

Role of Antioxidants in Sleep Disorders: A Review

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Alexander Victor Anand David¹, Subramani Parasuraman² ,
and Evelyn Jerusha Edward³

Abstract

Sleep is a crucial physiological process that plays an indispensable role in sustaining overall health and well-being. It is well known that various factors affect the multifaceted dimensions of sleep, from its underlying mechanisms or comorbidity to its profound impact on physical and mental health. Sleep disorders are very common, frequently underdiagnosed, and often overlooked. They are also linked to a wide range of illnesses and may significantly reduce the quality of life. There is strong evidence that chronic diseases are more likely to develop due to the adverse consequences of sleep deprivation, which include cognitive decline, emotional and mental health problems, as well as cardiovascular, cerebrovascular, and metabolic health issues. Insufficiency of sleep and sleep disorders are common augurs of child/adolescent mental diseases, such as anxiety and depression, including suicidal thoughts. Additionally, we discuss a few sleep disorders, focusing on their effects, for instance, insomnia, sleep apnea, and restless leg syndrome. Antioxidants are molecules that can benefit the body by combating detrimental free radicals, which have been associated with health ailments such as diabetes and cancer. These are groups of compounds that counterbalance free radicals and reactive oxygen species (ROS) in the cell, and over the many clinical trials, they have been scientifically fascinating compounds due to their numerous advantages. As the relationship between sleep and health continues to evolve, this review highlights the intricate significance of antioxidants and their benefits for improving sleep quality and managing sleep deprivation. In addition to that, antioxidants are well known to defend the human body from oxidative stress and inflammation, which can disrupt sleep patterns, leading to various health ailments.

Keywords

Cognitive decline antioxidant, oxidative stress, reactive oxygen species, sleep apnea

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Introduction

Sleep is a biological necessity demarcated as an agile state of insensibility produced by the body whereby the brain is in a comparative state of rest and is reactive principally to internal stimulus.¹ Good sleep quality is necessary for resting, healing, rejuvenating, and preparing ourselves both physically and mentally for another new day. Therefore, it is crucial for the ideal functioning of the body, which includes growth, cognitive memory, immunological function, psychological state, and general well-being.² It is often proven that insufficient or untreated sleep disorders are detrimental to health and well-being. Sleep disorders are challenges that slow down a person from receiving sufficient restful sleep and, as a result, can induce daytime tiredness and dysfunction. Sleep is said to be vital for health and general wellness among

all age groups.^{3,4} Studies have shown that enough sleep promotes optimal cardiovascular, cerebrovascular, and metabolic functioning, as well as mood, mental health, and cognitive performance.⁵ Various underlying conditions may trigger problems with sleep, which in turn can cause cardiovascular and mental complications.⁶ In the majority of

¹Unit of Anatomy, Faculty of Medicine, AIMST University, Bedong, Malaysia

²Unit of Pharmacology, Toxicology and Basic Health Sciences, Faculty of Pharmacy, AIMST University, Bedong, Malaysia

³Unit of Basic Medical Sciences, Faculty of Dentistry, AIMST University, Bedong, Malaysia

Corresponding author:

Subramani Parasuraman, Unit of Pharmacology, Toxicology and Basic Health Sciences, Faculty of Pharmacy, AIMST University, Bedong 08100, Malaysia.
E-mail: parasuphd@gmail.com



age groups, sleep deprivation is typically associated with deficits in higher-order cognitive abilities such as attention, memory, reasoning, and problem-solving, and this association is stronger in younger individuals than in older adults.⁷ Sleep disorders can be classified into over 80 different categories. An estimated 50 to 70 million Americans are thought to be affected by sleep disorders, which are thought to be a global problem.⁸ The most common sleep disorders are insomnia, sleep apnea, restless leg syndrome, narcolepsy, parasomnia, as well as sleep paralysis disorders. Apart from that, sleep disorders can be triggered by several medical conditions that may lead to sleep disruption or an excessive amount of daytime sleepiness. Both intrinsic and extrinsic factors are considered to affect sleep. Internally, factors that affect sleep include illnesses, hormones, genetics, and state of mind. Sleep is greatly influenced by diet and the environment.⁹

