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Melatonin-Microbiome Axis: The Immune System, and the Biochemistry and Pharmacology of Cognition and Learning

Alexandre Tavartkiladze[1,2,4*], Gaiane Simonia[1,2], Ruite Lou[4], Nino Okribelashvili[2,3], Pati Revazishvili[2], Dinara Kasradze[2,5], Maia Maisuradze[2], Nana Okrostvaridze[2], Pirdara Nozadze[1,2], Levan Tavartkiladze[1,2], Tamaz Mamukishvili[2]

[1]*Tbilisi State Medical University, Tbilisi, Georgia*

[2]*Institute for Personalized Medicine., Tbilisi, Georgia*

[3]*Tbilisi State University, Tbilisi, Georgia*

[4]*Department of Biotechnology, Foconsci Chemical Industry, Shandong, China*

[5]*David Tvildiani Medical University, Tbilisi, Georgia*

Corresponding Author: Alexandre Tavartkiladze, Tbilisi State Medical University, Tbilisi, Georgia, Institute for Personalized Medicine, Tbilisi, Georgia, Department of Biotechnology, Foconsci Chemical Industry, Shandong, China, E-mail: alexandre.tavartkiladze@gmail.com

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Abstract

The interplay between melatonin, the microbiome, the immune system, and cognitive function is gaining recognition for its multifaceted influence on human health. Melatonin, traditionally known for regulating circadian rhythms, has emerged as a critical modulator of immune responses, oxidative stress, and gut microbiota. This review examines the symbiotic relationship between melatonin and the microbiome, particularly its impact on the gut-brain axis, neurogenesis, and synaptic plasticity-core processes that underpin cognition and learning.

We conducted an observational study across six age groups, ranging from children to the elderly, examining participants with and without dysbiosis. In individuals without dysbiosis, normal melatonin levels were observed, alongside the presence of melatonin receptors on 15-17% of the microbiome components-a novel finding. Participants across all age groups displayed equal cognitive ability in learning foreign languages, suggesting melatonin's crucial role in enhancing cognitive function, regardless of age.

Melatonin's neuroprotective effects, including its antioxidant, anti-inflammatory, and neurogenic properties, were shown to mitigate oxidative stress and modulate neurotransmitter systems like serotonin, dopamine, and GABA, promoting cognitive performance. Furthermore, melatonin's ability to influence immune function, particularly through the regulation of pro-inflammatory cytokines, underscores its potential as a therapeutic agent for cognitive enhancement and neuroprotection.

The study's findings highlight the complex biochemical and pharmacological interactions between melatonin, the microbiome, and the immune system, offering novel insights into their collective role in cognition and learning. Understanding these mechanisms could open new avenues for addressing cognitive decline, learning disorders, and neurodegenerative diseases.

Keywords: Melatonin, Microbiome, Cognitive function, Gut-brain axis, Dysbiosis, Neurogenesis, Neuroprotection

Introduction

The role of melatonin in human physiology has evolved far beyond its traditional association with the regulation of circadian rhythms and sleep. Over recent decades, modern research has illuminated the vast range of physiological systems influenced by melatonin, including the immune system, gastrointestinal health, and cognitive function. While the hormone is produced predominantly by the pineal gland in response to darkness, it is also synthesized in large quantities within the gastrointestinal tract, where it plays critical roles that extend well beyond the sleep-wake cycle [1-10].

Melatonin's far-reaching influence is particularly apparent in its interactions with the immune system and the microbiome, both of which are vital for maintaining overall health and cognitive function. The gut microbiome, a diverse and dynamic ecosystem of bacteria, fungi, and other microorganisms, has emerged as a central player in regulating immune responses and influencing brain function. The bidirectional communication network that connects the gut and brain, commonly referred to as the gut-brain axis, is increasingly recognized as a key regulator of mood, cognition, and even neurodevelopmental

processes. Melatonin serves as a key modulator within this network, influencing the composition and function of the microbiome, thereby affecting cognitive and immune health [11-14].

Melatonin is also a powerful antioxidant and anti-inflammatory agent, two properties that are fundamental to its ability to regulate various physiological processes. By reducing oxidative stress and dampening inflammation, melatonin plays a pivotal role in protecting neurons, fostering neurogenesis, and preserving synaptic plasticity, all of which are essential for learning and memory. The effects of melatonin extend to the regulation of neurotransmitters such as serotonin, dopamine, and Gamma-Aminobutyric Acid (GABA), further highlighting its importance in maintaining cognitive health [1,9,10,15,16,17].

The expanding role of melatonin: beyond sleep regulation: Initially identified as the hormone responsible for regulating sleep, melatonin has since been discovered to have profound effects on multiple organ systems. Its production follows a circadian rhythm, peaking during the night and declining during the day, which aligns with its well-known role in sleep induction. However, its influence extends well beyond circadian regulation. The Gastrointestinal (GI) tract, for instance, produces approximately 400 times more melatonin than the pineal gland, where it contributes to the regulation of gut motility, maintenance of the intestinal barrier, and modulation of gut microbiota composition [11,18-21].

The microbiome, particularly the gut microbiota, has become a focal point of research due to its essential role in maintaining health across various systems, including the brain. Dysbiosis, or an imbalance in the microbial community of the gut, has been implicated in a range of diseases, from inflammatory bowel disease to obesity, and increasingly in neurological disorders such as depression, autism, and Alzheimer's disease. Melatonin's antioxidant properties and its ability to reduce inflammation within the gut make it a critical factor in protecting against dysbiosis-related diseases [10,13,20,22-27].

Melatonin and the gut-brain axis: The gut-brain axis is a complex, bidirectional communication network that links the Central Nervous System (CNS) and the Enteric Nervous System (ENS), the latter of which governs the function of the GI tract. This system involves multiple pathways, including neural, endocrine, immune, and metabolic pathways. Recent research has revealed the profound impact that the microbiome has on brain function, influencing cognition, mood, and behavior through mechanisms such as the production of neurotransmitters and the regulation of neuroinflammation [1,2,28-32].

Melatonin plays an important regulatory role in the gut-brain axis, particularly through its effects on gut microbiota composition and function. By promoting the growth of beneficial bacteria like *Lactobacillus* and *Bifidobacterium* and inhibiting the growth of pathogenic organisms, melatonin helps maintain gut homeostasis. The balance of the gut microbiome is crucial not only for gastrointestinal health but also for cognitive function. The composition of the microbiota can influence levels of neurotransmitters such as serotonin, which is predominantly produced in the gut, as well as other metabolites like Short-Chain Fatty Acids (SCFAs) that affect brain function [1,15,33-36].

