable deficiency in both their humoral and cellular immune responses [134]. Furthermore, in both healthy and immunosuppressed models, melatonin has demonstrated the potential to increase the activity of natural killer (NK) cells, monocytes, and the chemotactic response of neutrophils, as well as enhance the functioning of B cells and T helper 1 (Th1) cytokines, while simultaneously reducing the Th2 response [135]. Conversely, in the presence of inflammation, melatonin acts as an inhibitor of neutrophil infiltration [135], decrease the levels of proinflammatory cytokines such as IL-1 β , IL-6, and TNF- α , and induce the release of anti-inflammatory mediators, such as IL-10 [135]. It appears that one of the primary mechanisms through which this effect is achieved is the inhibition of nuclear factor kappa B (NF- κ B). This transcriptional factor controls the expression of a different of inflammatory mediators [136].

9. Conclusion

The gut microbiota plays a crucial role in maintaining overall health. An imbalance of the gut microbial community has been linked to various human illnesses. Melatonin, primarily produced in the GIT, has local and systemic effects and is closely connected to the intestinal microbiota.

The potential connection between melatonin and the MGB axis suggests that the enteric microbiota may play a significant role in brain-related diseases through melatonin modulation in the gut. The gut microbiome is a crucial factor contributed in the pathogenesis of neurodegenerative diseases, including MS, PD, and AD. Melatonin plays a vital role in the pathogenesis of neurodegenerative diseases through its antioxidative, mitochondrial regulation, circadian rhythm, and immunomodulatory functions. Melatonin can diminish the formation of ROS, facilitate the production of glutathione, and exhibit a more potent antioxidative impact than glutathione. It also optimizes mitochondrial function and regulates the circadian rhythm. Melatonin acts as an immune buffer that stimulates the immune response during immunosuppression and downregulates it during inflammation. These findings suggest that melatonin may have therapeutic potential in treating neurodegenerative diseases. The available melatonin levels appear to be significantly influenced by the intestinal environment. Therefore, under situations linked with dysbiosis, melatonin and the gut microbiota seem to coordinate and intensify one another. Thus, maintaining a healthy gut microbiome, reducing inflammation, optimizing melatonin levels, and supporting mitochondrial function may help prevent or slow the progression of MS, PD, and AD. Targeting these interconnected systems provides a promising multi-modal approach for managing and potentially reversing neurodegenerative disease. There is not research(s) on whether people with neurological disorders primarily affect pineal-derived melatonin production or gut-derived melatonin production. It does not seem to be a specific available laboratory method for distinguishing pineal-derived melatonin production from gut-derived melatonin. The design of animal models that be unable to produce pineal-derived melatonin can be useful in identifying the role of gut-derived melatonin in the development of neurological diseases. On the other hand, clinical studies can be done through probiotic and prebiotic interventions to improve the melatonin production and its outcomes in neurological diseases.

Ethical approval

This article does not contain any studies with animals performed by any of the authors.

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CRediT authorship contribution statement

Mina Yekani: Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Investigation, Conceptualization. **Mohammad Yousef Memar:** Writing – review & editing, Writing – original draft, Validation, Supervision, Conceptualization. **Mohammad Taghizadieh:** Writing – review & editing, Writing – original draft, Methodology. **Somayeh Ahmadi:** Writing – review & editing, Writing – original draft, Software. **Alka Hasani:** Writing – review & editing, Writing – original draft. **Elham Mehdizadehfard:** Writing – review & editing, Writing – original draft. **Hadi Feizi:** Writing – review & editing, Writing – original draft. **Javad Khalili Fard:** Writing – review & editing, Writing – original draft. **Masood Ansarin:** Writing – review & editing, Writing – original draft. **Hammed Hamishehkar:** Writing – review & editing, Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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