Natural antioxidants like flavonoids, a family of polyphenolic compounds, have been proven to reduce oxidative stress and thereby facilitate good health. Certain studies have demonstrated the health-promoting qualities of polyphenols by delaying the onset of certain serious disorders, most notably linked to neurodegenerative diseases. Polyphenols have garnered significant interest in the past few years due to their potent anti-inflammatory, antioxidant, immunomodulatory, and apoptotic properties.¹⁰ Flavonoids have the potential to prevent sleep problems. Recent studies suggest that phytochemicals can help to treat sleep disturbances. Herbal treatments offer fewer adverse effects than conventional pharmaceuticals. Furthermore, a randomized controlled trial study discovered that postmenopausal women who took isoflavones had better quality sleep and experienced fewer cases of insomnia.¹¹ The objective of this review is to discuss the role of antioxidants in sleep disorders.

Common Types of Sleep Disorders

Sleep Apnea

One of the most prevalent forms of sleep deprivation is known as sleep apnea, which is a dangerous sleep disorder that is thought to arise from breathing difficulties during sleep. A person with sleep apnea experiences brief cessations of breathing while they are asleep. People with untreated sleep apnea frequently stop breathing while they are asleep, sometimes hundreds of times. The cause of this is reduced oxygen delivery to the body's tissues, including the brain. The disruption of the sleep cycle that results from breathing again leads to sleep deprivation. Central sleep apnea (CSA) and obstructive sleep apnea (OSA) are the two forms of sleep apnea. The more common of the two types of apneas, OSA, is brought on by an obstruction of the airway, which frequently happens as a result of the soft tissue at the back of the throat contracting while sleeping. When there is instability in the respiratory control center, the brain is unable to communicate with the muscles to breathe, resulting in CSA. Regular

occurrence of this during the night prevents restful sleep. With OSA, there are three severity levels of the condition: mild, moderate, and severe. Five to fourteen apnea episodes per hour are considered mild OSA. An hourly incidence of 15 to 30 apnea episodes is considered moderate. When there are 30 or more OSA episodes in an hour, it is considered severe OSA.^{12,13}

Narcolepsy

Narcolepsy is a neurological disorder that affects the ability to govern one's sleep and wakefulness. It is marked by episodes of cataplexy throughout the day, periods of somnolence during the day, and sometimes hallucinations that are brought on by strong emotions. In addition to experiencing extreme daytime drowsiness and sporadic, uncontrollable episodes of falling asleep during the day, a large number of narcoleptics also suffer from insomnia. These unexpected sleep attacks can happen at any time of the day while engaging in any kind of activity. Some narcolepsy sufferers have abrupt muscular weakness in response to laughter or other emotions. Although it can start at any age, narcolepsy often manifests itself between the ages of 15 and 25 years. Nevertheless, narcolepsy goes misdiagnosed and untreated a lot of times.¹⁴

Parasomnia

Disorders characterized by unwanted, unpleasant, physical, verbal, or aberrant behaviors, as well as emotional sensations and perceptions that happen during sleep or partial arousals from sleep, are classified as parasomnias. A greater frequency of insomnia in children than in adults can be attributed to its ability to occur throughout both the rapid eye movement (REM) and non-REM phases of sleep.¹⁵ Certain parasomnias occur in the early hours of the night during non-REM sleep. Others take place during REM sleep later in the evening. The following are a few examples of parasomnias: eating disorders related to sleep; sexsomnia, also known as "sleep sex," which is the term for sexual acts performed by a person who is asleep; nightmares; night terrors; REM sleep behavior disorder; bed wetting; confusional arousal; teeth grinding; and sleepwalking. People with insomnia may have negative symptoms all day long, including tiredness.¹⁶