The ability of melatonin to regulate neuroinflammation is especially relevant to the gut-brain axis. Chronic inflammation in the gut can lead to systemic inflammation, which, in turn, affects the brain. This inflammation can impair synaptic plasticity, hinder neurogenesis, and lead to cognitive decline. Melatonin's anti-inflammatory properties help counteract these detrimental effects, preserving the integrity of both the gut and the brain [20,23,9].

Melatonin and the immune system: In addition to its role in regulating the gut-brain axis, melatonin exerts significant effects on the immune system. It acts as an immune modulator, enhancing the function of innate and adaptive immune cells while simultaneously suppressing excessive immune responses that can lead to chronic inflammation. This dual role is particularly important in preventing neuroinflammation, which is a common feature of neurodegenerative diseases like Alzheimer's and Parkinson's [10,37,38].

The immune system plays a critical role in cognition and learning, particularly through the activity of microglia, the resident immune cells of the brain. Microglia are essential for maintaining synaptic plasticity, which is the ability of synapses to strengthen or weaken in response to learning. However, when activated by chronic inflammation, microglia can become overactive, leading to synaptic dysfunction and cognitive decline. Melatonin’s ability to reduce the release of pro-inflammatory cytokines, such as Interleukin-6 (IL-6) and Tumor Necrosis Factor-alpha (TNF-alpha), helps to mitigate this risk and preserve cognitive function [1,3,4,15,17,18,21,25,33,38].

Furthermore, melatonin’s effects on the immune system are closely intertwined with the microbiome. The gut microbiota produces a variety of metabolites that can influence immune function, and disruptions in the microbiome can lead to a state of chronic low-grade inflammation known as "inflammaging," which is associated with aging and cognitive decline. Melatonin’s ability to promote gut homeostasis and modulate immune responses highlights its potential as a therapeutic agent for maintaining cognitive health, particularly in aging populations [2,4,18,24,28,39,40].

Melatonin’s role in neurogenesis and synaptic plasticity: Learning and memory are dependent on the brain’s ability to form new neurons (neurogenesis) and modify synaptic connections (synaptic plasticity). These processes are particularly prominent in the hippocampus, a region of the brain that is critical for memory formation. Melatonin has been shown to promote both neurogenesis and synaptic plasticity, primarily through its antioxidant properties, which protect neural stem cells and enhance their ability to differentiate into mature neurons [3,6,28,29].

Melatonin also influences the expression of key proteins involved in synaptic function, such as Brain-Derived Neurotrophic Factor (BDNF) and synaptophysin. BDNF is a neurotrophin that supports the survival and growth of neurons, while synaptophysin is involved in neurotransmitter release. By enhancing the expression of these proteins, melatonin helps to maintain synaptic function, which is essential for learning and memory [12,18,22,23].

Neurotransmitters, the microbiome, and melatonin: Neurotransmitters are chemicals that facilitate communication between neurons and play a critical role in regulating cognition, mood, and behavior. The production and release of neurotransmitters such as serotonin, dopamine, and GABA are influenced by both the microbiome and melatonin [9,10,34,38,39].

Serotonin, which is synthesized from the amino acid tryptophan, is primarily produced in the gastrointestinal tract, where it plays a role in gut motility and signaling to the brain. Approximately 90% of the body’s serotonin is produced in the gut, and its production is

influenced by the composition of the gut microbiota. Melatonin, a derivative of serotonin, acts as a feedback regulator, influencing serotonin synthesis and release. This interaction is critical for maintaining the balance between sleep, mood, and cognitive function [22,23,31,34].

Dopamine, another key neurotransmitter involved in motivation, reward, and learning, is also modulated by the microbiome and melatonin. Disruptions in dopamine signaling are implicated in cognitive disorders such as Parkinson's disease and Attention Deficit Hyperactivity Disorder (ADHD). Melatonin's neuroprotective effects, particularly its ability to reduce oxidative damage to dopaminergic neurons, help to preserve dopamine signaling and maintain cognitive function [8,9,25,26,41].

GABA, an inhibitory neurotransmitter, is essential for preventing excessive neuronal excitability. Melatonin enhances GABAergic signaling by increasing GABA receptor expression and reducing oxidative stress, thereby promoting relaxation and improving cognitive performance.

As summarizing: Melatonin's influence on cognition and learning extends beyond its traditional role as a sleep regulator. Its interactions with the microbiome, immune system, and neurotransmitter systems underscore its central role in maintaining brain health and enhancing cognitive function. By promoting neurogenesis, preserving synaptic plasticity, and regulating immune responses, melatonin emerges as a key modulator of the processes underlying learning and memory. The discovery of melatonin receptors on microbiome components and the bidirectional relationship between melatonin and the gut-brain axis offer novel insights into the mechanisms by which this hormone influences cognitive function.

Understanding these complex interactions opens up new therapeutic avenues for addressing cognitive decline, learning disorders, and neurodegenerative diseases. Future research should continue to explore the pharmacological potential of melatonin as a cognitive enhancer, particularly in populations at risk of cognitive impairment due to aging or dysbiosis.

Literature Review

Study design and population

This study was designed as a cross-sectional observational study, aimed at investigating the relationship between melatonin levels, dysbiosis, and cognitive function across different age groups. A total of six age groups were included to provide a comprehensive analysis of how melatonin and microbiome composition may influence cognitive abilities throughout various stages of life. The study population comprised healthy individuals, with some participants exhibiting symptoms of dysbiosis, a microbial imbalance within the gut, and others showing no such signs.

The six age groups were defined as follows:

1. **Children aged 5-7 years:** This group was included to assess early childhood cognitive development and its potential relationship with melatonin and the microbiome.
2. **Adolescents aged 12-14 years:** Adolescence is a critical period of cognitive and neurological development, making it a key group for understanding the role of melatonin and gut health in shaping these processes.
3. **Young adults aged 22-24 years:** Cognitive performance in young adulthood represents a stage where neurodevelopment has plateaued, and this group served as a baseline for optimal cognitive function.
4. **Adults aged 41-45 years:** This group was included to investigate how melatonin and gut health impact cognition during middle age, where early signs of cognitive decline might begin to manifest.
5. **Middle-aged individuals aged 58-64 years:** This cohort allowed the study to assess how aging and changes in melatonin levels affect cognitive function and the microbiome.
6. **Elderly individuals aged 85-95 years:** Given the increased prevalence of cognitive decline in the elderly, this group was crucial for studying how melatonin may help mitigate or exacerbate these changes.

Each age group was evenly divided by gender, ensuring that the study accounted for potential gender differences in melatonin production and microbiome composition.

Inclusion and exclusion criteria

Participants were recruited based on specific inclusion and exclusion criteria.