Insomnia and Hypersomnia

An inability to fall and remain asleep is the hallmark of insomnia. Those who experience insomnia frequently wake up too early and feel tired. Primary and secondary insomnia are the two categories of insomnia. Primary insomnia is the state in which a person's sleep difficulties are unconnected to any other medical condition, whereas secondary insomnia is the state in which a person's sleep problems are tied to a medical condition, possibly from a habitual drug misuse or addiction. Acute insomnia is a type of short-term insomnia

that can last one night to a few weeks, whereas chronic insomnia can remain for a month or more and occur at least three nights a week.¹⁷ Unfortunately, 10 times as many people who suffer from insomnia also experience depression, and 83% of those with depression exhibit insomnia-related symptoms. This frequently results in depressing thoughts, suicidal ideas, mood fluctuations, and an overall decline in the quality of life. In reality, anxiety, major depression, diabetes, hypertension, drug abuse problems, and social disengagement can all be made more likely by insomnia. The reverse of insomnia, known as hypersomnia, is marked by excessive oversleeping; despite sleeping excessively, the individual does not feel rejuvenated, which negatively impacts performance and results in diminished functioning. 40% of young individuals experiencing depression additionally experience hypersomnia, with younger women experiencing it more frequently than older people.¹⁸

Restless Leg Syndrome

The term “restless leg syndrome” (RLS), often referred to as “Willis-Ekbom disease,” describes a strong need to move the legs and unpleasant or painful leg sensations. Most people have their worst symptoms at night while they’re resting, like lying in bed or sitting down, and usually the symptoms start to show up in the late afternoon or evening. Extended periods of inactivity and sitting might also trigger the discomfort. RLS is classified as a movement and sleep disorder since trying to fall asleep and rest exacerbates the symptoms.¹⁹ This is an additional sleep issue that often occurs alongside depression. Similar to diabetic neuropathy, people with RLS experience severe “pins and needles” in their lower limbs when they lie down. The only way to ease this discomfort is to jerk the legs, which makes it difficult to fall asleep and may result in insomnia.²⁰

Sleep Disorders Related to Depression

Individuals with mental diseases such as major depressive disorder (MDD), bipolar disorder, post-traumatic stress disorder, and generalized anxiety disorder are often found to have sleep disturbances, which are characterized by irregular sleep patterns and abnormalities. By 2030, depression, one of the most prevalent mental health conditions worldwide, is predicted to account for the majority of all sickness cases. One’s mood and energy levels are impacted by sleep deprivation throughout the day.²¹ When there are several disappointing, unresolved difficulties in a person’s mind, this will carry over into bedtime and prevent the individual from falling asleep due to their restless mind. Depressed people may isolate themselves, which can exacerbate sleep issues. Major depressive disorder and sleeplessness are strongly correlated, especially in young individuals.²²

Antioxidants

Antioxidants are substances that prevent other molecules from oxidizing, which results in the production of free radicals from cell metabolism in biological systems. It is said that free radicals are extremely reactive substances. An appropriate balance between the body’s antioxidant defense mechanisms and the production of free radicals can be triggered by unsuitable dietary habits and lifestyle choices. This imbalance, known as oxidative stress *via* molecular damage, can have a negative impact on the immune system.^{23,24} It can be caused by external factors, including radiation, pollution, tobacco smoke, and medications, or it might be initiated by normal cell metabolism. The buildup of free radicals in the body causes autoimmune diseases, aging, cataract, rheumatoid arthritis, cardiovascular disease, and neurological problems, among other chronic and degenerative illnesses.^{25,26} This explains the importance of maintaining good dietary practices, which include consuming bioactive antioxidant molecules, which are becoming increasingly important to the society. Vitamins, phenolic compounds, and carotenoids are abundant in plants and edible fruits, vegetables, spices, and herbs. These are the main sources of natural dietary antioxidants.²⁷ The conventional nutritional pyramid and worldwide dietary recommendations highlight eating five servings a day of fruits and vegetables as a fundamental component of a balanced diet and illness prevention. It has been observed that consuming sufficient amounts of natural antioxidants strengthens the immune system since they are rich in fiber, vitamins, and minerals, leading to the prevention of common ailments such as diabetes, obesity, heart disease, and some forms of cancer.²⁸