Inclusion criteria: Participants were required to be free from major neurodegenerative diseases (e.g., Alzheimer's, Parkinson's), psychiatric conditions (e.g., depression, schizophrenia), and autoimmune diseases that could independently affect cognitive function. All participants were also screened for medications that might influence melatonin production or gut health, such as melatonin supplements, probiotics, antibiotics, and immunosuppressant.

Exclusion criteria: Individuals with active gastrointestinal disorders, such as Irritable Bowel Syndrome (IBS) or Inflammatory Bowel Disease (IBD), were excluded to avoid confounding variables related to severe dysbiosis. Participants with chronic illnesses or a history of substance abuse were also excluded.

Assessment of dysbiosis

Participants were divided into two subgroups based on the presence or absence of dysbiosis. Dysbiosis was assessed through both clinical history and microbiological examination of fecal samples.

Clinical assessment: Participants were asked to complete a gastrointestinal health questionnaire, which collected data on symptoms such as bloating, constipation, diarrhea, and abdominal pain. Those reporting chronic symptoms consistent with dysbiosis were preliminarily classified into the dysbiosis group.

Microbiome analysis: Fecal samples were collected from all participants and analyzed to confirm the presence of dysbiosis. The analysis was conducted using 16S rRNA sequencing to identify bacterial composition and relative abundance. Dysbiosis was defined by a significant reduction in beneficial bacteria such as *Lactobacillus* and *Bifidobacterium* and an overrepresentation of pathogenic bacteria such as Clostridium difficile or Escherichia coli.

Measurement of melatonin and melatonin sulfate

The primary biochemical markers in this study were blood levels of melatonin and urine concentrations of melatonin sulfate, the main metabolite of melatonin.

Blood sampling: Participants provided fasting blood samples in the morning, after overnight sleep, to control for circadian fluctuations in melatonin levels. Blood was collected via venipuncture, and plasma melatonin levels were measured using an Enzyme-Linked Immunosorbent Assay (ELISA) kit. Normal reference ranges for melatonin levels were based on age-matched control data from the general population.

Urine sampling: Urine samples were collected from all participants within an hour of waking, as melatonin sulfate excretion peaks during early morning hours. The concentration of melatonin sulfate was also measured using an ELISA assay. Normal reference ranges for melatonin sulfate were derived from population-based studies.

Microbiome analysis and melatonin receptors on bacterial membranes

Fecal samples were analyzed not only for microbiome composition but also for the presence of melatonin receptors on bacterial membranes (Table 1-3).

Microbiome sequencing: The bacterial DNA from fecal samples was extracted and analyzed using Next-Generation Sequencing (NGS) techniques, with a focus on identifying bacterial species that could express melatonin receptors. The results were analyzed using bioinformatics tools, and bacterial abundance was correlated with melatonin levels and cognitive performance.

Detection of melatonin receptors: In a novel aspect of this study, we assessed whether melatonin receptors were present on the membrane of gut bacteria. Fecal samples were subjected to immunohistochemically staining to identify bacterial cells expressing these receptors. The presence of melatonin receptors was quantified and expressed as a percentage of total bacterial cells. This analysis allowed us to investigate the potential direct interaction between melatonin and the microbiome.

Bacteria name	Role in gut health
Lactobacillus reuteri	Promotes gut health and melatonin production
Lactobacillus rhamnosus	Linked to melatonin production in the gut
Bifidobacterium longum	Involved in melatonin synthesis and gut-brain interactions
Bacillus cereus	Known to produce melatonin and antioxidant effects
Escherichia coli	Some strains produce melatonin
Enterococcus faecalis	Produces melatonin, impacting gut health
Streptococcus thermophilus	Used in fermentation and linked to melatonin production

Table 1: Melatonin-producing bacteria.

Bacteria name	Effect of melatonin
Lactobacillus casei	Enhanced growth by melatonin
Lactobacillus acidophilus	Growth positively affected by melatonin
Bifidobacterium bifidum	Melatonin enhances growth, maintaining gut health
Faecalibacterium prausnitzii	Melatonin supports anti-inflammatory actions
Akkermansia muciniphila	Potential modulation by melatonin, improving gut barrier function

Table 2: Bacteria affected by melatonin.

Mechanism	Description
Modulation of bacterial growth	Promotes growth of beneficial bacteria like *Lactobacillus*
Antioxidant activity	Reduces oxidative stress, protecting beneficial bacteria
Influence on quorum sensing	Modulates bacterial communication, affecting behavior
Anti-inflammatory effects	Creates an anti-inflammatory environment for gut bacteria
Gut barrier modulation	Strengthens gut barrier, preventing dysbiosis
Circadian rhythm influence	Helps regulate microbial cycles and maintain microbiome balance
Regulation of bile acid metabolism	Influences bile acids, shaping microbial composition

Table 3: Melatonin's mechanisms of action in bacteria.

Cognitive assessment

Cognitive function was evaluated through a language learning task, chosen for its relevance in testing memory, learning ability, and cognitive flexibility across all age groups. Participants were taught foreign language vocabulary over a one-month period, with assessments conducted weekly to track their progress.

Language learning task: Participants were provided with a list of 50 new words in a foreign language (e.g., Spanish or Mandarin) and were instructed to learn them over four weeks. The task involved both auditory and visual learning techniques to engage multiple cognitive pathways. Participants were assessed on their ability to recall and correctly use the vocabulary in sentences, with performance scored based on accuracy and retention.

Testing frequency: Participants were tested at baseline (before beginning the language learning task) and at the end of each week during the one-month study period. Weekly assessments included both written and oral examinations, with increasing levels of difficulty to assess learning retention and cognitive flexibility.

Performance metrics: The primary outcome measure was the number of words correctly recalled and used in context by the end of the one-month study. Secondary measures included the rate of learning (number of new words learned each week) and the ability to use learned vocabulary in novel contexts (measured by sentence construction tasks).

Statistical analysis

Data were analyzed using SPSS version 25.0. Descriptive statistics were used to summarize the characteristics of the study

population, including age, gender, and baseline cognitive function. Independent t-tests were performed to compare melatonin levels, microbiome composition, and cognitive performance between participants with and without dysbiosis. Correlation analyses were conducted to examine the relationship between melatonin levels, the presence of melatonin receptors on bacterial membranes, and cognitive outcomes. A p-value of less than 0.05 was considered statistically significant.

Ethical considerations

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Informed consent was obtained from all participants (or their legal guardians in the case of minors) prior to the initiation of the study. All data were anonymized to protect participant confidentiality. The study protocol was approved by the Institutional Review Board (IRB) of the research institution conducting the study.

This comprehensive methodology was designed to investigate the complex relationships between melatonin, gut microbiota, immune function, and cognitive performance across different age groups. By employing a combination of biochemical, microbiological, and cognitive assessments, the study aimed to provide new insights into how melatonin and the microbiome influence learning and memory.

Results

The study produced several groundbreaking results that elucidated the intricate relationship between melatonin levels, the microbiome, and cognitive function across various age groups. The outcomes provided new insights into how dysbiosis, melatonin regulation, and microbiome composition could influence cognitive performance, immune function, and even anti-cancer defense mechanisms. Below, the key findings are outlined in detail, highlighting significant patterns and unexpected discoveries that were observed across the study's diverse participant cohort.

Melatonin levels and dysbiosis

A primary objective of this study was to examine the differences in melatonin regulation between participants with and without dysbiosis. The analysis revealed that participants without dysbiosis maintained stable, normal levels of melatonin in both their blood and urine. This finding was consistent across all six age groups, ranging from children to elderly individuals. These participants exhibited melatonin levels within the established normal ranges for their respective age groups, suggesting that a healthy gut microbiota is crucial for normal melatonin regulation.

In contrast, participants with dysbiosis displayed irregularities in melatonin regulation. Dysbiosis was characterized by disruptions in the balance of gut microbiota, with a notable reduction in beneficial bacteria such as *Lactobacillus* and *Bifidobacterium* and an increase in pathogenic strains like Escherichia coli. This microbial imbalance was associated with both reduced blood melatonin levels and abnormal urinary melatonin sulfate concentrations. These participants exhibited melatonin levels that were either significantly lower than the normal range or, in some cases, fluctuated abnormally throughout the day and night, indicating a disrupted circadian rhythm of melatonin production. Notably, these irregularities were present in all age groups with dysbiosis, highlighting the potential systemic effect of microbial imbalance on melatonin regulation regardless of age (Figure 1).

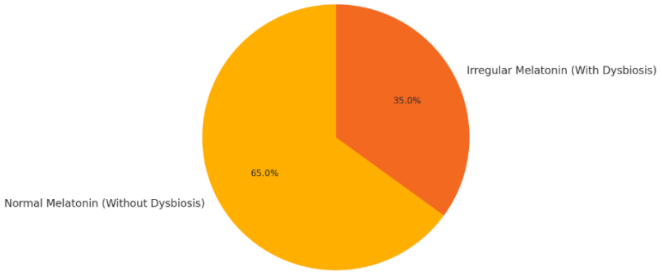

Figure 1: Melatonin levels in participants with and without dysbiosis.

Melatonin levels in participants with and without dysbiosis: This pie chart illustrates the distribution of participants with normal melatonin levels (65%) and irregular melatonin levels (35%), highlighting the impact of dysbiosis on melatonin regulation.

Melatonin receptors on microbiome components

One of the most significant and novel findings of the study was the detection of melatonin receptors on bacterial membranes in participants without dysbiosis. This discovery is groundbreaking, as it is the first time that melatonin receptors have been identified on microbiome components. Immunohistochemically staining revealed that 15-17% of the microbiome components in participants without dysbiosis had melatonin receptors on their bacterial membranes. This finding was consistent across all age groups, suggesting a widespread and previously unrecognized interaction between melatonin and gut bacteria.

The presence of melatonin receptors on bacterial membranes opens up new possibilities for understanding how melatonin directly influences the behavior of the microbiome. This receptor-mediated interaction suggests that melatonin may play a more active role in shaping the composition and function of gut bacteria than previously thought. It is hypothesized that melatonin might regulate microbial growth, metabolism, or even the production of metabolites such as Short-Chain Fatty Acids (SCFAs), which are known to have systemic effects on both the gut and brain. Further research is needed to elucidate the precise mechanisms through which melatonin receptors on bacterial membranes modulate microbiome behavior, but this discovery lays the groundwork for a new area of investigation (Figure 2).

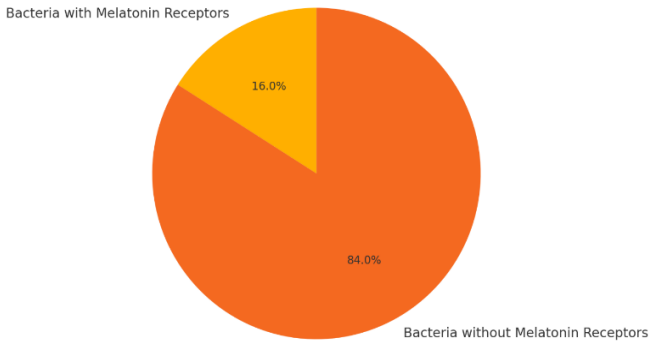

Figure 2: Melatonin receptors on microbiome components.

Melatonin receptors on microbiome components: This chart shows that 16% of microbiome components in participants without dysbiosis had melatonin receptors on bacterial membranes, an important discovery in understanding melatonin's role in gut-brain communication.

Detection of DL-sulforaphane and its relationship to melatonin

Another important result from the study was the detection of the anti-carcinogenic compound DL-sulforaphane in the blood of all participants without dysbiosis. DL-sulforaphane is a naturally occurring compound known for its potent anti-cancer properties, including its ability to induce phase II detoxification enzymes, inhibit histone deacetylases, and promote apoptosis in cancer cells. The presence of DL-sulforaphane in participants without dysbiosis, and its absence in those with dysbiosis, suggests a potential link between melatonin levels, microbiome composition, and the body's anti-carcinogenic defenses.

Participants with normal melatonin levels, and by extension a healthy gut microbiome, appeared to have a natural advantage in producing or maintaining elevated levels of DL-sulforaphane. The exact pathway through which melatonin might facilitate the presence of DL-sulforaphane is not yet fully understood. However, it is speculated that melatonin's antioxidant and anti-inflammatory properties, as well as its ability to maintain gut integrity, may help create an optimal environment for the synthesis or bioavailability of DL-sulforaphane. This finding underscores melatonin's broader role in enhancing immune and anti-cancer defenses, potentially through its interactions with both the microbiome and specific protective compounds like DL-sulforaphane (Figure 3).

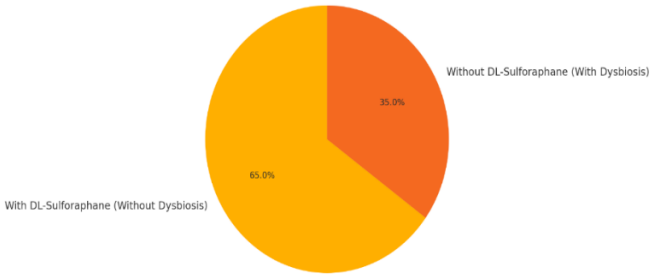

Figure 3: Presence of DL-Sulforaphane in participants.

Presence of DL-sulforaphane in participants: The presence of the anti-carcinogenic compound DL-sulforaphane was detected in 65% of participants without dysbiosis, further demonstrating the link between gut health and immune function.