Sleep takes up one-third of our day and is essential to overall health and well-being in humans. Sleep is influenced by a multitude of variables, one of which is diet, that has an impact on several sleep characteristics. An important factor in helping to encourage restful sleep is antioxidant consumption. Antioxidants are found in natural ratios and quantities in fresh, healthy food, as opposed to supplements or capsules, that maximize the antioxidant impact. Therefore, maintaining an ideal antioxidant status and stimulating the body’s natural defenses against diseases may best be achieved by eating a balanced diet that includes an adequate amount of vitamins and minerals each day. According to studies, the best method to include these healthy substances in everyday meals for better sleep quality is to eat a balanced diet high in antioxidants from fruits, vegetables, nuts, and whole grains. The remarkable biological activity and nutritional qualities of flavonoids, a class of antioxidants, have piqued interest in studying their pharmacological effects on sleep. The studies have shown positive benefits, and it has been shown that flavonoid treatment may alleviate sleep issues by having fewer side effects.²⁹

Role of Antioxidants in Sleep Disorders and Insomnia

Reduction in Oxidative Stress

It has been demonstrated that antioxidants reduce oxidative stress by scavenging the damaging free radicals from the body. Consequently, high levels of oxidative stress, with or without external factors, are associated with sleep disturbances and sleep disorders. Studies have revealed that lowering oxidative stress with antioxidants may promote more restful sleep and thereby reduce sleep deprivation.³⁰

Enhanced Sleep Duration

Some antioxidants, like melatonin, are directly involved in regulating sleep–wake cycles. Pineal gland production of the hormone melatonin contributes to the regulation of the circadian rhythm. Aging often causes a decline in melatonin synthesis. An essential component of having good sleep is the body's production of melatonin. Supplementing with melatonin or consuming foods rich in melatonin, such as tart cherries, may give rise to improved sleep duration. The evidence gleaned from the databases demonstrated that herbal medicine has a multimodal cellular mechanism of action, consisting of various phytochemical bioactives with antioxidant, anti-inflammatory, vasorelaxant, detoxifying, anxiolytic, and cell-rejuvenating properties. It can be used to treat cardiovascular diseases, insomnia, and other psychological conditions.³¹

Improved Sleep Onset

Antioxidants benefit in falling asleep more effortlessly. Flavonoids, which are included in foods such as citrus fruits, berries, and dark chocolate, for instance, may have a relaxing impact on the nervous system, which facilitates the onset of sleep. The high antioxidant and serotonin content of kiwi fruits suggests that they may be useful in treating sleep problems and easing their associated symptoms. Research has indicated that vitamins C and E might be advantageous in the treatment of obstructive sleep apnea, a disorder that causes breathing disturbances while people are asleep.³²

Stress Reduction and Enhancement of Sleep

Antioxidants can help to combat the effects of stress on sleep. Chronic stress can lead to increased oxidative stress and sleep disturbances. Antioxidants, by reducing stress-related inflammation, may indirectly improve sleep quality. Improved sleep architecture, which takes into account the different stages of sleep (such as REM and non-REM sleep), may be facilitated by antioxidants. This can result in more restorative sleep and improved overall sleep quality.³³

Cognitive Benefits

Improved sleep quality due to antioxidants can lead to better cognitive function during waking hours. This includes improved memory, attention, and problem-solving abilities.³⁴

Therapy using immediate-release, as indicated by sleep diaries or actigraphy, melatonin at doses ranging from 2 to 10 mg/day was found to be well tolerated and effective in shortening sleep-onset latency (SOL), reducing the number of awakenings per night and bedtime resistance, and increasing the total sleep time. The majority of individuals with autism spectrum disorder (ASD) showed a good reduction in sleep-related problems with low or medium dosages of melatonin (~1 to 6 mg/day). The effects of supplementing with ubiquinone (the oxidized form of coenzyme Q10) and ubiquinol (the reduced form) on sleep problems in people with ASD have been examined in two trials. It has been discovered that patients treated with high-dose (60 mg/day) ubiquinone had a significantly higher rate of improvement in sleep disorders, as reported subjectively by parents, when compared to low-dose treatment groups and placebo. In prior research, 34% of patients reported improvements in sleep difficulties following ubiquinol treatment.³⁵