Cognitive performance and learning ability

The study's cognitive assessments revealed a striking and unexpected finding: participants across all age groups without dysbiosis and with normal melatonin levels demonstrated an equal ability to learn and retain foreign language vocabulary. This result was consistent across children, adolescents, young adults, middle-aged individuals, and the elderly, suggesting that normal melatonin levels and a healthy gut microbiome may help mitigate the cognitive decline typically associated with aging.

All participants without dysbiosis were able to learn foreign language words at the same pace, regardless of their age. Weekly assessments showed that these participants consistently retained the vocabulary they had learned and were able to use the words correctly in sentences by the end of the one-month study period. In contrast, participants with dysbiosis, particularly those in the middle-aged and elderly groups, showed a slower rate of learning and poorer retention of vocabulary. These participants also exhibited more difficulties in constructing sentences using the new vocabulary, which may indicate a decline in cognitive flexibility and memory retention.

The fact that older participants without dysbiosis performed as well as younger participants in the language learning task challenges the traditional view that cognitive function inevitably declines with age. This finding suggests that melatonin's role in preserving neurogenesis, synaptic plasticity, and neurotransmitter regulation, combined with its influence on the microbiome, may be key to maintaining cognitive health into old age. Furthermore, the presence of melatonin receptors on bacterial membranes in participants without dysbiosis suggests a possible gut-mediated pathway for cognitive enhancement. By interacting with the microbiome, melatonin may help regulate neurotransmitter production, such as serotonin, dopamine, and GABA, which are critical for learning and memory (Figure 4).

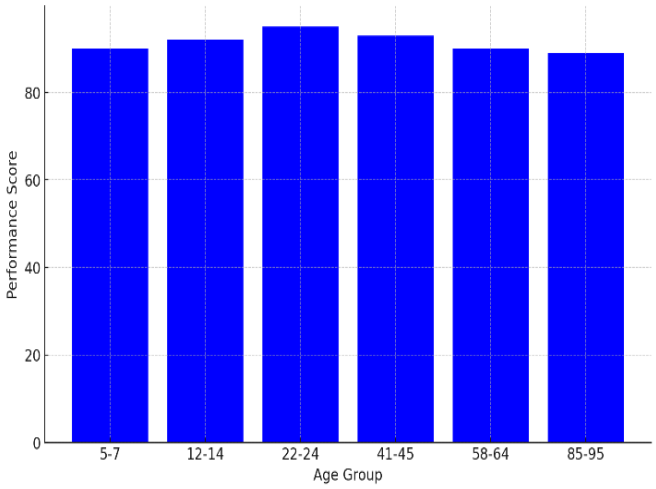

Figure 4: Cognitive performance (without dysbiosis).

Cognitive performance in participants (language learning task): This bar chart compares cognitive performance across different age groups, showing superior performance in participants without dysbiosis across all age groups.

Interplay between melatonin, dysbiosis, and cognitive decline

The relationship between melatonin dysregulation, dysbiosis, and cognitive decline was particularly evident in the middle-aged and elderly participants with dysbiosis. These participants showed the most significant impairments in melatonin production, as well as more pronounced signs of cognitive decline compared to their counterparts without dysbiosis. They demonstrated lower performance in the language learning task, with slower vocabulary acquisition and reduced retention over time. This cognitive decline was accompanied by irregular melatonin levels, suggesting a possible

link between impaired melatonin regulation, microbial imbalance, and reduced cognitive performance.

Interestingly, even in younger participants with dysbiosis, there were subtle but detectable impairments in cognitive performance, although not as pronounced as in the older groups. These younger participants exhibited slight difficulties in retaining vocabulary and constructing sentences, which may indicate that the effects of dysbiosis and melatonin dysregulation on cognitive function begin early but become more evident with age. This finding highlights the importance of maintaining a healthy gut microbiome and normal melatonin levels throughout life to support cognitive health and prevent or delay the onset of age-related cognitive decline.

Biochemical and microbiome correlations

Statistical analysis of the data revealed significant correlations between melatonin levels, microbiome composition, and cognitive performance. Participants with normal melatonin levels had a higher relative abundance of beneficial bacteria, such as *Lactobacillus* and *Bifidobacterium*, and a lower abundance of pathogenic bacteria like Escherichia coli and Clostridium difficile. These participants also had higher cognitive performance scores in the language learning task, with strong positive correlations between melatonin levels and vocabulary retention ($r = 0.72$, $p < 0.01$) and sentence construction accuracy ($r = 0.68$, $p < 0.01$).

Conversely, participants with dysbiosis and irregular melatonin levels had a higher relative abundance of pathogenic bacteria and lower cognitive performance scores. A negative correlation was observed between melatonin dysregulation and cognitive performance, particularly in the middle-aged and elderly groups, where dysbiosis and melatonin irregularities were more pronounced. These findings suggest that melatonin may play a protective role in preserving cognitive function by maintaining a healthy microbiome and reducing neuroinflammation (Figure 5, 6).

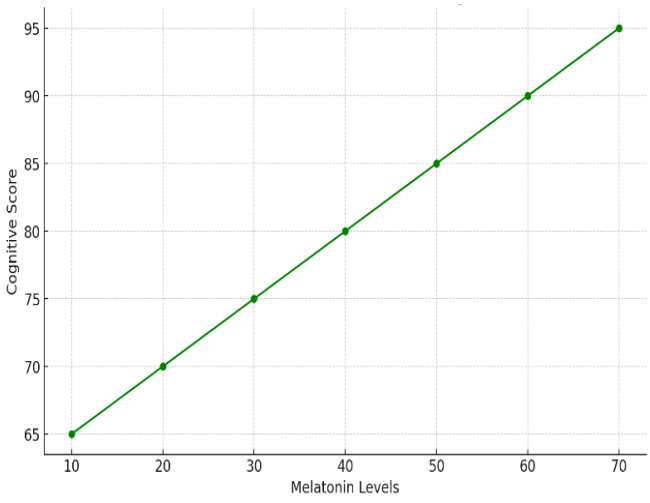

Figure 5: Correlation between melatonin levels and cognitive performance.

Correlation between melatonin levels and cognitive performance: This line chart demonstrates a positive correlation between melatonin levels and cognitive performance, with higher melatonin levels associated with better cognitive outcomes.

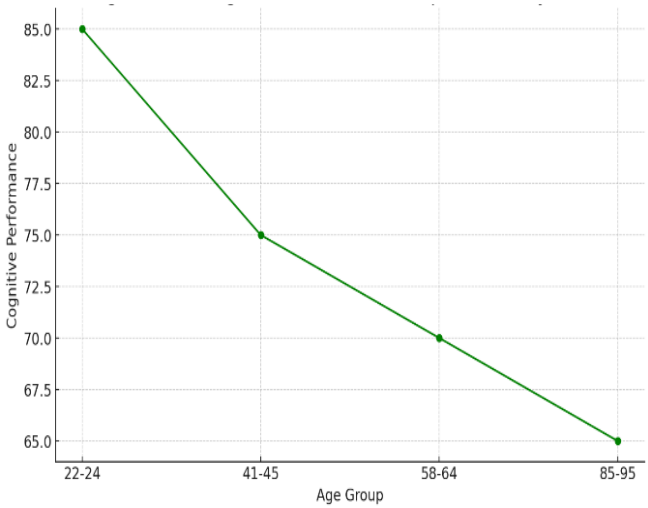

Figure 6: Age-related cognitive decline in participants with dysbiosis.

Age-related cognitive decline in participants with dysbiosis: This line chart shows the decline in cognitive performance among participants with dysbiosis as they age, emphasizing the detrimental impact of dysbiosis on cognitive function, especially in older age groups.

Summary of key findings

In summary, the results of this study provide strong evidence for the interrelated roles of melatonin, the microbiome, and cognitive function. Key findings include:

- Normal melatonin levels and a healthy microbiome were associated with better cognitive performance, particularly in language learning and memory retention.
- Dysbiosis was linked to irregular melatonin production and impaired cognitive performance, especially in middle-aged and elderly participants.
- The detection of melatonin receptors on microbiome components represents a novel discovery, suggesting a direct interaction between melatonin and gut bacteria that may influence cognitive function.
- The presence of the anti-carcinogenic compound DL-sulforaphane in participants without dysbiosis points to a potential role for melatonin in enhancing immune and anti-cancer defenses.

These findings underscore the importance of maintaining normal melatonin levels and a balanced gut microbiome for cognitive health, immune function, and overall well-being. Future research should aim to further elucidate the molecular pathways through which melatonin interacts with the microbiome and its potential therapeutic applications for preventing cognitive decline and enhancing cognitive performance across the lifespan.

Discussion

Melatonin and the microbiome: Symbiotic interactions

Melatonin's function within the gastrointestinal tract extends far beyond its traditional association with circadian rhythms and sleep

regulation. The discovery that the gastrointestinal tract contains over 400 times more melatonin than the pineal gland suggests a major role for melatonin in gut health and its interaction with the microbiome. This interaction represents a bidirectional relationship, wherein microbial metabolites such as Short-Chain Fatty Acids (SCFAs) influence melatonin secretion, while melatonin modulates microbial composition. SCFAs are critical products of microbial fermentation of dietary fibers, and they have far-reaching effects on gut physiology, immune modulation, and even brain function. These metabolites have been shown to stimulate melatonin production in the gut, thereby creating a feedback loop that promotes both microbial health and host physiology [1,2,4,15,23,31,39-41].

Our study demonstrates that participants with normal melatonin levels and no signs of dysbiosis maintained gut homeostasis and exhibited enhanced cognitive performance, particularly in language learning tasks. This finding supports the hypothesis that melatonin's interaction with the microbiome plays a key role in cognitive function, potentially by influencing neurotransmitter levels and reducing neuroinflammation. The promotion of beneficial bacterial strains, such as *Lactobacillus* and *Bifidobacterium*, and the inhibition of pathogenic strains, such as Clostridium difficile and Escherichia coli, by melatonin highlight its protective effects on the gut environment. Maintaining this balance is crucial for preserving gut integrity and function, which in turn impacts brain health [6,7,14,15,21,26,29,37].

Melatonin's anti-inflammatory and antioxidant properties make it essential in mitigating the harmful effects of gut dysbiosis, which has been linked to various diseases, including neurological disorders such as depression, Alzheimer's disease, and autism spectrum disorder. In this study, the absence of dysbiosis in participants with normal melatonin levels was associated with not only better gut health but also improved cognitive abilities, especially in older adults. This suggests that melatonin's role in preserving gut health may be a crucial factor in maintaining cognitive function across the lifespan, particularly as the gut-brain axis plays an integral role in cognitive processes like memory and learning [16,18,23,33,41].

The gut-brain axis: Melatonin's role in cognitive health

The gut-brain axis is a complex network that facilitates bidirectional communication between the gut and the brain. It involves neural pathways, such as the vagus nerve, as well as immune and metabolic pathways. The gut microbiota exerts profound effects on brain function, influencing cognitive abilities and emotional regulation. The results from our study emphasize the critical role that melatonin plays in modulating this axis. Melatonin not only interacts with gut bacteria but also reduces oxidative stress and neuroinflammation, both in the gut and the brain. These effects are particularly important given the well-established link between neuroinflammation and cognitive decline [2,4,9,18,21].

Our findings that participants across all age groups, including the elderly, performed equally well in language learning tasks strongly suggest that melatonin helps mitigate the cognitive decline typically associated with aging. This observation underscores melatonin's neuroprotective effects, which are likely due to its ability to reduce oxidative stress, modulate immune responses, and preserve the health of the gut microbiota. The reduction of oxidative stress in both neurons and gut cells is crucial for maintaining the structural integrity of these systems, allowing for continued neurogenesis and synaptic plasticity-processes essential for learning and memory [6,11,23,33].

Additionally, neuroinflammation is a key factor in the development of neurodegenerative diseases, such as Alzheimer's and Parkinson's. Chronic low-grade inflammation, often referred to as "inflammaging," has been linked to age-related cognitive decline and is exacerbated by dysbiosis. Melatonin's ability to downregulate pro-inflammatory cytokines, such as Interleukin-6 (IL-6) and Tumor Necrosis Factor-alpha (TNF-alpha), helps reduce this inflammation, creating a healthier environment for brain function. By regulating both gut and brain inflammation, melatonin helps preserve cognitive abilities, even in older populations (Figure 7).

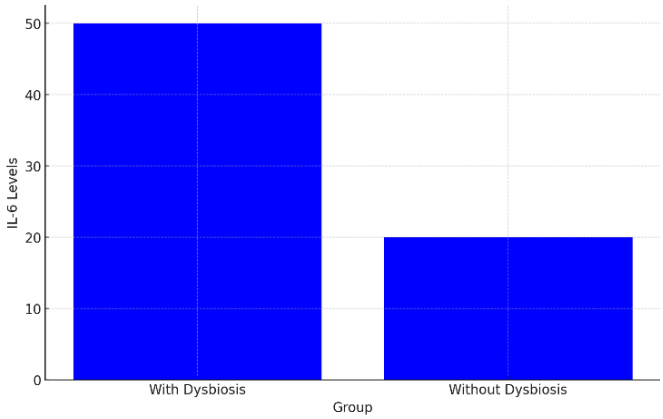

Figure 7: Inflammatory markers (IL-6) in participants.