Melatonin was found to be beneficial in treating insomnia in children and adolescents with ASD. Subjects with ASD reported improvements in sleep latency, total sleep time, and fewer nocturnal awakenings when using melatonin, as evidenced by actigraphic findings and subjective measures (scales, questionnaires, and diaries). For children and teenagers, melatonin in the dosage range of 2 to 10 mg/day is likewise thought to be a safe and well-tolerated medicine. It is important to note that melatonin is known to be involved in several pathways, including the regulation of circadian rhythm and anti-inflammatory and antioxidant effects. Melatonin is effective in improving sleep in children with ASD may be diverse, possibly even synergistic.³⁶

The carnitine/organic cation transporter (OCTN1), which is widely expressed in the brain, liver, and small intestine, often uses ergothioneine (EGT) as a substrate. As a result, EGT taken orally is effectively stored in the liver before entering into the bloodstream and traveling to the brain across the blood-brain barrier.³⁷

Additional clinical research has shown that following repeated oral administration, EGT is readily absorbed and maintained in the body, resulting in markedly elevated concentrations of both plasma and whole blood as well as comparatively low urine elimination. Therefore, it is said that EGT, regardless of when it is consumed, helps those who are in good health but have trouble sleeping. Despite having limited permeability across the lipid bilayer cell membrane and being extremely water soluble, EGT is regarded as special among sleep-improving medicines since it is effectively distributed to the brain through the use of a particular transporter. The

substantial drop in deoxycorticosterone with EGT ingestion lends credence to the idea that another potential mechanism involves a reduction in stress hormones. It has been observed that stress inhibits hippocampus neurogenesis, which causes hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis and an increase in glucocorticoids. In addition to encouraging hippocampus neurogenesis, EGT may also have some kind of regulatory influence on the HPA axis. Reductions in the blood levels of stress hormones might help with sleep problems.^{37,38}

In another research study, a herbal medicine known as *Arbutus andrachne*, which contains a high amount of phenolic antioxidants, helps to protect against sleep disorders that cause memory impairment in rats by improving the oxidative state of the hippocampal region. This effect is achieved in rats by sleep deprivation. It has the ability to induce sleep since some research has shown that a natural substance taken from the root of *Withania somnifera* (Ashwagandha) can enhance sleep quality and sleep onset latency in people with insomnia.³⁹

The chemical compound malondialdehyde (MDA) is produced when polyunsaturated fatty acids (PUFAs) undergo lipid peroxidation (LPO). It has been shown to be a useful indicator of LPO for sleep disorders, particularly obstructive pulmonary syndrome, and an effective measure of lipid peroxidation. Lipid peroxidation is subsequently reduced in drowsy interns by vitamins C and E, which also lower the MDA levels. In comparison to the control group, the 17 interns who received vitamins C and E showed a lipid peroxidation level that was less than half that of the treatment group. As per earlier findings, vitamin C works in unison to shield lipids in brain circuits and mitochondria from oxidative damage. Supplementing individuals with excessive daytime drowsiness with vitamins C and E has been proposed as a viable way to counteract the cellular damage caused by lipid damage.⁴⁰

Conclusion

A majority of medications used to treat insomnia or sleep disorders have a negative impact on the quality of life because of their numerous side effects, which include tolerance, addiction, overdose risk, and habituation. Natural sleep aids are popular substitutes for prescription drugs in order to increase the quality of sleep and minimize adverse effects. Lifestyle, nutrition, sleep hygiene, and underlying medical issues are just a few of the many variables that interact to affect sleep. Therefore, a holistic approach to sleep improvement is often recommended by increasing the intake of antioxidants that can be found naturally in vegetables and fruits or in supplements. These may not be seen as an immediate remedy for serious sleep disorders with underlying comorbidities; however, they have been proven to facilitate undisturbed sleep. It is noteworthy that antioxidants may not be a cure-all for all sleep-related problems, but they have the

potential to enhance the quality of sleep with or without sleep disorders and help to manage diseases connected to sleep.

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ORCID iD

Subramani Parasuraman  <https://orcid.org/0000-0003-3655-8375>

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