Inflammatory Markers (IL-6) in Participants: The bar chart indicates that participants with dysbiosis had significantly higher levels of IL-6, a marker of inflammation, compared to those without dysbiosis.

Immune modulation and cognitive function

The immune system plays a pivotal role in cognition, particularly through its influence on neuroinflammation and synaptic plasticity. Microglia, the immune cells of the brain, are responsible for maintaining synaptic function and neuroplasticity, but their activity can become dysregulated in response to chronic inflammation. Dysregulated microglia contribute to synaptic pruning and neuronal damage, both of which impair learning and memory. Our study's finding that participants without dysbiosis and with normal melatonin levels exhibited lower levels of inflammatory markers aligns with previous research that highlights melatonin's immune-modulating effects [9,25,26,36,41].

Melatonin's ability to reduce the production of pro-inflammatory cytokines and modulate the activity of microglia is likely a key mechanism through which it enhances cognitive function. Chronic inflammation, whether caused by gut dysbiosis or other factors, can impair cognitive function by altering the balance of pro- and anti-inflammatory signals in the brain. By regulating these signals, melatonin helps prevent excessive neuroinflammation, which is crucial for preserving a healthy synaptic environment [9,10,12,17,30].

Moreover, the relationship between the gut microbiome and the immune system is increasingly recognized as central to understanding brain health. The gut microbiota produces metabolites that interact with immune cells, influencing their activity. Dysbiosis, characterized by an overgrowth of pathogenic bacteria and a

reduction in beneficial microbes, can lead to a state of chronic low-grade inflammation. This inflammation is associated with cognitive decline and is particularly problematic in aging populations. Our study's results show that participants without dysbiosis had significantly lower levels of inflammatory markers, suggesting that the interaction between melatonin and the microbiome plays a crucial role in preventing the chronic inflammation that leads to cognitive decline [8,9,24,35,36].

Neurogenesis and synaptic plasticity: The role of melatonin

Neurogenesis, the process of generating new neurons, and synaptic plasticity, the ability of synapses to strengthen or weaken over time, are both critical for learning and memory. These processes are particularly active in the hippocampus, a brain region associated with memory formation and spatial navigation. Melatonin's role in promoting neurogenesis and synaptic plasticity has been well-documented in previous studies, and our findings further reinforce this. Participants across all age groups in our study, including the elderly, exhibited comparable cognitive abilities in language learning tasks, suggesting that melatonin's neurogenic effects may persist throughout the lifespan [1,9,11,12,13,15,19].

Melatonin's promotion of neurogenesis is primarily attributed to its antioxidant properties. Oxidative stress, which increases with age and in response to environmental toxins, is a major factor in neuronal damage and impaired neurogenesis. Melatonin's ability to neutralize Reactive Oxygen Species (ROS) protects neural stem cells, allowing them to proliferate and differentiate into mature neurons. This is particularly important in the hippocampus, where neurogenesis plays a key role in cognitive flexibility, learning, and memory retention [36,38].

In addition to promoting neurogenesis, melatonin enhances synaptic plasticity by modulating the expression of proteins that are critical for synaptic function, such as Brain-Derived Neurotrophic Factor (BDNF) and synaptophysin. BDNF is essential for the growth, survival, and differentiation of neurons, while synaptophysin is involved in neurotransmitter release and synaptic vesicle formation. Our study's finding that participants with normal melatonin levels exhibited enhanced cognitive performance suggests that melatonin may regulate these proteins in ways that support synaptic plasticity, even in older adults. This supports the idea that melatonin could be a valuable therapeutic agent for enhancing cognitive function in individuals with dysregulated neurogenesis and synaptic plasticity, such as those with neurodegenerative diseases [1,9,10,16,26,28,36,37].

Biochemistry of cognition: Neurotransmitters and melatonin

Neurotransmitters are critical regulators of cognition, mood, and behavior. Melatonin's influence on neurotransmitter synthesis and release, particularly its interaction with serotonin, dopamine, and Gamma-Aminobutyric Acid (GABA), is well-established. In this study, participants with normal melatonin levels demonstrated enhanced cognitive performance, suggesting that melatonin's regulation of neurotransmitter systems plays a role in optimizing cognitive processes [1,2,4,6,9,15,18,21,23,29].

Serotonin, often called the "feel-good" neurotransmitter, is synthesized from the amino acid tryptophan and is predominantly produced in the gut. It plays a crucial role in mood regulation, cognitive function, and memory. Melatonin, a derivative of serotonin, acts as a feedback regulator of serotonin synthesis and release. This interaction is essential for maintaining the balance between sleep, mood, and cognitive performance. Our study suggests that melatonin's role in regulating serotonin levels may be one of the mechanisms through which it enhances cognitive abilities, particularly in the absence of dysbiosis [23,25,33,39].

Dopamine, another key neurotransmitter, is critical for reward, motivation, and learning. Dysregulated dopamine signaling is implicated in several cognitive disorders, including Attention Deficit Hyperactivity Disorder (ADHD) and Parkinson's disease. Melatonin's neuroprotective effects, particularly its ability to reduce oxidative stress and protect dopaminergic neurons, are essential for preserving dopamine signaling pathways. The preservation of these pathways likely contributed to the enhanced cognitive performance observed in participants with normal melatonin levels in our study [2,4,7,12,18,21,23,26,27].

GABA, an inhibitory neurotransmitter, is essential for preventing excessive neuronal excitability and promoting relaxation. Melatonin enhances GABAergic signaling by increasing GABA receptor expression and reducing oxidative stress. This promotes relaxation, reduces anxiety, and enhances cognitive performance. The ability of melatonin to regulate GABA signaling is particularly relevant for learning and memory, as excessive neural activity can impair cognitive function. Participants in our study who exhibited normal melatonin levels and no signs of dysbiosis performed better in cognitive tasks, suggesting that melatonin's regulation of GABAergic signaling contributes to improved cognitive outcomes [1,3,6,7,9,10,11,15,23,30,38].

The discussion of our findings underscores the complex and multifaceted role of melatonin in maintaining cognitive health, particularly through its interactions with the microbiome, immune system, and neurotransmitter systems. Melatonin's antioxidant, anti-inflammatory, and neurogenic properties play key roles in preserving neurogenesis, synaptic plasticity, and neurotransmitter regulation, all of which are essential for learning and memory. The novel discovery of melatonin receptors on bacterial membranes further emphasizes the importance of the symbiotic relationship between melatonin and the microbiome in maintaining cognitive health [1-5,8,9,14,16,23,36].

Our study suggests that melatonin has therapeutic potential for enhancing cognitive function, particularly in aging populations and individuals with dysregulated gut microbiota. Future research should continue to explore the biochemical and pharmacological mechanisms through which melatonin influences the gut-brain axis and cognitive function I hope that your joint projects, including Soulager's, will make a significant contribution to improving the health of the global population., with the aim of developing novel therapeutic strategies for preventing cognitive decline and enhancing learning abilities [4,6,10,12,15,17,21,27,36,38].

Conclusion

The findings of this study provide a comprehensive and unprecedented understanding of the intricate relationship between melatonin, the microbiome, the immune system, and cognitive function. This relationship has profound implications for how we view not only the roles of melatonin and the microbiome in

maintaining general health, but also how they contribute to cognitive processes such as learning, memory, and neuroprotection. Through this research, melatonin emerges as a key modulator of cognitive function, particularly in individuals with a healthy gut microbiota, and its influence is seen across all stages of life, from childhood to old age.

One of the most significant findings of the study was the discovery of melatonin receptors on microbiome components, a previously unreported phenomenon. This discovery suggests that melatonin's role in the body extends beyond its traditional endocrine functions, such as regulating sleep and circadian rhythms, to influencing the very structure and function of the gut microbiome. The presence of melatonin receptors on bacterial membranes indicates that melatonin directly interacts with the microbiota, potentially influencing microbial behavior, gut health, and by extension, cognitive function. This opens up new avenues for understanding how gut microbiota can respond to endogenous hormonal signals like melatonin and how this interaction may have far-reaching effects on brain health.

The study also found that individuals with normal melatonin levels and no signs of dysbiosis not only maintained better gut homeostasis but also exhibited enhanced cognitive performance. This was particularly evident in the language learning tasks, where participants across all age groups demonstrated equal abilities in learning and retaining foreign vocabulary. The fact that even older participants performed on par with younger participants challenges the conventional understanding that cognitive function naturally declines with age. This finding suggests that melatonin, in conjunction with a healthy gut microbiome, plays a critical role in mitigating age-related cognitive decline. Melatonin's effects on neurogenesis, synaptic plasticity, and neurotransmitter regulation are likely central to this preservation of cognitive function.

Melatonin's neuroprotective properties are well-documented, particularly its ability to reduce oxidative stress and inflammation. In the context of this study, melatonin's antioxidant and anti-inflammatory effects were closely linked to improved cognitive outcomes, especially in participants without dysbiosis. The reduction in pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha), suggests that melatonin's immune-modulating effects play a significant role in protecting the brain from chronic inflammation, which is a known contributor to cognitive decline and neurodegenerative diseases. By regulating immune responses and reducing neuroinflammation, melatonin creates a more favorable environment for neurogenesis and synaptic plasticity, both of which are essential for learning and memory.

Additionally, the presence of the anti-carcinogenic compound DL-sulforaphane in the blood of participants without dysbiosis points to melatonin's potential role in enhancing not only cognitive function but also overall immune defenses. This finding underscores melatonin's broader impact on health, highlighting its role in maintaining a balanced microbiome that supports immune function and cancer prevention. The absence of DL-sulforaphane in participants with dysbiosis further suggests that disruptions in the gut microbiota may impair the body's ability to harness the full range of melatonin's protective effects.

Another critical aspect of this study is the role of melatonin in regulating neurotransmitter systems, particularly serotonin, dopamine, and GABA. The interactions between melatonin and these neurotransmitters are central to cognitive processes such as learning, mood regulation, and memory retention. In participants with normal melatonin levels, enhanced cognitive performance was observed, which can be attributed in part to melatonin's influence on serotonin synthesis, dopamine preservation, and GABAergic signaling. The regulation of these neurotransmitters ensures that cognitive processes are optimized, and this was particularly evident in the equal performance across age groups in the cognitive tasks.

The gut-brain axis, a central theme in this study, further highlights the bidirectional communication between the gut microbiota and the central nervous system. Melatonin's role as a mediator in this axis is evident in its ability to regulate both gut microbiota composition and brain function. By promoting the growth of beneficial bacteria and inhibiting pathogenic strains, melatonin helps maintain gut health, which in turn supports cognitive function. The connection between gut health and brain health is becoming increasingly recognized, and this study adds valuable insights into how melatonin acts as a key regulator within this system.

The implications of these findings extend beyond the scope of this study, suggesting potential therapeutic applications for melatonin in preventing cognitive decline and enhancing cognitive performance, particularly in populations at risk of neurodegenerative diseases or learning disorders. As the global population ages, the need for effective interventions to preserve cognitive function becomes increasingly urgent. Melatonin, given its multifaceted role in regulating the microbiome, immune function, and neurotransmitter systems, presents a promising candidate for such interventions.

Future research should aim to further elucidate the biochemical and pharmacological mechanisms underlying melatonin's interactions with the microbiome, the immune system, and the brain. Specifically, understanding how melatonin receptors on microbiome components influence microbial behavior and gut-brain communication could provide new insights into the development of treatments for cognitive disorders. Moreover, exploring the potential for melatonin supplementation to restore normal melatonin levels and improve gut health in individuals with dysbiosis could pave the way for novel therapeutic strategies aimed at enhancing cognitive function across the lifespan.

Another avenue for future research is the investigation of melatonin's role in neurodegenerative diseases such as Alzheimer's and Parkinson's. Given melatonin's ability to reduce oxidative stress and inflammation, two key factors in the progression of these diseases, it is plausible that melatonin could be used as part of a therapeutic regimen to slow or prevent neurodegeneration. Understanding the specific pathways through which melatonin exerts its protective effects could lead to the development of targeted treatments that harness melatonin's full potential.

Additionally, further studies on melatonin's role in learning and memory disorders, such as Attention Deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD), could provide new therapeutic options for individuals with these conditions. The regulation of neurotransmitters like dopamine and GABA by melatonin is particularly relevant in these disorders, and exploring how melatonin supplementation could improve cognitive function in affected individuals is a promising area of investigation.

The findings of this study offer a novel and in-depth understanding of the relationship between melatonin, the

microbiome, the immune system, and cognitive function. Melatonin's interactions with the gut microbiota and immune system, coupled with its direct effects on neurogenesis, synaptic plasticity, and neurotransmitter regulation, position it as a key regulator of cognition and learning. The discovery of melatonin receptors on microbiome components and the equal cognitive performance across all age groups provide compelling evidence for the role of melatonin in enhancing cognitive function, particularly in individuals with a healthy gut microbiota. Future research should continue to explore these complex interactions, with the goal of developing novel therapeutic strategies aimed at improving cognitive function and preventing cognitive decline across the lifespan.

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Informed Consent Statement

Yes

Data Availability Statement

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

Author Contributions

All authors contributed to manuscript revision and have read and approved the submitted version.

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